NEUROBIOLOGY OF SENSORY DEVIANCE: USING EEG TO MEASURE VISUAL AND AUDITORY MISMATCH NEGATIVITY IN CHILDREN WITH AUTISM

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ABSTRACT

KATHERINE MCLAURIN CLEARY: Neurobiology of Sensory Deviance: Using EEG to Measure Visual and Auditory Mismatch Negativity in Children with Autism
(Under the direction of Aysenil Belger)

Sensory processing, in particular processing of sensory deviance in one's environment, is important for functioning in a fast-paced world. Deficits in sensory processing may underlie the deficits in social interaction, communication, and restricted or repetitive behaviors seen in autism. We can use Event Related Potential (ERP) research to investigate processing of sensory changes through the mismatch negativity (MMN), or a difference ERP waveform computed by subtracting a neural response to a frequently-occurring standard event from a rare deviant event. Until recently, most research has focused on mismatch negativity in the auditory modality, but there is evidence that visual mismatch negativity (vMMN) can provide important information about sensory processing in both typical development and autism. In addition, the ways in which auditory ERP components interact with behavioral responses to changing sensory stimuli measured through behavioral observations and parent reports are poorly understood. Preliminary results in the auditory modality showed that the amplitude of the P3a and N2 ERP components predicted high levels of sensory seeking behaviors, and further that this relationship was dependent on the amplitude of P1. This suggests that task orienting may be related to sensory seeking behaviors, given modulation by early mechanisms of stimulus detection. Preliminary data also indicate relationships between auditory ERP components and behaviorally measured sensory response

patterns. The goal of this research was two-fold. The first aim was to characterize vMMN in typically developing 8-12-year-old children, and the second aim was to investigate differences in vMMN observed in children with autism. Results from this work showed that both typically developing children and children with autism display a vMMN with two negativities, while adults only display one negativity. Further, the first negativity observed in the children with autism occurred earlier than in the typically developing children, and amplitude of the second negativity correlated with age in the typically developing children only. These results suggest that children with autism may exhibit enhanced processing of basic stimulus features and attenuated processing of memory comparisons with standard events. Further research may result in improved intervention strategies customized to individual sensory processing deficit type and severity.

DEDICATION

This dissertation is dedicated to Dr. Garrett Milliken, who brought the love of neurobiology into my life and has taught me that “it’s your movie; you’re directing.”

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CHAPTER ONE: GENERAL INTRODUCTION

Every moment, we constantly encounter sensory experiences in our environments, from the feeling of a cotton shirt against our skin, to the change of a traffic light from red to green, to the trilling of a telephone. These stimuli are in unceasing motion, ever changing as we unconsciously adapt to the thousands of sensory changes that occur in our environment within a single second. For some individuals, this process occurs seamlessly and unconsciously, as we constantly make tiny adjustments to our perception of the environment: deciding which stimuli are important and planning our reactions accordingly; allocating ever-changing degrees of resources to particular stimuli depending on their relevance; and maximizing our ability to engage efficiently with our environments. However, for others, this sensory processing can be a relentless struggle if their ability to process changes in sensory information is disrupted. These deficits may impair the ability to learn language, which is dependent on many tiny distinctions of auditory stimuli, the ability to associate that language with printed letters and words, the subsequent ability to use those words to interact with others, or even impact other sensory modalities such as touch and taste. In addition, these deficits could interfere with broader processes of perception, emotion processing, and socialization and as such have a profound impact on those who suffer from them.

The ability to accurately detect sensory changes and adjust responses accordingly is often impaired in many developmental disorders, including autism. The profound negative impact that deficits in sensory processing can have on individuals with

autism, particularly children, has lead researchers to investigate ways to better understand sensory processing in both typical and disordered development. This knowledge will help orchestrate more effective clinical interventions for children affected by deficits in sensory processing. Behavioral research through observational and self/parent reports has contributed to the knowledge of sensory processing deficits, but a biological approach to investigate response to sensory changes is necessary to provide a more complete understanding of these concepts. Through event related potential (ERP) research, we possess the ability to measure both conscious and unconscious responses to changes in sensory stimuli at the level of milliseconds, and this technique has already lead to answers for many underlying questions of how the brain processes stimulus deviance. Using a phenomenon known as the mismatch negativity (MMN), research has painted a detailed picture of stimulus deviance through many developmental phases, clinical states and stimulus modalities, but more questions remain. Through investigation of stimulus deviance in the visual modality in childhood and relationships to specific sensory features found in autism in the auditory modality, the current studies seek to build a broader knowledge base of how children relate to their sensory environment in both typical development and in autism.

1.1 Brief introduction to autism: features, symptoms, deficit domains, and avenues for research into sensory features

Autism is a complex spectrum of neurodevelopmental disorders characterized by three main deficit domains: impaired social interaction, communication deficits, and restricted or repetitive behaviors or interests (DSM-IV-TR, 2000). Deficits in social interaction are often observable very early in children with autism, especially through

retrospective video analysis of home movies recorded in infancy (Osterling and Dawson 1994; Baranek 1999) and prospective studies of high risk siblings (e.g. Zwaigenbaum et al. 2009). These infants may engage less in social behaviors, including responding to their name being called or looking and smiling at other individuals, and initiate or sustain less eye contact than their typically developing peers (Baranek 1999; Volkmar et al 2005). Later in development, preschoolers with autism may exhibit difficulties with turn-taking and socially approaching others, and have poorer understanding of social norms and others' emotions (Sigman et al 2004). Later in life, many of these individuals find it difficult to make and maintain friends, and social development deficits represent a strong negative impact on their lives (Burgess and Gutstein 2007).

Deficits in communication, especially with regard to language acquisition and production, are also prevalent in autism. Language deficits observed in individuals with autism differ widely, with some high functioning individuals displaying little to no language-related symptoms and some lower-functioning individuals being completely nonverbal (Lord et al. 2000). As seen in social interaction deficits described above, communication deficits may begin in infancy with decreased or delayed onset of babbling and unusual gestures, as well as lack of verbal cues taken from the caregiver; these deficits can further in the preschool years with increased reliance on nonverbal communication and the onset of echolalia, or the repetition of others' words (Landa 2007). These children may also have difficulties with joint attention, or the focus on two individuals or objects (Volkmar et al. 2005); for example, many are unable to follow the gaze of an individual who is pointing out an object, and look at the pointing hand instead. Although higher functioning adolescents and adults with autism may have basic language skills on par with or superior to their typically-developing peers, their complex understanding of language comprehension, especially symbolic language and inference,

is limited (Williams et al 2006). These deficits make it difficult to function in a reality driven by verbal communication, and as many as one half of children with autism do not develop sufficient language skills to communicate independently (Noens et al. 2006). Restricted and repetitive behaviors or interests are common in autism and can occur in many forms, as measured by the Repetitive Behaviors Scale-Revised (RBS-R; Bodfish, Symons and Lewis 1999). Individuals with autism may exhibit movement stereotypy such as hand-flapping; compulsive or ritualistic behaviors associated with inability to cope with change in routine or arranging objects; limited interests such as a particular video game or topic; and a preference for sameness in their environments and a poor tolerance of change (Lam and Arman 2007). These behaviors in particular suggest difficulties with stimulus change in the sensory environments of individuals with autism and may be partially explained by atypical sensory processing in these individuals. Indeed, profound sensory deficits and unusual sensory features have been observed in individuals with autism, particularly children, as discussed below, and these and other symptoms have a profound impact.

Autism is both a rapidly expanding and highly costly societal issue, and many individuals with autism exhibit symptoms not explicitly inside the three core symptom domains. Current statistics state that about 1 in 110 children are diagnosed with autism (http:///cdc.gov), making it more common than pediatric cancer, diabetes and AIDS combined. The prevalence of autism increases about 10-17 percent annually, and the average lifetime cost to care for an individual with autism is estimated at 3.2 million (Ganz 2007). In addition to the core deficits, abnormal sensory processing features are commonly observed in individuals with autism throughout the lifespan with regard to visual, auditory, gustatory and tactile stimulation. Hyporesponsiveness (behavioral under-reactivity to sensory input), hyperesponsiveness (behavioral over-reactivity to

sensory input) and sensory seeking (craving certain types of sensory input) are three classifications of behavior common in children with autism (Boyd et al. 2010). These unusual sensory features cause significant negative consequences to both the individuals affected by them and their families (Boyd et al. 2010).

Because autism is highly heterogeneous in nature, the severity and manifestation of symptoms vary widely, both between individuals with autism and across development. Some individuals have severe behavioral deficits and remain completely nonverbal throughout their lifespan, while others have milder impairments in speech patterns, eye gaze, and stereotyped behaviors. These large variations in symptoms have significant predictive and diagnostic relevance (Luyster, Qui, Lopez and Lord 2007), but have thus far remained unresolved. As a result, many children are not correctly diagnosed with autism until 2 to 3 years after symptoms appear (Filipek et al. 1999; Bryson, Rogers and Fombonne, 2003). Recent research has shown that examining the biology and behavior behind deficits in sensory processing may hold the key to these diagnostic and research challenges. Cognitive science has attempted to explain sensory deficits in autism in several different ways, and three main theories underlying these deficits will be discussed below.

There are three major cognitive theories in autism dominant in psychological and cognitive research: the Theory of Mind hypothesis, the Theory of Executive Dysfunction, and the Weak Central Coherence theory (Rajendran and Mitchell 2007). While these theories each explain unique aspects about the core deficits of autism, a combined approach is probably the most complete explanation of the unique deficits observed in this disorder. The Theory of Mind hypothesis is related to the empathizing-systemizing theory, which states that while individuals with autism are efficient at developing internal rules of operation, they are less efficient at handling events generated by others and in

turn empathizing with others (Rajendran and Mitchell 2007). This hypothesis focuses on the social and communication deficits seen in autism. Theory of Mind, or the ability to recognize that others outside of oneself have a point-of-view, was originally postulated by Premack and Woodruff (1978) and, in this hypothesis, is impaired in individuals with autism. This hypothesis is supported by atypical responses of children with autism to tests for unexpected transfer of false belief pioneered by Wimmer and Perner (1983), in which a story is told to a child whereby a puppet has a belief about an object's location that is incongruous with its true location. This requires the child to make inferences about the puppet's mental state, and in this widely-replicated finding, a majority of children with autism were unable to do this. A weakness of this theory is that many studies have found that individuals with autism have more difficulty with complex emotional states of others, rather than simple opposing viewpoints (Hamilton 2009). In addition, responses of children with autism to the classic Theory of Mind test (Wimmer and Perner 1983) vary, and indeed some children with autism are capable of taking the puppet's perspective. This is probably related to the strong heterogeneity of autism and suggests that while the Theory of Mind may explain some aspects of autism for some individuals, it is not a complete hypothesis (Rajendran and Mitchell 2007).

The second hypothesis focuses more generally on the non-social deficits seen in autism, particularly repetitive behaviors and sensory deficits. The Theory of Executive Dysfunction postulates that autism can be explained by deficits in executive functions such as working memory, action planning, and behavioral initiation, sustainability, shifting, and inhibition (Rajendran and Mitchell 2007). These abilities are measured by standardized tasks such as the Wisconsin Card Sorting Task and the Tower of Hanoi task. Numerous studies, reviewed by Kenworthy et al. (2008) have demonstrated that individuals with autism often perform poorly on executive function tasks relative to

typically-developing individuals, and that even when their performance is on par with that of typical individuals, they often recruit different neural networks in order to perform the task. Poor performance on executive function tasks is also predictive of repetitive behaviors, especially stereotypies and mental inflexibility, although not all children with autism perform poorly on executive function tasks, and performance on some tasks, such as the Stroop task, tend to be unimpaired in children with autism (Hill 2004). However, Kenworthy et al. (2008) also note that this hypothesis may be incomplete; in some cases when the human examiner is replaced by a computer, individuals with autism improve their performance of executive function tasks, indicating that cognitive hypotheses of social interaction deficits and executive function deficits may interact.

The third cognitive hypothesis is the Weak Central Coherence Theory (Frith 1989), which helps to merge the non-social and social theories and is applicable across multiple domains. This theory states that while typically-developing individuals tend to derive overall meaning from information they come across in their environments, individuals with autism tend to focus on smaller details of this information rather than the "big picture," or global coherence (Rajendran and Mitchell 2007). This theory is related to the idea that individuals with autism exhibit enhanced perceptual functioning, especially when concerned with detail-focused stimuli and local (versus global) stimulus processing (Mottron et al 2006). This theory fits in well with the idea of underconnectivity in autism, proposed by Just et al. (2004), which states that deficits associated with autism, especially language, arise from poorer information integration and synchronization across large-scale cortical networks. Recent research has re-characterized this deficit of global processing as superior local processing, and focuses more on the consideration of weak central coherence as a differing cognitive style, rather than a deficit as seen in the Executive Function and Theory of Mind hypotheses

(Rajendran and Mitchell 2007). Rajendran and Mitchell (2007) also emphasize that while individuals with autism may be biased to detail processing over global processing, they may be able to process global information with increased effort or strategies that differ from typically-developing individuals.

Overall, none of these three cognitive theories of autism can fully explain this disorder on its own, likely due to the vast heterogeneity of autism and its multi-deficit presentation. However, Weak Central Coherence Theory may be particularly important in sensory processing. For example, there is evidence that deficits in visual processing may be particularly related to global, holistic stimulus properties in autism that primarily affect the parvocellular pathway, a system that allows for the processing of properties such as form, detail, and color. This theory may partially explain facial processing deficits seen in autism and postulates that a perceptual trend to perceive visual details over global features may be working independently from faces as a social stimulus (Behrmann et al. 2006). In addition, as noted above, individuals with autism may be able to process global information, but they may do so in a manner very different to typically-developing individuals: Iarocci and McDonald (2006) reviewed a number of studies on sensory integration in autism and argue that global processing is often intact in situations where only that particular type of processing was necessary. When situations required the integration of both local and global processing, individuals with autism tend to rely far more on local processing than typically-developing individuals (Iarocci and McDonald 2006). This theory indicates that weak central coherence is perhaps more complicated than previously thought, and is dependent upon context in which the stimulus is presented as well as the task at hand. Iarocci and McDonald (2006) call for investigation into the consequences of enhanced local perception in individuals with autism, especially in terms of multi-sensory integration. In any case, a

bias toward local processing and poor connectivity with other neural systems could have a negative impact on the way individuals with autism experience the world, and could partially explain the sensory features often found in autism, discussed below.

The three core symptom domains of autism may be further explained in the context of unusual sensory features. Sensory features occur often in autism, especially in children, exist on a continuum of severity and often persist into adulthood (Marco 2011). There is a wide variety of expression of sensory features, and individuals may experience them in some but not all sensory modalities, or even respond quite differently to stimuli in the same sensory modality. For example, children with autism may exhibit a profoundly diminished response to touch, crave certain textures or foods, or react very strongly to loud noises in ways that their typically-developing peers do not. These unusual sensory features appear to be behavioral expressions that aggregate into three distinct categories or sensory response patterns: (a) sensory hyporesponsiveness (i.e., failure to behaviorally react with sufficient magnitude or attention to a sensory stimulus; for example, no response to name being called), (b) sensory hyperresponsiveness (i.e., exaggerated behavioral reaction, aversion, or avoidance to a sensory stimulus; for example, extreme aversion to telephone ringing), and (c) sensory seeking behavior (i.e., cravings for sensory stimuli). A number of studies have examined sensory features in autism using play-based behavioral assessments and parent reports (Boyd et al 2010). High levels of hyporesponsive behaviors are associated with both increased social-communicated symptom severity and decreased language and social adaptive skill among children with autism (Watson et al 2010). In addition, high levels of hyperresponsiveness are associated with increased presence of repetitive behaviors in children with autism (Boyd et al 2010, Liss et al 2006). There has been some debate concerning whether sensory features are unique to autism, as well as whether certain

types of sensory features are more likely to occur in this disorder relative to other developmental disorders (Rogers and Ozonoff 2005). In a review of the empirical evidence of sensory features in autism, Rogers and Ozonoff (2005) found more evidence for hyporesponsive behaviors in children with autism as compared to children with other developmental disorders, but the authors also highlighted the lack of replicated findings and lack of group differences in many studies. These authors recommend more stringent diagnostic criteria and careful matching across study groups, as well as the inclusion of multiple sensory modalities and consistent biological measures to better interpret future research's findings.

These unusual sensory features, discussed in more detail in Chapter Two, may be related to each of the core deficits of autism. When a stimulus is introduced that deviates from the expected norms in an individual with autism's environment, these individuals may respond in ways that deviate significantly from individuals with typical development. Deficits in processing auditory stimuli, (e.g., hypo- or hyperresponsiveness) could lead to difficulty with the learning and subsequent production of language. Inability to process changes in an individual's environment and respond appropriately, especially those of a social nature such as facial expressions or touch, could lead to both deficits in social interaction and subsequent avoidance of such interactions. Finally, difficulties with responding to stimulus change could result in a desire for sameness, and result in the repetitive behaviors and interests often seen in autism. Studying sensory processing deficits in children with autism may help deconstruct the immense symptom variability found in autism and better parse the heterogeneity of this disorder.

Although behavioral research, which focuses primarily on observational, play-based measures and parent- and/or self- reports of the presence of sensory features

(Baranek 2006; Boyd et al. 2010), these measures currently lack biological correlates. Very few studies (e.g. Gomot et al. 2011) have researched sensory features using imaging methods, but this field has the potential to result in earlier diagnoses and intervention methods by uncovering markers for certain types of sensory deficits, described above. Taken together, this suggests that researching the biological bases of stimulus deviance is an excellent avenue to understand sensory processing in autism, as well as how deficits in that processing could influence the expression of the core symptom domains. Since most sensory stimuli are introduced quite quickly, a method with excellent temporal resolution is necessary to examine sensory deficits in autism. Event Related Potentials (ERPs), a type of electroencephalography (EEG) research, provides the necessary tools to study these questions. In addition, ERPs allow for the study of stimulus deviance per se in addition to basic sensory processing deficits. Such research can be efficiently conducted using a phenomenon observed in neural evoked potentials called mismatch negativity.

1.2 ERP as a measurement of sensory processing: Mismatch Negativity

Electroencephalography (EEG) is a method of measuring tiny electrical impulses from ionic current flow of neurons and the associated electrical activity of voltage fluctuations produced in the brain (Niedermeyer and da Silva 2004). Using this method, the aggregate of electric voltage fields from millions of neurons and associated spontaneous fluxes in brain activity can be recorded over a period of time. The first recording of electrical activity of the human brain was done by Hans Berger in 1924, and measured the voltage difference between two brain areas. EEG reflects the summed activity of post-synaptic, dendritic currents that have a similar spatial orientation radial to

the scalp. EEG is very useful in clinical and research settings due to its excellent temporal resolution, its noninvasiveness, its ability to directly measure brain activity and its relatively low cost. Clinical uses for EEG include seizure and sleep disorder diagnosis, monitoring states of consciousness, and diagnosing coma, encephalopathies or brain death.

Clinical uses for EEG normally focus on the collection of continuous data, but EEG can also be used to study evoked related potentials (ERPs) or averages of EEG activity time-locked to the presentation of an event and its associated processing. This allows for the measure of complex electrophysiological responses to a sensory, cognitive or motor event or stimulus. However, because EEG reflects myriad neural activity and brain processing occurring simultaneously, the response to a particular stimulus event is not visible in an EEG recording with the presentation of only one stimulus trial. Therefore, when ERPs are measured, many trials are presented and then averaged together. This waveform that remains, the ERP, usually consists of several positive and negative deflections of voltage (i.e. ERP components) usually referenced by a letter indicating polarity (i.e. 'P' for positive and 'N' for negative), followed by a number indicating the number of milliseconds post-stimulus presentation that the event appears, or latency. For example, a common positive-going component generally associated with the orienting response to an infrequent target event is the P300, or the P3. These latencies may vary according to subject population studied, paradigm, task parameters, and stimuli presented. An ERP to a certain stimulus event usually consists of several sequential positivities and negativities, with each being commonly associated with certain elements of stimulus processing. Often 'higher' cognitive processing such as memory, event expectation, orienting to a stimulus, or attention are involved. ERP research is very useful to measure processing of stimuli at various cognitive levels, and

can be used even populations who cannot follow directions, such as coma patients, infants, or individuals with profound cognitive deficits or developmental delays. Either used separately or together with behavioral research, ERP provides specific information about the timing of stimulus processing at the level of milliseconds, even when there is not necessarily a behavioral change in response to a stimulus. This makes it a particularly interesting tool to study neural responses that may occur very rapidly, and allows for timing measurements of information processing in different areas of the brain. These factors make ERP research useful for studying sensory processing in many modalities.

Two unique aspects of ERP research that make it particularly appealing for the study of stimulus change are both that it is possible to obtain ERPs even when a subject is not consciously attending to a stimulus, and to measure the brain's ability to detect a change in a stimulus when compared to a series of standard stimuli. The mismatch negativity (MMN) is a component of the ERP that occurs in response to a small, rare change in a series of frequently-occurring standard stimuli. MMN can be measured in any modality, although it is most commonly studied in the auditory and, more recently, the visual modality. In addition, many types of stimulus changes can elicit MMN, including pitch/frequency, duration, and intensity. It is usually computed by subtracting the ERP waveform elicited by a standard event from that of the deviant event, resulting in a difference wave that reflects the processing of change between the two stimulus events. This difference wave generally shows a negativity presenting over fronto-temporal electrode locations that peaks around 100 to 200ms post-stimulus presentation, although exact parameters depend on the nature of the deviance, the task paradigm, stimuli used, and the population studied (Naatanen 1995).

Much research has centered around the neural correlates of the MMN and its

associated cognitive processes. Generators for the MMN were first proposed bilaterally in the auditory cortex and in prefrontal areas (Naatanen and Michie 1979), and today the auditory MMN is thought to mainly originate from primary and secondary auditory cortices. Animal studies have revealed that other brain areas may contribute to MMN, including the thalamus (Kraus et al. 1995) and the hippocampus (Csepe et al. 1989). Different types of auditory deviants (e.g., frequency, duration) as well as deviants of varying complexities (e.g. phonemes versus simple tones) have been shown to have different generators within the auditory cortex (Alho 1995). Activation of prefrontal areas, such as the dorsolateral prefrontal cortex, might also occur due to the involuntary shifting of attention towards stimulus change (Giard et al. 1991; Escera et al. 2003), or connectivity input from frontal to auditory cortices (Alho et al. 1994). In this "memory-adjustment" theory, deviations in a particular established standard auditory sequence generate a response in a temporo-prefrontal network that compares the deviation with the previously-experienced memory trace of standard stimuli (Garrido et al 2009). This idea has been challenged by studies such as Jaaskelainen et al (2004) that found robust MMNs in the presence of a single standard stimulus, despite the idea that repeated standard stimuli are necessary to elicit an MMN. The authors hypothesized that the MMN is actually a result of auditory "adaptation" in the auditory cortex that causes attenuation and delay of the N1 response. The N1, or N100, is a large, negative-going peak occurring approximately 100ms post-stimulus presentation elicited by an unpredictable stimulus independent of task demands. However, the scalp distribution of the N1 is different from the MMN (Giard et al. 1990), and studies of patients with prefrontal lesions have revealed that N1 itself is influenced by prefrontal areas (Blenner and Yingling 1994). Furthermore, new evidence from pharmacological studies and more refined oddball paradigms designed to minimize the effect of N1 (for a review see

Garrido et al. 2009) has suggested that while the N1, and thereby the primary auditory cortex, has an effect on the MMN, it cannot explain the MMN entirely. It is likely that both the adaptation and memory-adjustment hypothesis contribute to the MMN. Garrido et al. (2009) proposed a model of predictive-coding that reconciles these two hypotheses and associated brain areas. In this view, integration of both sensory information from the environment and predictions formed based on what caused this sensory information work together to form perceptions. Interactions among auditory cortical hierarchies help to control prediction error, but when this does occur, as is the case with MMN, this model must be automatically and rapidly adjusted. Interestingly, a similar model has been proposed in the visual system whereby top-down processes make predictions based on input from bottom-up processes, which are then continuously modified to reflect actual sensory input (Yuille and Kersten 2006). Viewed this way, MMN is an important construct of perceptual learning and is reflective of changing connection strengths over repeated presentations of the same stimulus to more accurately reflect perceptual reality and reduce prediction error. This process requires input from both primary (i.e. auditory cortices) and higher-order (i.e. prefrontal areas) areas and allows for the reconciliation of the adaptation and the memory-adjustment hypotheses (Garrido et al. 2009).

The MMN is thought to be an objective measure of individual discrimination ability for stimulus features and, subsequently, ability to process sensory deviance and short-term sensory memory (Naatanen 1995). These concepts are particularly important for functioning in one's sensory environment, as discussed above, and the potential consequences for deficits in these processes makes MMN a popular field of study in many sensory-related disorders. MMN has been used in many previous studies to investigate various clinical populations, including individuals with schizophrenia, major depression, Alzheimer's disease and autism. MMN is particularly useful in investigating

disorders associated with deficits in language acquisition and production (e.g. Naatanen 1995; Roberts et al. 2011) or sensory processing deficits (e.g. Gomot et al. 2011; Donkers et al., in review). Both of these deficits are often observed in autism, making MMN a useful avenue to better understand how individuals with autism relate to their sensory environment in the auditory modality and beyond.

1.3: Visual mismatch negativity: A new modality for investigation of stimulus change

The presence of a visual mismatch negativity (vMMN) has been the subject of some debate, but recent research (reviewed by Pazo-Alvarez, Cadaveira and Amenedo, 2003; Czigler, 2007) has provided convincing evidence that the brain can unconsciously detect small changes in visual stimuli. Czigler, Balazs and Winkler (2002) first demonstrably demonstrated the existence of a visual mismatch negativity (MMN) in healthy participants who viewed different color gratings unrelated to the task at hand. This visual MMN was manifested in a posterior negativity and anterior positivity between 120-160ms post-stimulus presentation. However, the authors note that large deviances were necessary to elicit a visual MMN, as the small deviant condition did not produce a significant negativity. Since then, vMMN has been investigated and elicited in many different visual stimulus deviance paradigms, including color (Horimoto et al. 2002; Czigler, Weisz and Winkler 2006; Berti 2009), spatial frequency (Heslenfeld 2003; Fu et al. 2003), line orientation (Kimura et al. 2009; Czigler and Sulykos 2010), position (Muller et a. 2012; Berti 2009) and even complex stimuli such as facial emotions (Stefanics et al. 2011, Gayle et al. 2012). General commonalities of the studies mentioned above include the elicitation of an occipito-parietal negativity somewhere around 100 to 300ms

post-stimulus, this negativity's independence of stimulus properties, standard stimuli being present for comparison against the deviant stimuli, and conscious attention being unnecessary to elicit this negativity. This research has led to the conclusion that a visual homologue of the auditory MMN exists and may be a useful tool in clinical and cognitive neuroscience (Kimura et al. 2011).

Factors that affect visual MMN in previous studies include presentation of standards and unconscious change, task relevance, and the type of visual stimulus presented. Small changes in a frequently-occurring visual stimulus can be processed unconsciously, as demonstrated by Fu, Fan and Chen (2003). Visual gratings that had a different orientation to the previously-presented grating elicited P84 and N192 amplitudes in the occipital and temporal regions respectively. Although these authors found a pattern not directly analogous to the auditory MMN, this study indicates that changes in visual stimuli may be processed after only one standard presentation of a stimulus, and that the visual dimension of stimulus deviance is perhaps even more powerful than the auditory. Czigler and Sulykos (2010) showed that task relevance can affect visual MMN. In a set of healthy subjects, reaction time was slower when the irrelevant background visual stimuli matched the relevant target-related change. The authors also observed a posterior negativity to deviant background stimuli themselves, but the visual MMN was smaller in cases in which the task-relevant stimuli matched the irrelevant background stimuli. The authors suggest that the discrepancy between relevant and non-relevant background stimuli can be explained by subjects learning that "not all deviants are significant" in cases where the task-relevant and irrelevant stimuli match. The stimulus itself also affects the appearance of a visual MMN. When deviant stimuli were embedded in a task-relevant stimulus (Berti, 2009), position deviants located in the upper visual field elicited a detectable visual MMN, but color deviants and

deviants presented in the lower visual field did not. This indicates that obtaining a reliable visual MMN depends on both location and nature of the stimulus. Type of stimulus may be particularly important to visual MMN due to the topography of the human visual system and its organization into two distinct-but-interacting processing streams, i.e. dorsal and ventral. This idea will be discussed in detail in Chapter Four.

Number of negativities elicited, and their associated functional relevance, has also been a topic of concern in visual MMN research. Although the visual MMN is expressed as a negativity between 100-250 ms, there has been some debate as to whether this negativity represents a refractory effect of the visual stimulus or a true detection of change based on memory comparison. Kimura et al. (2009) addressed this question by presenting healthy subjects with two paradigms: the equiprobable (all types of stimuli presented at equal frequencies) and the oddball (standard stimuli in 80% of presentations and deviant stimuli 20%). The equiprobable paradigm elicited two negativities, one bilateral around 100-150, and one right-dominant around 200-250, while the oddball paradigm only exhibited the latter negativity. This indicates that the early negativity is related to the refractory effect, while the later one is related to the memory component of stimulus change detection. Similarly, Czigler, Weisz, and Winkler (2006) found two occipital/centro-parietal negativities in healthy adults viewing a set order of color grids that was periodically displaced. One negativity occurred at 100-140ms poststimulus and another at 210-280ms poststimulus. The purpose of the set pattern of alternating colors was to determine if the visual MMN was related to a change in stimuli themselves or a detection of deviance from a pre-established pattern of change in stimuli. Only the negativity at 210-280ms was elicited when the pattern of color grids was violated, indicating that this later waveform reflects a comparison to an established stimulus pattern and not stimulus change per se. For a detailed discussion of the first

and second negativities sometimes observed in vMMN and their potential functional applications, see Chapter Four.

Perhaps because visual MMN is a relatively new field of investigation, studies have primarily examined this difference wave in populations of typically-developing adults. A small number of studies have investigated vMMN in children (Horimoto et al. 2002; Tomio et al 2012; Clery et al 2012, 2013), both typically-developing and children with developmental disorders such as mental retardation (Horimoto et al. 2002) and autism (Clery et al. 2013). These studies will be described in more detail in Chapter Four and raise many questions about the development of vMMN in both typically-developing children and children with autism. In particular, the results of some of these studies have been inconsistent in typically-developing children (see Clery et al. 2012, 2013), leading to questions about their accuracy when used as a comparison group to children with autism. Comparatively little is known about vMMN in children with autism in relation to auditory MMN in this group, and there has been sparse speculation about the relationship between vMMN differences in these children. Looking to the relatively well-characterized auditory modality may help to answer these questions, as well as considering previous behavioral research into sensory features and the broader cognitive deficit domains of autism.

1.4 Brief Goals of Current Projects

In this chapter, we have seen that the ability to efficiently respond to changes in sensory input is important for functioning in an individual's environment on many levels. Sensory processing deficits, as manifested by unusual sensory features, are common in children with autism, and can have a profound negative impact on these children and their families. In addition, many questions still remain about the processing of stimulus

change in typical development; a better understanding of typical stimulus change processing is critical to understanding how and why this process is different in autism, as well as what interventions might be effective to improve it. ERP research has provided much knowledge in terms of how individuals process changes in their sensory environments, particularly through the mismatch negativity, a unique measure of unconscious stimulus deviance processing. The current projects will investigate visual mismatch negativity in typical development and in children with autism, as well as further the already-robust body of research on auditory mismatch negativity in children with autism by correlating MMN with sensory features evident in these children. To this end, the current projects will work to answer the following questions:

Visual MMN has advanced greatly as a field in the last two decades, but there is still sparse research on how MMN in the visual modality manifests in children. In addition, very few studies have investigated MMN in children with autism. The current project will therefore investigate the development of vMMN in a sample of typically-developing children and children with autism. The goal of this project both to characterize vMMN at a particular stage of development (in this case, eight- to twelve-year-old children) and to open the door for future studies relating vMMN to sensory features found in children with autism and other developmental disorders.

Although there is a rich field of research concerning auditory MMN in children with autism, how differences in aMMN in this population relate to specific sensory features common in these children is poorly understood. The current project will therefore investigate these relationships through a multi-measure study using observational and parent reports of sensory behaviors combined with a passive auditory oddball ERP paradigm designed to measure unusual auditory MMN in children with autism as compared to typically-developing children. The goal of this project is to better

understand how sensory features observed in the clinic relate to biological measures of neural activity, in this case ERP components. For a detailed description of specific aims and research methods, see Chapter Two and Chapter Four respectively.

The overarching goal of these projects is to provide a more complete description of how typically-developing children and children with autism process sensory changes in their environment in both the visual and auditory modality. As discussed in Chapter One, autism is a multi-faceted and heterogeneous disorder that cannot be understood via only one cognitive model. This research seeks to add to the knowledge that already exists with respect to sensory processing in autism, and to better explain the findings of previous ERP studies in autism, by synthesizing findings across two different modalities and across behavioral and biological measures. In chapters Two and Four respectively, auditory and visual MMN will be discussed in the context of both previous research and outstanding questions that still remain, including a discussion of how the current projects could address these questions. In Chapter Three, preliminary data will be presented concerning auditory MMN in children. In Chapter Five, the current studies will be described and discussed concerning visual MMN in children. In Chapter Six, this work will be discussed in the context of the cognitive models of autism introduced in Chapter One, and recommendations will be made for future work in ERP research concerning sensory processing. With future research, this work may provide a better understanding of sensory interventions for children with autism, as well as open the door to further work correlating observed sensory behaviors and measured biological ERP findings.

CHAPTER TWO: SENSORY PROCESSING IN AUTISM INVESTIGATED USING AUDITORY MISMATCH NEGATIVITY

2.1: Auditory MMN in typical development

Mismatch negativity in the auditory modality (aMMN) has been well-studied in both typical development and in autism, and is defined as the brain's response to a rare change in a series of frequently occurring standard stimuli (Naatanen and Escera 2000). This deviance can be detected in one or more features of the stimulus such as pitch/frequency, duration, or intensity. The adult auditory MMN was first described by Naatanen, Gaillard and Mantysalo (1978) as a negativity in response to auditory stimuli varying slightly in either intensity and frequency. It manifests as a fronto-central negativity associated with primary and secondary auditory cortices, and occurs approximately 150-200ms post-stimulus presentation. Larger stimulus deviations result in larger amplitudes and shorter latencies of the MMN, and comparison with a standard stimulus is necessary to elicit this measure of auditory sensory memory. Functional applications of the auditory MMN include possible neural correlates underlying basic sensory feature discrimination, ability to discriminate at the level of basic stimulus features, higher-order cognition of language, automatic anticipation of stimuli in the auditory cortex, and attentional switching (reviewed by Naatanen et al. 2007). This difference wave can be detected relatively early in development and automatically manifests in response to differences between a currently-displayed stimuli and previously-detected stimuli (Duncan et al. 2009).

There are several reasons that make aMMN a useful research tool to study sensory deviance processing in both clinical and typically-developing populations. aMMN can be studied even in very young or very impaired populations who cannot follow instructions. In addition, aMMN is particularly suited to the investigation of many aspects of symptoms commonly seen in developmental disorders. aMMN is thought to be related to language development, as there are many finely tuned discriminations between sounds that must occur when learning to produce language, and as such it is a popular tool to investigate disorders associated with language delay. Finally, aMMN occurs very quickly and can be easily measured with EEG's high temporal resolution, allowing for the precise study of sensory responses that occur on the order of milliseconds. These factors make aMMN an important tool in cognitive neuroscience for the investigation of developmental disorders, as well as the study of sensory processing in typically development.

Although research has noted some discrepancies, the aMMN in typical development is relatively well understood. Infants as young as two months may express aMMN-like negativities around 200ms (Ceponiene 2002), however, there is also evidence that very young infants may instead display a positive slow wave that increases in amplitude in response to auditory deviants (Trainor 2003). Research generally agrees that this response is relatively stable in older infants, where the deviance response is expressed in an increased negativity that mimics the adult aMMN at around six months. This maturation may reflect development of layer IV cortex, which is unsynchronized in younger infants (Trainor 2003) as evidenced by the appearance of the positive slow wave. Trainor et al. (2003) hypothesized that this occurs due to either increased thalamocoritcal input to the cortex during the presentation of deviant stimuli, or that deviant input to thalamocortical areas activates a different set of unadapted neurons

and can therefore fire at faster rates. The emergence of MMN-like responses is likely a reflection of the maturation of deeper cortical layers (Trainor et al 2003).

In terms of peak topography, the aMMN is very similar to adults by childhood (around age seven), but many studies suggest that it is not yet fully mature; specifically, it seems to be larger in amplitude and longer in latency in children versus adults and older adolescents. Oades et al. (1997) found that aMMNs were larger in ten to fourteen year old children than in seventeen to twenty-one year old young adults. In addition, there may be a right frontal bias in younger children that is not evident in the older age group. In a sample of four to ten year old typically-developing children and adults, Shafer et al. (2000) found that the aMMN was expressed as a frontal negativity occurring around 200ms post-stimulus in children. This peak decreased in latency by 11ms/year of age across the span of child participants, and the overall amplitude of the aMMN was significantly larger in children versus adults. Kraus et al. (1997) also found larger aMMN amplitudes in school-age children versus adults, although these authors did not find any significant differences in latency. This could be due to the stimuli used in this particular study, which were restricted to perceptively different speech phonemes. There could be a perceptual benefit to further language-related auditory stimuli in typically-developing children. Indeed, Korpilahti et al. (2001) found stronger aMMNs to deviations in pseudoword stimuli versus words, although it is important to note that in this study, word deviances elicited a later aMMN around 400ms poststimulus. This latency difference may have been due to increased complexity of the stimuli used by Korpilahti et al. as compared to Kraus et al., i.e. whole words versus simple phonemes. This concept is discussed further below in the context of children with autism and other language delays. Finally, differences in aMMN between children and adults may have localization factors in terms of different neural sources. Gomot et al. (2000) found that while both children

and adults displayed aMMNs to small frequency deviances at temporal and frontal electrode sites, the amplitude of aMMN was greater at temporal electrode sites only in the children. The authors concluded that aMMN may be mediated by two distinct neural systems that may be temporally connected, with the system associated with the auditory cortex also associated with pre-attentive mechanisms and maturing later than that of frontal areas. This multi-component, successive view of aMMN has also been postulated in the visual modality as discussed in previous chapters. Generally, however, the aMMN seems to decrease in both latency and amplitude with age, which indicates both faster and more efficient processing of auditory deviance with increasing age and biological maturation.

2.2: MMN as a measure of sensory features in autism

The studies described in previous chapters have investigated stimulus deviance processing in the visual modality using populations of children with autism as well as typically-developing adults and children. Impaired processing of rare stimulus deviance may affect individuals with autism in many ways, including adaptation to a changing environment and stimulus filtering. Individuals with autism often have difficulty identifying salient portions of stimuli and allocating reduced cognitive resources to those that are less important or repetitive. In dynamic environments, this could produce marked difficulties with social interaction and communication. Some difficulties that might be encountered include language deficits that are often observed in individuals with autism, difficulty extracting information from emotional facial expressions and in planning behaviors accordingly. The MMN has long been thought of as a useful clinical

tool to measure stimulus deviance processing due to its non-invasive, unconscious nature, and it has been posited that MMN holds clinical applications in the areas of language deficits, overall cognitive functioning, sensory memory, and states of consciousness (see Naatanen 2003 for a review). Many of these potential applications are relevant to the core features of autism. Evidence presented in previous chapters indicates that not only do individuals with autism have difficulty with these broader, top-down processes; they may also have deficits at more fundamental levels of stimulus discrimination and deviant recognition, which may go on to explain the more commonly-observed symptom domains in autism spectrum disorders. For example, an individual who has a reduced response to task-irrelevant, small differences in spatial frequency at components of the ERP associated with early primary visual areas may have difficulty recognizing at an unconscious level when a portion of their environment has changed. Or, deficits in later ERP components may point to greater processing resources allocated, or resources allocated in inappropriate distributions, leading to excess strain in experiencing one's sensory environment. These problems may lead to difficulties in adjusting behavior appropriately in everyday functioning, as sensory experiences impact these individuals more. Consequently, such individuals may begin to avoid situations, e.g. social interaction, in which these experiences may arise. Clearly visual sensory deficits, even at the very basic level of primary auditory cortex, can have a strong impact on individuals with autism. However, this research question has many detailed facets that necessitate further exploration.

While the field of visual deviance processing is still emerging, and more research like that presented in previous chapters is strongly needed to characterize it, the most commonly reported sensory features in children with autism occur in the auditory modality (Marco et al. 2011). However, these features occur across all sensory

modalities and their relationship is complicated. As a result, recent research has characterized sensory features as part of a continuum and organized them into distinct sensory response patterns including hyporesponsiveness, hyperresponsiveness and sensory seeking behaviors. Many unusual sensory behaviors can be related to over- or underreactivity to stimulus deviance, such as a child who prefers repetitive conditions and becomes profoundly upset when this repetition is violated, or changes in auditory or visual stimuli (such as a blinking light or a blender being turned on) that elicit far more or less of a response than would be otherwise appropriate. Craving of sensory input, or sensory seeking behaviors, can also occur. More than ninety-six percent of children with autism exhibit some form of sensory hyper- or hyporesponsivity, and these deficits exist on a continuum of severity and often persist into adulthood (Marco 2011). MMN's nature as the response to a rare change in a series of frequently occurring standard stimuli makes it an ideal avenue to investigate atypical sensory features. Currently, categories of sensory features such as hyporesponsiveness, hyperresponsiveness, and sensory seeking behavior are primarily assessed using observed behavioral measures and parent reports such as the Sensory Processing Assessment for Young Children (SPA; Baranek 1999, unpublished manuscript), the Sensory Experiences Questionnaire (SEQ; Baranek 1999, unpublished manuscript; Baranek et al. 2006) and the Sensory Profile (SP; Dunn 1999). These categories of sensory features have been associated with core deficits of autism. In particular, Boyd et al. (2010) found that high levels of hyperresponsiveness predicted high levels of repetitive behaviors as measured by the Repetitive Behavior Scales – Revised (RBS-R; Bodfish, Symons and Lewis 1999) in both children with autism and those with other developmental delays. In addition, these three categories of sensory features can co-occur, and Boyd et al. (2010) found that hyporesponsiveness was moderately correlated with hyperresponsiveness and sensory

seeking behaviors. However, each category is not necessarily related to one another, i.e. sensory seeking and hyperresponsiveness were not correlated in Boyd et al. (2010)'s analysis. Sensory seeking appears to be related to ritualistic/sameness behavior dimensions of repetitive behaviors (Boyd et al. 2010), while previous studies (Gay et al. 2008) have found that social communication deficits may be associated with high levels of both sensory seeking and hyporesponsive behaviors. While it is important to note that these general associations were often seen in children with other developmental delays in addition to children with autism, children with autism were more likely to have higher scores on both measures of sensory features and on the RBS-R. This indicates that there could be different systems of neurobiological deficits underlying each sensory feature category, and further that these categories could better explain the three core deficits of autism. Furthermore, although the interactions between sensory features and, for example, repetitive behaviors may be similar in children with autism and other developmental delays, it is likely that these deficits are more severe in children with autism and much more likely to occur (Marco 2011; Dawson and Watling 2000).

However, the neurobiological underpinnings of sensory features remain unclear. Although auditory MMN has been well-studied in both typically-developing populations and in children with autism, no studies have correlated this measure with sensory features using behavioral and parent report measures. Studies examining MMN alone, in either the auditory or visual modality, can provide important information about the neurobiology of stimulus deviance processing. Moreover, correlating these measures with the behavioral consequences of autism, in this case the often-observed presence of unusual sensory features, would further explain how these deviances are related to real-world behavioral changes. Therefore, it follows to investigate paradigms correlating ERP data with standardized reports of sensory features as a logical further direction of

stimulus deviance research. These correlations could help explain the heterogeneity of autism and provide for more targeted interventions that would address the individual child's specific sensory difficulties.

2.3: Clinical applications of Auditory MMN studies in autism

There have been a wide variety of interventions to address sensory features in children with autism, including Sensory Integration (i.e. exposure to a wide variety of sensory experiences), Auditory Integration Training (i.e. electronically modulated or filtered music provided through earphones), and Sensory Stimulation (i.e. providing organized sensory stimulation of one type and modality, e.g. pressure) approaches (Baranek 2002). These sensory-focused interventions are not substitutes for core educational curricula and are likely most useful as supplementary portions of an overall intervention program. Baranek (2002) recommends a conservative approach for applying these interventions, as there is limited scientific basis for the efficacy of these therapies. Most evidence comes from case studies and small intervention studies and these findings are mixed, with any observed improvements often disappearing following cessation of treatment; large-scale experimental studies on the efficacy of sensory-based interventions are lacking (Baranek 2002). In addition, some interventions such as AIT have been criticized for potential adverse effects including lack of safeguards against hearing loss.

In general, while sensory-based interventions for children with autism have significant potential to positively impact children with significant sensory processing deficits, the wide variety of individual deficits, as well as the lack of large experimental studies into the efficacy of such interventions, provides a significant roadblock to positive

outcomes. Baranek (2002) recommends longitudinal and cross-sectional studies documenting the efficacy of these interventions using replicated, methodologically rigorous designs with randomized controlled trials. Baranek (2002) also emphasizes the importance of identification of specific behavioral and physiological patterns that differentiate those who respond well to these treatments from those who do not. This pattern identification can be addressed through studying individual sensory features, both behaviorally through observational and parent report methods, and neurobiologically through ERP investigations such as aMMN studies. Research on sensory features shows that individual children with autism can have vastly different sensory processing profiles (e.g. Boyd et al. 2010), and there is unlikely to be any "one-size-fits-all" intervention treatment for deficits in sensory processing. However, studies of aMMN may be useful as a clinical assessment tool in differentiating which children might be most responsive to certain types of sensory-based interventions. These potential benefits, when combined with large experimental intervention studies, could help tailor treatment plans to individual children's needs. A major avenue for pursuing aMMN research with the goal of improved, individualized sensory-based interventions is the correlation of aMMN and other subtypes of auditory ERP responses to measures of autism severity and auditory processing. Several recent studies, discussed below, have begun to address these questions.

Ability to discriminate between similar auditory stimuli may be related to both sensory processing deficits and their associated sensory features, and this could have strong implications for treatment and intervention. In one recent study of auditory discrimination and sensory features in adolescents, Jones et al. (2009) found that a subset of roughly twenty percent of these adolescents possessed superior auditory frequency discrimination ability, compared to only four percent of typically-developing

adolescents who reached the same performance threshold. This effect was not observed in intensity of duration discrimination of auditory stimuli, but frequency discrimination ability did not correlate with auditory sensory behaviors as measured by the Adult/Adolescent Sensory Profile (AASP; Brown and Dunn 2002). Further, individuals with autism who were more proficient at auditory duration discrimination self-reported more auditory sensory behaviors on the AASP. However, individuals with autism who performed poorly on auditory intensity discrimination were more likely to report sensory behaviors related to coping with loudness levels. This study, while not collecting ERP data, indicates that a subset of adolescents with autism exhibit superior auditory frequency discrimination, and the authors hypothesize that they may represent a specific phenotype. However, this superior frequency discrimination group was not associated with sensory features. This paper is indicative of the complicated relationship between auditory deviance types, associated sensory features, and performance among individuals with autism. The authors note that items on the AASP rarely deal with frequency discrimination and are more focused on loud noises and lack of response to auditory stimuli; it is possible that frequency-specific auditory sensory features may be present in this group. Future work should determine what is 'special' about frequency discrimination in autism, as well as any associated neurological differences that depend on sensory processing profile; this could be approached using ERP, as other studies described below have begun to investigate.

Gomot et al. (2011) investigated the relationship between tolerance of change and aMMN to frequency-deviant tones in a sample of school-aged children with autism and age-matched typically-developing controls. In this study, children heard tones of 1000Hz and infrequent tones of 1100Hz. MMN and P3a latency and amplitudes were correlated with their score on the Behavior Summarized Evaluations scale (BSE-R,

Barthelemy et al. 1997), a questionnaire for evaluating symptoms of autism such as deficits in social interaction as well as verbal and non-verbal communication, abnormal eye contact and responses to auditory stimuli, and ritual uses of objects. The authors selected items that were relevant to their hypotheses, including unusual responses to auditory stimuli and disproportionate frustration or anger when activities are interrupted, objects forbidden, or expectations unsatisfied. Gomot et al. (2011) found shorter MMN latencies in children with autism compared to typically-developing controls at frontal and central electrode sites, and no significant group difference in MMN amplitude. Additionally, while no differences were noted in P3a latency, its amplitude was larger in children with autism at both frontal and central electrode sites. Overall, children with autism seem hypersensitive to novel auditory frequencies, a finding replicated in many other MMN studies (see Gomot et al. 2002; Ferri et al. 2003; Jones et al. 2009). Perhaps more importantly, however, children with autism who scored higher on intolerance of change on the BSE-R had significantly shorter MMN latencies at Fz and P3a latencies at Cz, compared to children with autism scoring low on this item. According to Gomot et al. (2011), MMN may be a useful endophenotype for behaviors related to intolerance of change, especially since the authors note that this latency shortening of MMN observed in autism appears to be specific to this disorder versus other developmental delays. Understanding MMN as a partial measure of the need to preserve sameness may be useful in autism research. This concept is similar to the work of Perry et al. (2007), who found that decreased pre-pulse inhibition (PPI) in adults with autism was associated with increased ratings of repetitive behaviors as determined by the repetitive behaviors subscale of the ADI-R. The authors hypothesized that these differences may be related to inhibitory failure leading to cognitive and behavioral effects observed in the form of increased repetitive behaviors. A similar mechanism may be

occurring in abnormalities observed in MMN, particularly in the subset of individuals with autism scoring high on preference for sameness, and distress when routines are disrupted.

2.4: Auditory MMN in Autism and its relationship to sensory features

The body of literature concerning aMMN in autism is inconsistent (e.g. Bomba and Pang 2004; Jeste and Nelson 2009; see Marco et al. 2011 for a review), and many different findings have been reported. This is likely due to several factors, including the heterogeneity of autism spectrum disorders, and consequently the subject populations chosen for each study, and the different paradigms used to investigate aMMN. Although this topic has been well-researched previously and resolving the remaining discrepancies is beyond the scope of this work, a brief review of aMMN findings in autism will be presented here, as well as remaining questions as they relate to sensory features' role in stimulus deviance processing.

Previous studies have found decreased MMN amplitudes and latencies in AU children when presented with important components of language such as vowel perception (Oram et al. 2005) and small changes in pitch (Gomot et al. 2002). However, some types of stimuli, such as pitch-deviant tones, elicit larger MMNs (Ferri et al. 2003) in children with AU, and some studies report autism MMNs on par with typically-developing controls (Ceponiene et al. 2003). Numerous factors may explain these discrepancies, leading to a better understanding of auditory processing in autism. Concurrent cognitive deficits and level of functioning or symptomatology could strongly affect aMMN. The participants in Ferri et al.'s study were also affected by mental

retardation, and the authors hypothesize that their results may have been influenced by low functioning cognitive impairment. This both highlights aMMN's usefulness as a tool to investigate brain functioning even in individuals who cannot cooperate or follow instructions, since this ERP component occurs unconsciously and makes it very easy to deliver auditory stimuli in a passive paradigm, and yet also indicates potential differences between low and high functioning individuals with autism. It is worth noting, however, that another study (Gomot et al., 2002) found decreased aMMNs in children with autism that were unaffected by the level of mental retardation of the children in their sample. The potential distribution using scalp current density (SCD) mapping was altered both in autism versus control children, and in the autism group subdivided into more and less severe levels of mental retardation. In other words, children with autism exhibited an abnormal bilateral distribution over central electrodes as compared to frontal electrodes in typically-developing children, and this effect was most profound in the children within the autism group with high levels of mental retardation. Gomot et al. (2002) also used SCD to observe different aMMN generators in children with autism, with earlier left temporal activation preceded by an abnormal early left frontal component, versus typically-developing children. The authors hypothesize possible left frontal cortex dysfunction underlying their observed reduced aMMNs, potentially involving parallel nonprimary thalamo-cortical projections that could be overactivated in children with autism. Gomot et al. (2002) also noted the presence of a P3a-like component in children with autism following the aMMN. The P3a is a later component of an ERP reflecting more conscious attention to a stimulus and especially stimulus orienting. It is possible that overactivation of the left frontal cortex and hypersensitive involuntary orienting toward deviant stimuli cause children with autism to switch attention toward this deviant stimulus, becoming distracted and distressed when such stimulus

changes would normally not pass into conscious awareness in control children. This hypothesis is especially important in hyperresponsive children and may explain their overreaction to environmental stimuli.

Age is also an important factor in characterizing aMMN in autism, and it may interact with severity of deficit to paint a more complete picture of how deviance processing is altered in autism. In a sample of adults diagnosed with Asperger's disorder, Kujala et al. (2007) found increased amplitude of the aMMN in fronto-central electrodes in duration-deviant stimuli compared to typically-developing adults, and also shorter latencies of aMMN and P3a in frequency deviant stimuli. The authors argue for enhanced speed of cortical processing and hypersensitivity to stimulus deviants in individuals with Asperger's disorder, which may relate to these individuals' increased detail-oriented perception rather than holistic perception in a dynamic environment. The authors also note that another study (Lepisto et al. 2006) using the exact same paradigm and stimuli found the opposite effect in children with Asperger's disorder and autism (2005), in that these children had attenuated aMMN amplitudes to duration deviant auditory stimuli. There are possible developmental effects at work here that point to studying adolescents with autism in order to determine where the ERP shift occurs. However, Lepisto et al. (2006) also noted that the children in their study had larger aMMN amplitudes in response to frequency deviant stimuli, indicating that while at first glance the exact opposite effect occurred in a different age group, stimulus deviance type also plays a role. These studies are significant because the same results were found when Lepisto et al. applied the paradigm to children with autism as well as Asperger's disorder, indicating similar auditory deviance processing despite large differences in clinical diagnoses, outcomes, and symptom severity in the two disorders.

However, another study (Dunn et al. 2008) found decreased aMMN amplitudes in

children with autism as compared to typically-developing children in response to frequency-deviant tones. Potential explanations could be the different stimuli used, stimulus duration, and the particular sample of children with autism. Dunn et al. only used a 1000Hz and 1200Hz tone, while Lepisto et al. (2005, 2006) used standard tones of 500, 1000 and 1500Hz, and these deviants also occurred more often (24% vs 10%). Perhaps children with Asperger's disorder and autism are more sensitive to increased variety of stimulus deviance. Interestingly, when Dunn et al. (2008) instructed the children to attend to the auditory stimuli, the smaller amplitude of aMMN in children with autism vanished. This indicates that consciousness may play a larger role in auditory deviance processing in children with autism, and with increased cognitive resources devoted to a stimulus they may be able to overcome differences from their typically-developing peers. Covariance for language development did not explain differences in aMMN in Dunn et al. (2008)'s sample, and the children with autism were able to behaviorally discriminate between the two tones on par with the control children, although amplitude of aMMN did tend to increase with age in the children with autism. The authors concluded that auditory processing requires more effort in children with autism and continues to require conscious attention long after typically-developing children process the information automatically. There appear to be some factors that elicit typical aMMNs in children with autism, such as increasing age, larger differences between standard and deviant stimuli, and most interestingly, conscious attention. It is therefore possible that auditory stimulus discrimination could be "trained" as suggested by Dunn et al. (2008), leading to improved automatic processing of stimuli generalized beyond that used in a particular paradigm. This concept is particularly important in light of individuals with sensory features, especially if such training might result in reduced hyperresponsive behaviors even when confronted with different auditory stimuli than the

ones used in “training.” Furthermore, changes in aMMN dysfunction might be extrapolated to stimulus deviance in other modalities, and therefore future studies should investigate conscious attention’s effect on vMMN in children with autism.

Taken together, there appear to be many different factors at work in characterizing differences in the aMMN between children with autism and typically-developing controls. However, recent research is beginning to piece together discrepancies found in previous studies. It appears that children with autism generally have hypersensitivities to auditory deviance, as evidenced by increased aMMN amplitudes or decreased latencies, when the stimuli used in the task, such as tones or environmental sounds, do not relate directly to language acquisition or development. However, when stimuli directly mimic speech sounds such as vowels, consonants, or phonemes, children with autism often have attenuated aMMN amplitudes or longer latencies, indicating poorer auditory processing of stimuli related to language. In other words, children with autism are hypersensitive to auditory stimuli in their environments, which may cause distress and resulting auditory sensory features often seen in autism, yet they are also less responsive to small auditory changes necessary to understand and produce speech, leading them to be less likely to engage in language production and less successful in social communication. This explanation would largely account for the discrepancies seen in the literature around aMMN amplitude and latency. Indeed, Lepisto et al. (2006) found that MMN amplitudes were attenuated in children with Asperger syndrome in the left hemisphere, but enhanced in the right hemisphere when compared to typically-developing controls. Lepisto et al. (2006) also found that P3a amplitudes were diminished in children with Asperger syndrome only in the case of speech-related sounds, while other sounds were left intact. Recent work by Roberts et al. (2011) lends credence to this theory, as these authors found associations between

delayed magnetic mismatch field latency (in a magnetoencephalography study) and concomitant language impairment. Children with autism who also had language impairments tended to have longer latencies of auditory deviance processing of tones and vowels than children with autism who lacked language impairments. However, Naatanen and Kajula (2011) note that this effect may be due to sub-optimal language processing in general, rather than language impairments in autism specifically. These authors note that aMMN amplitude in response to speech sounds has been found to decrease in children with general learning disabilities, premature infants, and children with dyslexia. They further state that overall cognitive impairment may be a factor in aMMN differences seen in autism. Indeed, Naatanen et al. (2011) recently argued that attenuated or delayed MMNs reflect overall cognitive and functional decline in patients with schizophrenia and many other disorders, including Down syndrome and Alzheimer's disease, and suggested that research on aMMN should go beyond auditory cortex deficits and consider global effects of, for example, neurotransmitter dysfunctions. Overall, although there are still questions to consider related to overall brain dysfunction, it appears that language processing deficits might strongly relate to aMMN hyposensitivity in autism, while stimuli that are not related to language tend to produce aMMN hypersensitivity in this group. Currently, the field of aMMN would benefit from investigating types of unusual sensory features in autism, as this could both further the distinction between subtypes and severities of autism and help explain why children with autism are hypersensitive to non-language auditory deviant stimuli. We may be able to determine the neurobiological nature of these sensitivities and their behavioral and clinical consequences by investigating differences in MMN – or possibly other ERP components – related to hyperresponsiveness, hyporesponsiveness, or sensory seeking behaviors in children with autism.

2.5: Future directions of sensory processing investigation in MMN and rationale for current studies

Currently, there is a vast body of research investigating sensory processing in terms of MMN as a measure of neurobiological response to stimulus deviance, behavioral observation and parental report studies of sensory features, and the relationship of these two research concepts to autism and other disorders with a strong relationship to sensory processing deficits.

Going forward, an integrative approach may help to answer outstanding questions regarding process of stimulus deviance in typical and disordered development. Many studies (see Jones et al. 2009; Perry et al. 2007; Gomot et al. 2011) have begun to correlate behavioral measures of sensory processing deficits with auditory discrimination ability, basic sensory responses, and ERP patterns, respectively. This work has helped identify potential sensory subcategories of autism and sensory processing deviance, building on work such as Boyd et al. (2008) and Baranek et al. (2006), dedicated to distinguishing sensory processing deficits based on subcategories of sensory features. Future studies should consider relationships built between subcategories of sensory features, such as hyporesponsiveness, hyperresponsiveness, and sensory seeking behaviors, in context of behavioral and biological measures such as PPI, auditory discrimination ability, and in particular the MMN as investigated using ERP research. Such distinctions will allow for more individualized sensory processing profiles, as well as supplement the results reported in questionnaires and observational measures with biological and sensory findings.

While we have gained much knowledge about performance on both behavioral

and biological tasks and their relationship to core deficits of autism, particularly with regard to stimulus features, many questions remain unanswered. In particular, we do not know what neurobiological mechanisms underlie these 'subsets' of populations among children with autism who respond differently in the paradigms discussed here. What separates auditory frequency deviance processing from other kinds of auditory deviance, and why are certain subsets of children with autism particularly gifted at distinguishing it (Jones et al. 2009)? What, neurobiologically, causes the relationship between repetitive behaviors and high levels of hyperresponsiveness (Boyd et al. 2008)? And finally, how can we apply these measures to the clinic to provide better interventions to children with autism and their families? MMN is a useful tool to answer some aspects of these questions, as research discussed in this chapter has demonstrated that it is a neurobiological measure of deviance detection relevant to many aspects of autism and sensory processing, and has much potential as a biomarker for certain subsets of sensory processing deficits. But we have seen in previous chapters that MMN is not limited to the auditory modality; visual MMN is still developing as a field, but already has garnered interest in exploring biological mechanisms of visual deviance processing in both typically-developing populations and those with many neurobiological disorders, including autism. In the future, multi-sensory studies may strongly add to our knowledge of how children with autism relate to their integrated sensory environment; all studies focused on a single sensory modality present an artificial model of the world, which in reality is enriched with constant input from multiple sensory modalities. Indeed, some research has even begun to investigate somatosensory MMN (Restuccia et al. 2009), revealing that it is possible to elicit an MMN-like response to changes in location of electrical stimulation on the right hand while typically-developing children are engaged in a demanding video game. Naatanen (2009) argued that MMN in the somatosensory

modality would be particularly useful for investigation in children with autism, who frequently have difficulties with stimulus input in this modality (e.g. brushing hair, touch, clothing against skin). The possibility of multi-sensory MMN studies opens the door to further understanding sensory feature categories investigated by Baranek (2006). In the future, such work may serve as preamble to biomarkers for vulnerability to hyperresponsiveness, hyporesponsiveness, or sensory seeking behaviors, which would have profound implications for clinical interventions.

To this end, it is critical to continue investigating MMN in multiple modalities, both building on the thus-far modest research on development of the visual MMN, and investigating relationships between sensory features and the comparatively well-researched field of auditory MMN. The current series of research studies will build on the aforementioned knowledge base for both auditory and visual MMN by further defining development of visual MMN, and integrating our current understanding of auditory MMN with relationships between sensory features. In the future, this work should both add to the knowledge of MMN in typical development and pave the way for more complete associations built between autism core deficits and abnormalities in the stimulus deviance processing.

2.6: Summary and Specific Aims

Autism is a complex and heterogeneous disorder characterized by deficits in social communication, delayed or absent language development and restricted or repetitive behaviors. Differences in the way children with autism process changes in sensory stimuli may underscore all three of these core deficits. The brain's ability to process and respond to small changes in its sensory environment allows it to develop language, respond appropriately to environmental stimuli, and interact effectively with

others. Mismatch negativity (MMN), or the brain's response to rare changes in its sensory environment, is well documented in the auditory domain, and recent evidence suggests that a visual homologue also exists. Auditory MMN is often altered in individuals with autism, though these findings are inconsistent and may be further explained by the presence of unusual sensory features in autism. Few studies have examined the development of visual MMN in children, and how this phenomenon differs in children with autism is poorly understood.

In addition to the core deficits of autism, abnormal sensory processing features are commonly observed in individuals with autism throughout the lifespan with regard to visual, auditory, gustatory and tactile stimulation. Hyporesponsiveness (behavioral under-reactivity to sensory input), hyperesponsiveness (behavioral over-reactivity to sensory input) and sensory seeking behaviors (craving of sensory input) are common in children with autism (Boyd et al. 2010). Our preliminary data (see **Chapter Three**) investigated the relationship between sensory features in autism and auditory MMN. We used a novel ERP visual task to investigate visual MMN in typically-developing (TYP) children and children with autism.

Preliminary Data: Together with the Sensory Experiences Project (SEP), we examined the relationship between severity of sensory features (hyper, hypo) and ERP response to auditory stimuli among children with autism. We hypothesized that differences observed in ERP analysis (see **Preliminary Data**) depend on levels of severity for each of three behavioral constructs: hyporesponsiveness, hyperresponsiveness, and sensory seeking. Within the autism group, we therefore correlated a subject's degree of deficit in each category with the amplitude of their P1, N1 and P3 wave components.

Aim 1: Characterize the nature of the visual MMN in typically-developing children.

Fifteen typically-developing (TYP) children ranging from eight to twelve years old will complete a visual oddball task while viewing vertical, black-and-white gratings of high and low visual frequency. Target stimuli will be presented in the center of the screen while irrelevant visual stimuli are presented simultaneously in the periphery. We expect a visual MMN manifested as a posterior negativity and anterior positivity between 120-160ms post-stimulus presentation

Aim 2: Test whether autism and TYP children differ in visual MMN as measured by relevant components of the ERP.

We will compare ERP data of children taken from the TYP group recruited in Aim 1 to data from a sample of fifteen children with autism completing an identical task. This sub-group will range from eight to twelve years and will be age-matched within six months. Based on our preliminary data indicating similar results in our auditory MMN paradigm, we expect that children with AU will generally exhibit smaller visual MMN amplitudes than TYP children.

CHAPTER THREE: PRELIMINARY DATA IN AUDITORY EVENT-RELATED POTENTIALS AND THEIR RELATIONSHIPS WITH SENSORY PROECCESING IN CHILDREN WITH AUTISM[1]

3.1. Introduction:

Sensory features in autism have been reported in infancy (Ben-Sasson et al. 2008), childhood (Leekam et al. 2007; Liss et al. 2006) and adulthood (Crane et al. 2009; Harrison and Hare 2004), with reported prevalence rates ranging from 42% to as much as 100% (Baranek et al. 2006; Dawson and Watling 2000) and varying levels of severity. For a detailed explanation of sensory hyporesponsiveness, hyperresponsiveness and sensory seeking behaviors, see Chapters One and Two. See Chapter One for a detailed description of ERP research and peak topography of averaged ERP waveforms.

In typically-developing children, the presentation of repeated tones in a sequence elicits a series of midlatency peaks identified as P1 and N1/N2; conversely, P1, N1 and P2 peaks can be discerned in adults. The N1 and P2 peaks are typically not seen in

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[1] *These Preliminary Data were collected as part of the Sensory Experiences Project (SEP) funded by NICHD (R01-HD42168) and are currently under review as Donkers et al. (2013, in review). The SEP team conceived this study, conducted the behavioral assessments, led statistical analyses and contributed to the writing of the published manuscript. The author of this dissertation collected and analyzed ERP data, assisted with statistical analyses conducted at the Belger Lab, and assisted with writing the manuscript that is currently under review. Sections below are excerpted from the team co-authored manuscript.*

children under approximately nine years of age, although the likelihood of observing these components increases with longer inter-stimulus intervals. The lack of these peaks results in the early ERP responses in children being dominated by the N2 peak, which appears to decrease in size from 5-10 years of age and become expressed primarily as an N1 in adults (Ceponiene et al. 1998; Sussman et al. 2008). The N2 peak occurs between 220 and 280ms, and is thought to have biliateral sources in the supratemporal auditory cortex (Bruneau and Gomot 1998) and a non-specific subcortical neural generator (Bishop et al. 2007). These evoked potentials are elicited in the absence of an overt task and are pre-attentive, reflecting the physical properties of a stimulus (Ceponiene et al. 2002; Lepisto et al. 2005) as well as detection, classification, auditory inhibition and orientation (Key et al. 2005). Interspersing an occasional infrequent deviant sound in a series of frequent standard stimuli can also allow for the measure of sound discrimination, determined by subtracting the standard ERP from the deviant ERP (mismatch negativity, or MMN). While the MMN is pre-attentive and reflects involuntary capture of attention (see Nataanen et al. 1978), salient deviance will cause an individual's attention to shift toward the stimulus and result in a later positive deflection known as the P3a. This peak is elicited roughly 300ms post-stimulus and is attention dependent, reflecting higher cognitive processing of stimuli (Comerchero and Polich 1998).

No studies have yet to correlate auditory ERP findings with aggregates of unusual sensory response patterns. In the current study, we examined responses to sensory stimulation, measured by both parent report and observations assessments in a group of children with autism and gender- and age-matched typically-developing children from four to twelve years of age. We used these clinical measures to obtain severity scores across three sensory response patterns (hyperresponsiveness,

hyporesponsiveness and sensory seeking behavior). The same children participated in an auditory oddball ERP paradigm for which we focused on analysis of the P1, N1/N2 and P3a components. Given developmental maturation effects and potential fusing of the N1 and N2 components during our age window, henceforth we will refer to this component as the N2 for simplification. In this study, we aimed to characterize and compare brain responses to different types of auditory stimuli in children with autism, and to examine the association between auditory brain responses and clinical sensory response patterns within children with autism, as measured through both observational and parental report assessments.

3.2. Method:

Participants:

Data were collected and analyzed from a total of sixty-seven children between the ages of four and twelve, including typically developing children (n=39) and children with autism (n=28). A total of seventeen children, including seventeen with autism and seven with typical development, were excluded from data analysis; for details, see Donkers et al. (in review). Children in the autism group met algorithm cut-offs for autism on the Autism Diagnostic Interview-Revised (ADI-R; Lord et al 1994) and the Autism Diagnostic Observation Schedules (ADOS; Lord et al 1999), and their diagnosis was confirmed by a licensed psychologist or physician. Typically-developing children had no history of developmental delays or interventions and no cognitive or adaptive behavior abnormalities. None of the children in this study had a concurrent diagnosis of a known genetic condition (such as tuberous sclerosis or Down syndrome), seizure disorder with evidence of activity within the past twelve months, significant physical impairments or limitations, diagnosis of schizophrenia, bipolar disorder or any other psychiatric condition

with hallucinations or delusions, and none were taking antipsychotic medications.

Clinical/Behavioral Measures:

The purposes of the laboratory assessments were to validate diagnoses (if applicable), measure cognitive level/IQ, measure child adaptive and maladaptive behaviors and family functioning, and to measure the level of sensory features present in children. All children completed a battery of sensory assessments consisting of two parent report questionnaires and two observational measures. These included: The Sensory Experiences Questionnaire (SEQ), Sensory Profile (SP), Sensory Processing Assessment for Young Children (SPA), and Tactile Defensiveness and Discrimination Test-Revised (TDDT-R); they are described in detail in previous papers (Watson et al 2010, Boyd et al 2010). The sensory battery is designed to assess sensory features across modalities and includes measures of auditory discrimination, hearing and visual acuity, frequency of child's unusual sensory reactions, play-based measures of sensory response patterns, and tactile processing. Scores for each of the three sensory constructs of interest (hyperresponsiveness, hyporesponsiveness, and sensory seeking) were derived separately for the two parent report (SEQ & SP), and the two observational (SPA & TDDT-R) measures, yielding six aggregate scores for analyses purposes. Higher scores indicated greater levels of severity across these variables.

ERP Paradigm and Analysis:

To acclimate and desensitize children to the procedure, subjects were mailed a non-functional EEG cap and allowed to play with it at home. On the test day, subjects were fitted with an ECI Electro Cap containing 20 tin electrodes, only 11 of which were used for recording data: F4, Fz, F3, T7, Cz, C3, C4, T8, P4, Pz, and P3. We used a right mastoid reference, and AFz served as the ground. EEG data were amplified,

bandpass filtered (0.15Hz-70Hz) and digitized at 500Hz. Tin electrodes placed at the outer canthi of both eyes and above and below the right eye measured vertical and horizontal electro-oculogram (VEOG and HEOG) bipolar recordings. Children were instructed to remain still and relaxed with their eyes focused on the video screen at all times, and to try not to move, tense their facial muscles or speak. They then entered a sound-attenuated, dimly lit testing booth accompanied by a parent or guardian, who either stood behind them or held the child in their arms while sitting in an adjustable chair.

During the ERP recording, subjects watched a self-chosen video on a screen positioned roughly at eye level with the child's head, with low sound (<60dB) to enhance auditory inattention. During the video, tones from 4 categories were randomly presented through speakers placed 80cm from subjects: frequent standard tones (200ms, 1000Hz) (88% of events), infrequent pitch-deviant tones (200 ms, 1100Hz, 4%), infrequent duration-deviant tones (190ms, 1000Hz, 4%) and infrequent novel sounds (200ms, environmental sounds such as dog bark, 4%). At least two standard tones followed each deviant or novel tone with an inter-stimulus interval of 600ms (offset-to-onset). Sounds were presented at an average of 80dB as measured by Radio Shack Sound Level Meter (Cat. No 33-2055). Stimuli were presented using Presentation 13.4. Six blocks of 500 stimuli were presented, for a total experiment time of thirty minutes. In order to acclimate children to the sounds and to build up a memory trace for the "frequent familiar" standard tone, the first run was not recorded. Novel sounds were not included in this first run, ensuring that pitch and duration deviant tones were categorized as "infrequent familiar" tones while novel sounds were "infrequent unfamiliar" stimuli.

ERPs were computed for each category using Neuroscan Edit 4.4, following removal of large noise artifacts due to subject's motion, gross facial movements, or other

irregularities such as eye blinks, using manual methods and regression algorithms (Semlitsch et al 1986). We applied a bandpass zerophase shift digital filter (1-12Hz), and continuous recordings were epoched, time-locked to each event presentation and averaged to produce average EEG responses occurring between -100ms and +500ms around each stimulus category. Epochs were passed through an automatic artifact detection algorithm to remove epochs with EEG activity in excess of -90uV or +90uV, allowing for the rejection of epochs containing abnormally distributed data (joint probability or kurtosis >5 standard deviations from expected mean values). ERPs were obtained by averaging baseline corrected EEG epochs for each stimulus category and for each participant. Deviant and novelty-related mismatch negativity (MMN) amplitudes were derived by subtracting ERPs to standard stimuli from ERPs to deviant or novel stimuli. P1, N2 and P3a peaks were identified by an automatic peak detection procedure, with P1 and N2 defined respectively as the most positive and negative peak within a specified window after stimulus onset. Mean amplitudes were then identified as the mean voltage in a 50ms window around this selected peak. Peak latencies were measured relative to stimulus onset; mean amplitudes were measured relative to the mean voltage across a 100-ms prestimulus baseline period. P1 windows were 80-150ms for standard tones, 90-180ms for frequency deviant tones, and 70-160ms for duration deviant tones. N2 windows were 150-274ms for standard tones, 174-274ms for frequency deviant tones, and 150-274 for duration deviant tones. P3a was identified as the most positive peak between 200 and 400ms after stimulus onset, and quantified as the mean voltage in a 50ms window around this peak.

Analysis Strategy:

The first objective of this study was to evaluate between-group differences

(typically-developing versus autism) in ERP components. To this end, we first compared group differences separately for each ERP component with a 3-way (2 groups {autism, TYP} x 3 anterior-posterior positions {frontal, central, parietal} x 3 lateral positions {left, center, right}) repeated-measures MANOVA to examine the effects of electrode location and group. We then compared group differences with t-tests separately for each ERP component using a composite of multiple electrode locations based on the results of the previous analysis step. This composite was obtained by including only electrodes at which the strongest values were found, to reduce directionality effects across both groups and ERP components. This composite is further discussed in *Results*. All statistical analyses were conducted using SAS (SAS Institite, Inc., Cary, NC USA). Because the morphology of the ERP waveform changes during childhood, we examined the grand average waveforms of children eight to twelve years of age and compared them to the grand average waveforms of children four to twelve years of age. In this comparison, we found similar structure of P1-N2 and therefore chose to average together ERPs of children four to twelve years of age.

We were also interested in a preliminary analysis of associations between ERP components and measures of sensory features as determined by observational and parent reports. To this end, we used a series of ordinary least squares regression models. We then generated a model comprising of all predictors, including mental age and ADOS severity as covariates, all three ERP composites as main effects, and all possible two-way interactions between ERP components. This allowed us to examine all potential conditional associations between ERP components and the six indices of sensory response patterns (hyperresponsiveness, hyporesponsiveness, and sensory seeking for both parent report and observed measures). Significant interaction terms were investigated by defining a given ERP composite in terms of "low" (25^{th} percentile)

and “high” (75th percentile) and then evaluating simple slopes between a given ERP composite and the sensory response pattern at conditional values of the second ERP composite.

3.3. Results

For full results, see Donkers et al. (in review). Results most relevant to this dissertation are presented below.

Between-Group Comparisons:

Standard and Novel stimuli:

Group x anterior position x lateral position MANOVA analyses indicated significantly smaller amplitudes at N2 in the autism group ($F(1, 66)=4.8$, $p=0.03$) and significantly smaller P3a amplitudes to novel stimuli ($F(1,65)=5.8$, $p=0.02$). We also found that the central electrodes had the highest signal for both groups in the form of main effects of Anterior electrode position for standard tones at P1 ($F(2,132)=55.5$, $p<0.0001$), standard tones at N2 ($F(2,132)=28.7$, $p<0.0001$) and novel stimuli at P3a ($F(2, 130) = 58.0$, $p<0.0001$). Group averages for ERPs to standard (Figure 1) and novel (Figure 2) tones are presented below.

The above results were then used to create composite ERP measurements for each component. To reduce the dimensionality of the data for later analyses, and because all of the above ERP components had strongest values for central electrode position, measurements were only included from central electrodes (C3, Cz, C4, see Figure 3). This composite average for central electrodes was used in a simple t-test on the P1 and N2 response to standard tones, as well as the P3a response to novel tones. From these values, we found that the children in the autism group had attenuated P1 and N2 response amplitudes to standard tones and an attenuated P3a response to

novel tones, compared to the typically-developing group.

Pitch and Duration Deviant Tones:

Group x anterior position x lateral position analyses revealed no significant differences for these stimuli at any of the remaining ERP components. Pitch and duration deviant stimuli were therefore excluded from all further analyses.

Within Autism Group Analyses:

Analysis of relationships between ERP components and sensory features is currently ongoing with associated collaborators. However, we performed a number of exploratory, preliminary analyses, presented here. For a discussion of the measures of hyporesponsiveness, hyperresponsiveness and sensory seeking behaviors, see Chapters 1 and 2.

Among participants with autism, the ERP composites obtained as described in the above section were used to predict clinical indicators of sensory response patterns (hyperresponsiveness, hyporesponsiveness, and sensory seeking behaviors, as indexed by parent report and observational measures). Bivariate correlations among the predictors and outcomes for regression models were computed. In general, sensory measures were only weakly associated with ERP composites and failed to reach statistical significance, likely due in part to the small sample size relative to behavioral studies. However, some correlations emerged when interaction effects were considered, which are described below:

Sensory Seeking:

The set of ERP composite and covariates was significantly predictive of greater

levels of observed sensory seeking behaviors (F (8, 17) = 7.72, p = 0.0002, Adjusted R2 = .68). Significant interactions were found in terms of P1 x P3a and P1 x N2, but not for N2 x P3a. The P1 x N2 interaction indicated that attenuated N2 amplitudes were associated with higher levels of observed sensory seeking behaviors at lower but not higher amplitudes of P1. The P1 x P3a interaction indicated that lower amplitudes of P3a were associated with higher levels of observed sensory seeking behaviors at higher but not lower amplitudes of P1. While these significant interaction effects were observed in relation to observed behavioral measures, there was no evidence of significant ERP composite interactions with parent report measures of sensory seeking behaviors (F (8, 19) = 0.90).

Sensory Hyperresponsiveness and Hyperresponsiveness:

The full set of ERP composites and covariates was not statistically associated with either observed or parent report measures of sensory hyporesponsiveness or hyperresponsiveness

Selection Effects:

In order to test for selection effects of the capping procedure causing higher-functioning children with autism to be more likely to enroll in this study (see Discussion), we performed a post-hoc analysis comparing a sample of the children with autism who participated in the EEG study (N=38) to a sample of the children with autism who elected not to participate or withdrew during the session (N=52). Successful EEG participants with autism had lower severity scores on all observed sensory features, including hyperresponsiveness (t(83) = 3.24, p = 0.002), hyporesponsiveness t(83) = 3.43, p = 0.001), and sensory seeking behaviors (t(83) = 2.65, p = 0.01). This suggests that

participants in this study represent a subset of the autism population with more mild sensory features, which may have contributed to the lack of significant interactions in terms of observed hyperresponsivness and hyporesponsiveness.

3.4. Discussion

Between-Groups Findings:

This study revealed that children with autism showed reduced amplitudes of P1, N2 and P3a, relative to typically-developing children, during passive exposure to repeated auditory stimuli wherein said stimuli correlated with selected aspects of behavioral sensory features. This suggests that children with autism experience a disruption of auditory processing in both lower and higher levels of sensory processing. In terms of the early component (P1 and N2) attenuation of amplitude, some studies have echoed this finding (e.g. Bruneau et al. 1999) while others have not (e.g. Kemner et al. 1995; Lincoln et al. 1995). With regard to the P3a, these findings are consistent with certain studies that have found attenuated or nonexistent P3a amplitudes in children with autism (e.g. Ceponiene et al. 2003; Lepisto et al. 2005), but not with other studies that have found higher amplitudes of P3a in these children (Gomot et al. 2002; Ferri et al. 2003; Gomot et al. 2011). Differences in task design, stimuli, and functioning levels of the studied population likely contribute to these mixed findings.

Contrary to expectation, this study did not find significant group differences in ERP components to pitch or duration deviant tones, although a visual inspection revealed that both of these categories elicited slightly attenuated amplitudes of both P1 and N2. This may have been due to the small difference between standard and deviant stimuli in this study (1000Hz vs 1100Hz for pitch deviant and 200ms vs 190ms for

duration deviant). The negative findings might have also been due to the relatively small number of deviant stimuli resulting in less reliable ERPs. Within the standard tone, however, we found attenuated peak amplitudes at both early (P1, N2) and late (P3a) ERP components. This indicates disruption in both bottom-up and top-down neural sensory processing.

Given the relatively simple nature of our stimuli, differences at early components are indicative of deficits in low level sensory processing that may be generalized to a wide category of sound events. This finding supports a neural basis of atypical sensory encoding in autism. The finding that the P3a to standard tones was attenuated in children with autism may indicate deficits in higher order cognitive processing of stimuli in children with autism, such as attentional orienting or salience evaluation. These components may also interact with one another or impact multisensory integration. It is possible that if P1/N2 responses are dysfunctional, greater attentional resources or greater alerting mechanisms are needed to compensate for such deficits. If concomitant deficits exist in P3a, there may be fewer resources to use as a compensatory mechanism, which could have implications for clinical outcomes in the form of deficits in orienting to novel stimuli. This idea of early ERP components interacting with later components is especially interesting and salient in light of our within-group findings, discussed below, in which relationships between the P3a or N2 components and sensory seeking behaviors were often dependent on P1 amplitudes.

Within-Autism Group Findings:

Specific components of the ERP composite were shown to relate to clinical measure of sensory seeking within the autism group. First, children with autism observed to exhibit more severe sensory seeking behaviors were found to have

attenuated amplitudes of N2 to standard tones, at lower amplitudes of P1 to standard tones. That is, lower amplitudes (i.e. more attenuated responses) of N2 are selectively associated with more severe sensory seeking behaviors given lower P1 amplitude values. Second, at higher amplitudes of P1 to standard tones, larger P3a amplitudes to novel tones are associated with less severe observed sensory seeking behaviors in children with autism. That is, higher amplitudes of P3a (i.e. higher levels of orienting response) selectively associated with less severe sensory seeking behaviors and may represent a protective factor in children with autism, found only in those children with higher amplitudes of P1 to standard tones. This study demonstrates that the relationship between auditory ERPs and sensory response patterns in children with autism is quite complex, and the aim to clarify these findings is still ongoing.

To our knowledge, this is the first study to correlate ERP components with three sensory response patterns as indexed by clinical measures. These findings indicate that sensory seeking behaviors are conditionally associated with amplitudes of P3a and N2, but may be modulated by the amplitude of P1. Because P1 is a very early ERP component associated with basic stimulus detection, it is possible that low level sensory encoding underlies the severity of sensory features in autism, and could have implications for both higher order neural processes and clinical outcomes. It is also possible that top-down attentional control, manifested by P3a and to some degree N2, affects the behavioral characteristics related to observed sensory seeking behaviors in children with autism. Disrupted attentional control could diminish orienting responses to novel stimuli, causing some children with autism to appear preoccupied with intense and repetitive sensory activities because they are unable to disengage and refocus on other environmental events. This disruption could also lead to hyper-engagement with existing stimuli or sensory-driven activities due to disruptions in reward pathways.

More research is needed to fully understand the connection between these ERP components and sensory behaviors. In particular, further examination of attentional orienting in the context of overt attention switching tasks in individuals with autism may further explain the mechanisms taking place with regard to P3a's relationship to sensory seeking behaviors. Given that we found significant results primarily in the sensory response pattern of sensory seeking behaviors, future studies using measures targeting sensory seeking as a response pattern may be more successful in uncovering neural relationships with these behaviors. This study is especially interesting in light of previous research focused on the relationship between ERP components and repetitive behaviors. For example, Gomot et al. (2011) found that children with autism who scored higher on intolerance of change on the Behavior Summarized Evaluations scale (BSE-R, Barthelemy et al. 1997) had significantly shorter MMN latencies at frontal sites and P3a latencies at central sites compared to children with autism who scored lower on this term. Future work should investigate the neural relationship between intolerance of change and attentional orienting dysfunction in autism.

Limitations:

Despite an observed relationship between ERP components to behavioral sensory measures and both novel and standard stimuli, the only relationships to receive focus were amplitude differences of ERP components. The scope of this study does not include MMN difference waves due to the significant group differences for the standard P1 and N2 ERP components, compared to the absence of group differences for N1 and P2 components to the duration and pitch deviant stimuli. Finally, we did not find any group differences with regard to pitch or duration stimuli in this study. These findings are inconsistent with the existing literature (e.g. Ferri et al. 2003; Gomot et al. 2011) and

may be explained by several limitations of this study. While our sample size for an ERP study was quite large, relative to the behavioral and parent report measures, our sample was very heterogeneous and rather small. It is also possible that the small number of pitch or duration deviant tones impacted our ability to collect a consistent waveform in this category given our young subjects with autism. Finally, the differences in our pitch and duration deviant stimuli were minor; several other studies have used larger deviants in pitch in particular (e.g. Gomot et al. 2002) in young populations with autism. This smaller difference in our study may have obscured any effects and therefore impacted our ability to measure the MMN difference waves. It is apparent from other research (Gomot et al. 2011) that MMN latency may be correlated with sensory behaviors observed in autism, particularly intolerance of change, and therefore this concept merits future study.

It is also possible that our clinical measures were not sufficiently sensitive to capture the full range of hyporesponsive features, particularly at the most extreme. These measures might also be impacted by our relatively small sample size. In addition, the simple nature of our ERP stimuli, when compared with the complex and multi-faceted nature of our observational and parent report composites, may not be analogous to one another. Our clinical measure probe sensory features across all modalities and in a wide variety of contexts, while our ERP paradigm investigates a simple auditory tone. Perhaps more specific measures such as performance on single items that are more similar to our ERP paradigm would produce stronger results. In one previous study, Gomot et al. (2011) used a single questionnaire for evaluating symptoms of autism and selected only items that were relevant to their paradigm and hypotheses, including unusual responses to auditory stimuli, and disproportionate frustration or anger when activities are interrupted, objects forbidden or expectations unsatisfied. Given that very

few studies have investigated the relationship between sensory features and ERP components, perhaps a simpler model more focused on direct comparisons between clinical measures and the ERP paradigm in question would be more effective at this early stage of investigation.

Another consideration is the difficulty of ERP data collection on low functioning individuals, especially those with profound sensory features. While EEG is noninvasive, relatively inexpensive and simple to collect when compared to other methods such as functional magnetic resonance imaging (fMRI), it is important to note that the capping procedure can be quite difficult in low functioning children with autism. Children who are uncooperative during set-up and/or task administration can make data collection overly complicated or unfeasible, especially when considering the importance of remaining still and reducing facial tension during the data collection process. Children with high levels of sensory features may find this stressful or even impossible, and low functioning or non-verbal subjects may have extreme difficulty understanding instructions. For example, even in passive paradigms, participants must remain still and try to avoid moving, speaking, or touching the cap or electrodes. They also must tolerate tactile stimulation such as facial electrode placement; tight-fitting EEG caps; the process of impedance lowering, which often requires scalp abrasion; and the insertion of electrogel. Some participants may move so excessively that not enough successful trials can be collected; they may not tolerate the lowering of the electrode impedance to sufficient levels; or they may remove the face or scalp electrodes during the testing procedure. Behavioral management training may help alleviate these concerns, but it is unrealistic to expect high success rates in low functioning children or in those with high levels of sensory features. This could produce a selection bias in which subjects with the most severe sensory features or most debilitating autism symptoms either do not enroll in the

study or do not have valid data due to their inability to tolerate the capping procedure. Indeed, a post-hoc analysis of our sample revealed that, among children with autism, the children who participated in the EEG study were higher functioning, as measured by IQ, mental age, and observed sensory features, when compared to the children who elected not to participate or withdrew during the session. This possibility should be considered in further ERP studies investigating low functioning children with autism, as sensory features are often more severe in lower functioning populations and present substantial difficulties due to the nature of EEG setup.

Conclusion:

This study compared children with autism to typically-developing children ages four to twelve, and provided new evidence of multiple sensory processing dysfunctions at the neural level in the children with autism. Sensory features have been well documented in studies of autism; however, this study is one of the only ones to focus on the potential neural origins of various behaviors. Specifically, this study suggests that more severe sensory seeking behaviors in children with autism may be associated with higher amplitudes at N2 and lower amplitudes at P3a, both modulated by the amplitude of P1. This study also suggests that both low level stimulus-driven processes and top down attentional orienting processes are disrupted in children with autism in the auditory modality. Furthermore, these two processes may interact to affect clinical observed measures, but not parent reports of sensory features. Although these findings are very preliminary, future studies of sensory features in autism and their interactions with ERP components may help pave the way for more targeted clinical interventions and a better understanding of the neurobiology of sensory processing. Investigating ERPs in the

visual modality may help address the multiple modalities probed in the observational and parent report measures used in this study, as well as provide a framework of feasibility for future investigations of sensory feature relationships with ERP in the visual modality.

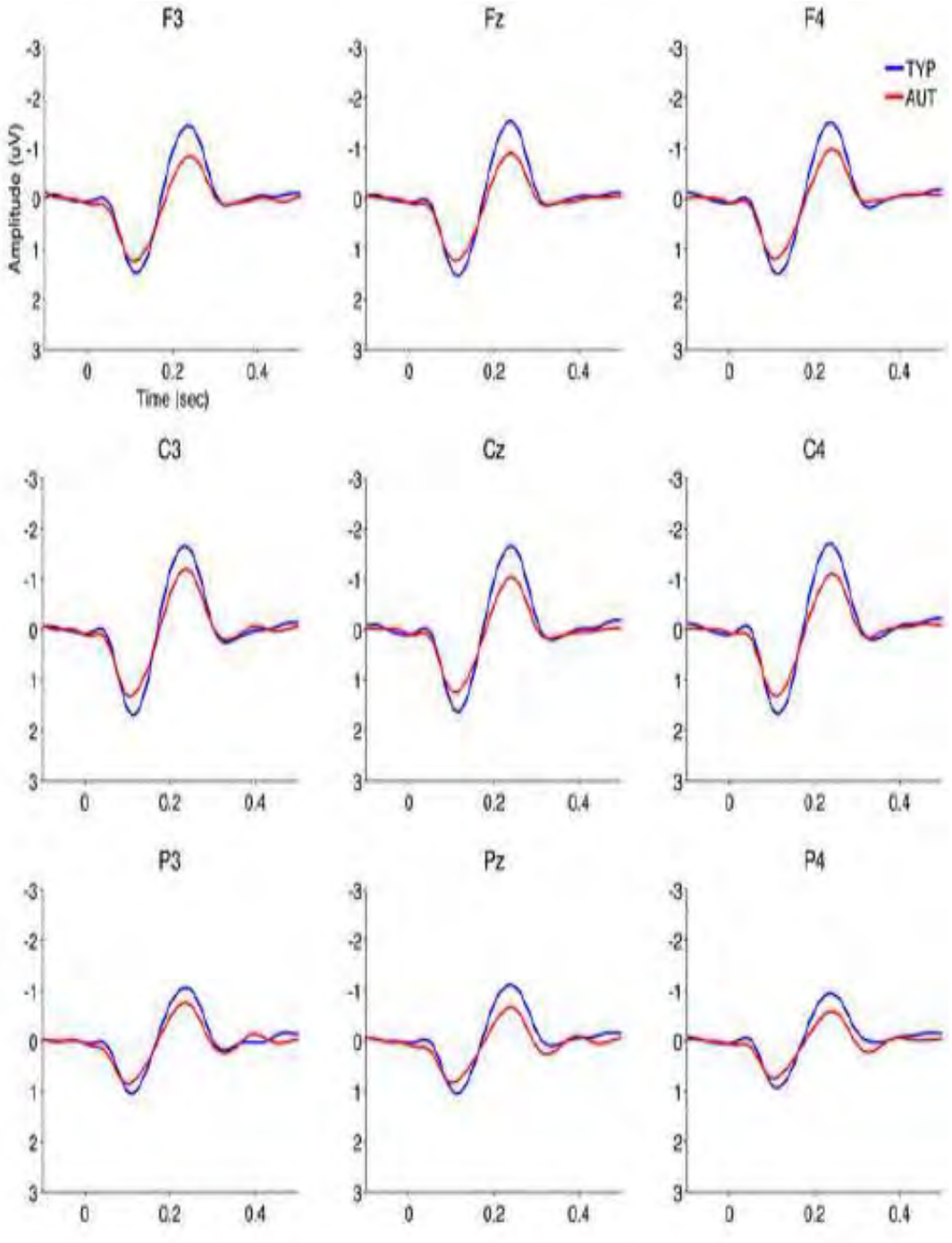

Figure 1: Group averaged ERPs to standard stimuli.

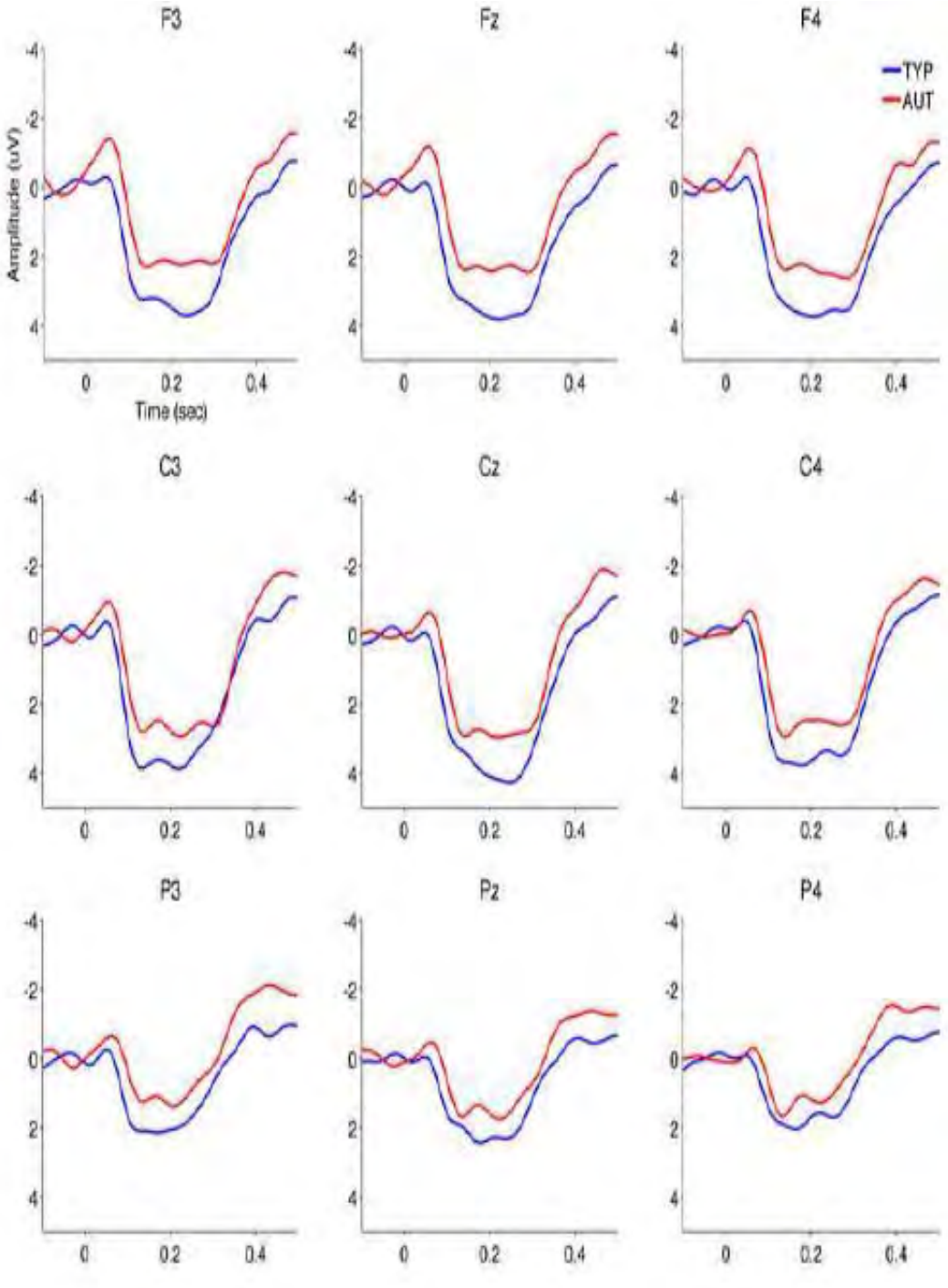

Figure 2: Group averaged ERPs to novel stimuli.

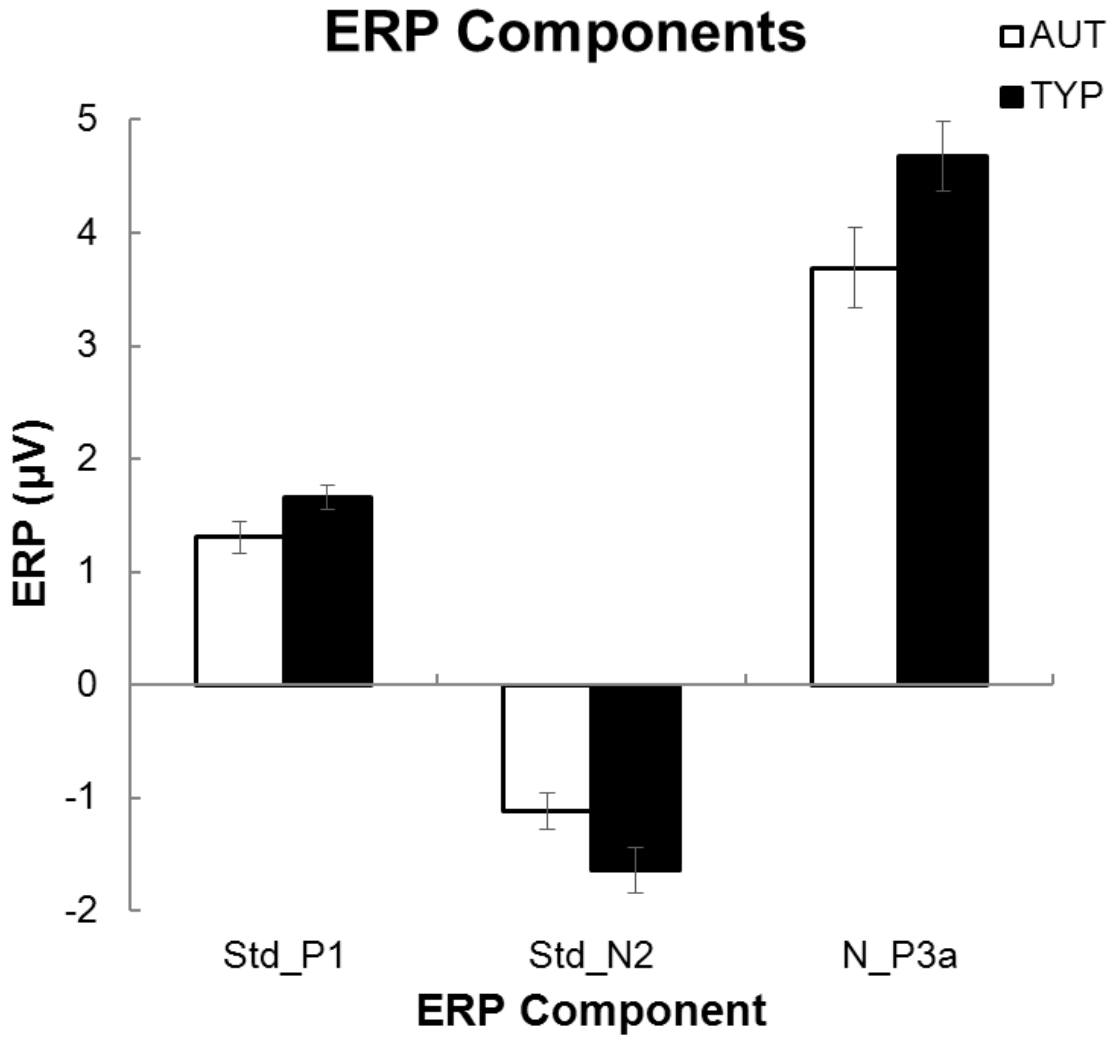

Figure 3: ERP composite values across groups.

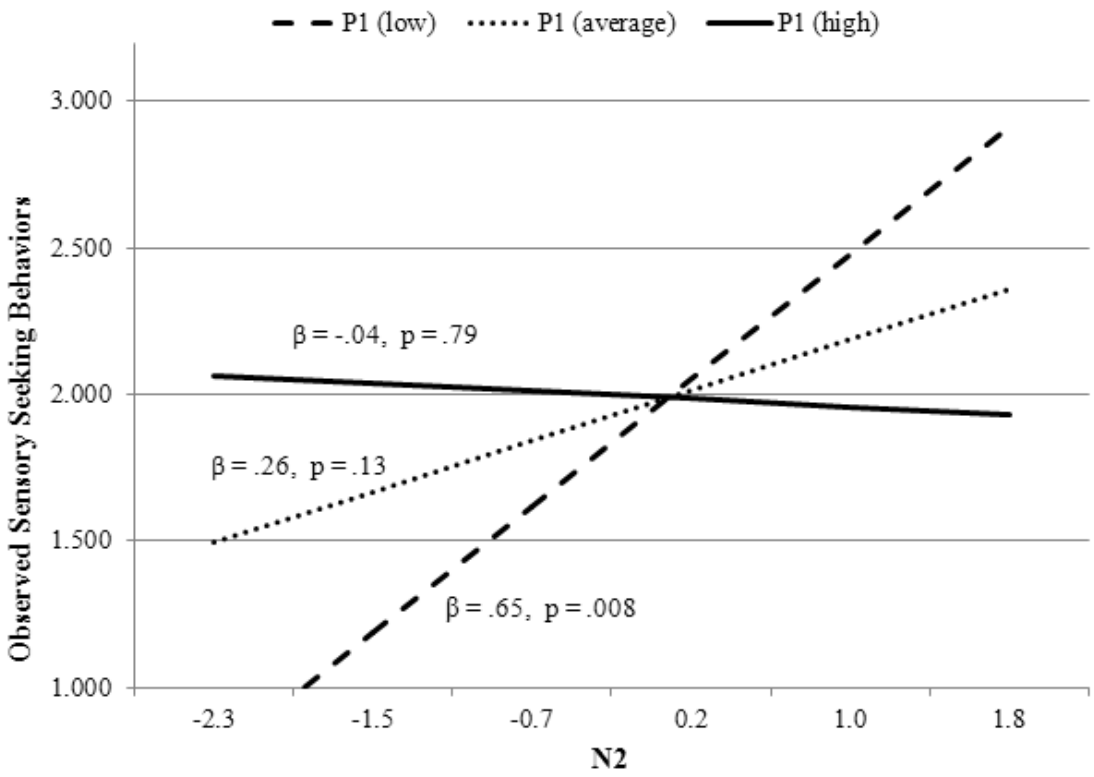

Figure 4: Interactions between P1 and N2 in the prediction of observed sensory seeking behaviors.

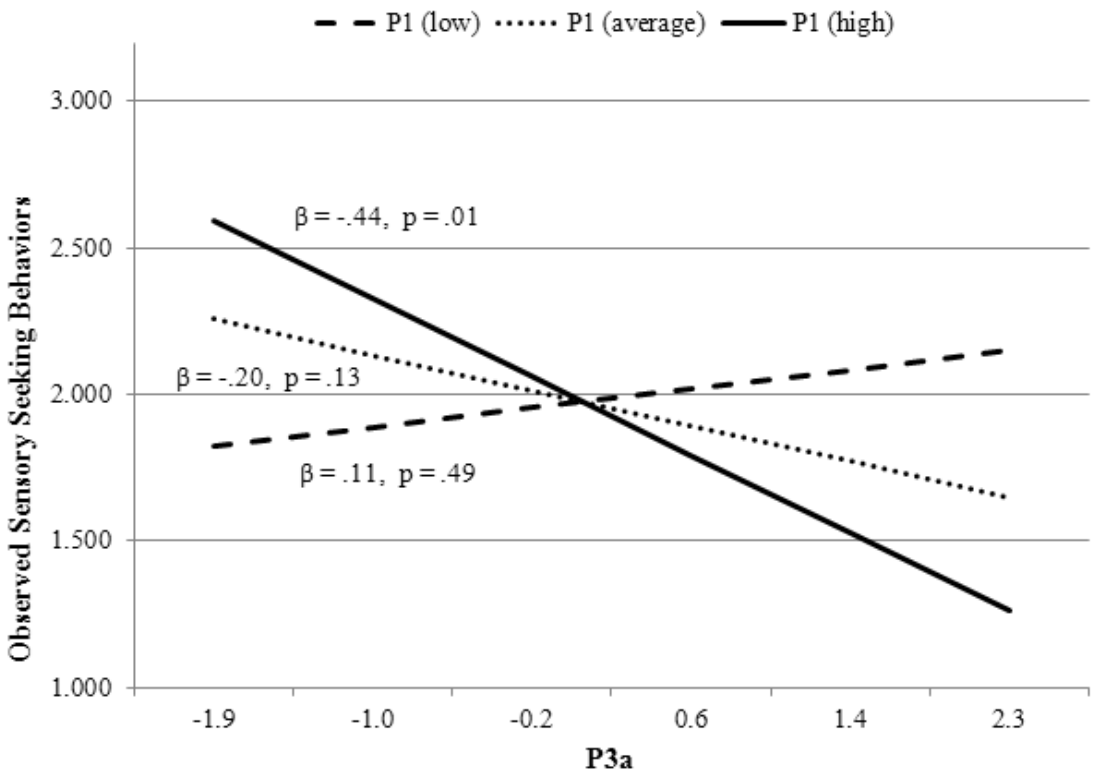

Figure 5: Interactions between P1 and P3a in the prediction of observed sensory seeking behavior

CHAPTER FOUR: VISUAL MISMATCH NEGATIVITY: TYPICAL DEVELOPMENT AND CLINICAL APPLICATIONS

4.1: Functional relevance of vMMN

Mismatch negativity in the visual modality (vMMN) is expressed as an occipito-parietal negativity with primary activations in visual extrastriate cortex. vMMN normally peaks around 200-400ms post-stimulus presentation (Kimura et al. 2011), although some earlier studies (reviewed by Pazo-Alvarez et al. 2003) have reported this negativity as early as 120ms post-stimulus. Previously, much debate (Pazo-Alvarez et al. 2003) revolved around whether vMMN could be considered an acceptable homologue to mismatch negativity in the auditory modality (aMMN), but recent research (reviewed by Kimura et al. 2011) has provided convincing evidence that this homologue exists. Like aMMN, vMMN must be independent of stimulus features and a true representation of a memory-based comparison, which can only be elicited by repeated standard stimuli with which to compare deviants. For a full discussion of properties of vMMN and a history thereof, see Chapter One.

Because it is a relatively recent phenomenon only confirmed within the last ten years, the underlying neuropsychological elements of vMMN are only beginning to be understood. One roadblock in interpreting vMMN might be its origin as a homologue to the auditory MMN, which concerns very different sensory modality and corresponding brain areas (Kimura et al. 2011). Early theories, reviewed by Pazo-Alvarez et al. 2003,

proposed that vMMN was a reflection of deviations from established sensory memory, and reflects the brain's ability to detect memory trace errors in a series of frequently-occurring standards. However, as discussed by Kimura et al. (2011), vMMN has also been observed when errors occur in more complicated patterns. This can be seen in pair-based patterns that do not rely on memory trace (i.e. red/blue, red/blue, red/blue, red/green), and in standards followed by deviants, indicating that vMMN is not simply a matter of any rare change in a series of identical repeated stimulus. Moreover, vMMN does not occur when deviants are part of a predictable pattern, indicating that pattern violation, rather than stimulus deviance per se, is more likely responsible for this visual difference wave (Kimura et al. 2011). Today, vMMN is thought to reflect an error-prediction mechanism in violations of previously-established patterns of stimuli, either in temporal context or structure. This is a more complex and detailed extension of the "memory-mismatch" account, modeled by Kimura et al (2011), described above. In this model, the brain must recognize stimulus features that may comprise a pattern; understand the pattern in a series of stimuli; use this understanding to form predictions about future stimuli; and compare future stimuli to that which it has already seen, in order to determine whether an error has been committed. This entire process occurs unintentionally, as vMMN can be elicited when participants pay no conscious attention to the stimuli, and there are usually no task benefits to understanding the pattern of stimuli in a vMMN study. Neural correlates of vMMN probably include the right hemisphere of occipital visual extrastriate cortex and the right hemisphere of medial prefrontal areas, in the case of deviation from a frequently-occurring standard. Violations of established alternating patterns involve both aforementioned brain areas as well as lateral prefrontal areas.

The concept of vMMN is similar to several other prediction-error phenomena

associated with very similar brain areas, including representational momentum and the flash-lag effect. None of these concepts contain neural substrates in motor areas such as the lateral premotor and posterior parietal cortices, lending credence to the idea of vMMN as an unconscious and unintentional mechanism. Kimura et al (2011) argue that this concept is a unique way to investigate unconscious error-prediction in the visual modality. This is advantageous for the brain; it can allocate resources to deviant (and therefore potentially important) information, while at the same time conserving resources that might be otherwise unnecessarily allocated to constant stimuli, diminishing processing demands and maximizing the use of available processing resources. This is very useful in navigating a dynamic environment full of stimuli, as it allows the brain to fill in missing information, retain constancy of stimulus properties, and adapt to changes in its environment while preventing exhaustion of processing resources. Therefore, if vMMN is diminished or impaired in individuals with developmental disorders such as autism, it could strongly impact their ability to navigate their sensory environments.

In addition to its relevance in allocation of cognitive resources to visual deviant stimuli, vMMN may also be related to language development. MMN in the auditory modality (aMMN) has been associated with both typical and disordered language development (Nataanen 2003), which makes it particularly useful in investigating clinical populations with symptoms associated with language impairment, such as autism. The process of learning audiovisual speech is highly intuitive, and visual deviants, when paired with auditory sounds, can elicit an auditory MMN even when the physical properties of the auditory stimulus are unchanged (Stekelenburg et al. 2004, but see Besle et al. 2005). This finding may be related to the McGurk Effect (McGurk and MacDonald 1976) in which subjects perceive a different sound (e.g. /da/) when presented with differing, simultaneous lip movement (e.g. /ga/) and auditory stimuli (e.g.

/ba/). These concepts indicate that language development might be related to both vMMN per se and audiovisual studies that combine aMMN and vMMN. Froyen et al. (2010) investigated the interaction between physical letters and sound integration in a multi-experiment paradigm including visual-only stimuli (standard letters, deviant letters, and non-letter deviants) and audiovisual stimuli (congruent sound-letter pairings, incongruent sound-letter pairings, and sound-non-letter pairings). In this case, the auditory stimuli were the same and the visual stimuli differed; the authors were looking for a vMMN rather than an aMMN. This paradigm did not show an influence on audiovisual congruence on vMMN, indicating that perhaps the auditory and visual cortices are recruited symmetrically in aMMN audiovisual paradigms, but not so in vMMN audiovisual paradigms. The authors hypothesized that this occurred because written language is only arbitrarily related to speech and therefore the same effect does not occur in reverse of the aMMN effect in audiovisual studies. However, the non-letter deviants did result in decreased amplitude of the vMMN. Another study found similar results using meaningless visual stimuli and auditory sounds (Besle et al. 2005). Froyen et al. (2010) hypothesized that this reduced amplitude to non-letter stimuli could be due to the context in which the stimuli were presented; i.e., an expectation had been built of letter-sound pairings, and the non-letter visual stimulus was perceived as less relevant. Regulatory feedback from audiovisual integration sites to the visual cortex may be responsible for this finding (Froyen et al. 2010). It would be interesting to perform this experiment in individuals with language deficits, especially those with deficits in speech production, to see if this reduction of amplitude also occurs in this group. It is possible that unconsciously perceiving non-letters as less relevant to letters, regardless of their auditory congruency, could be indicative of the language deficits seen in autism. As was discussed in Chapter Two, more multi-modality approaches could help further define

how visual deviancy affects overall sensory processing, including the learning and production of language.

4.2: Typical development of ERPs to visual stimuli

Because early research on vMMN was somewhat inconsistent in its ability to demonstrate an appropriate visual homologue to the auditory MMN, it is important to understand vMMN in the context of the visual system, which is neurologically quite different from the auditory system. It is also important to understand typical development of the visual system and maturation of visual ERPs in normal development before this information can be applied to neurodevelopmental disorders. A number of studies have investigated differences in visual processing in typically-developing children and adults. In a categorization study (Batty and Taylor 2002) in which subjects responded to target images of animals but not to non-animals, P1 was much smaller in adult subjects than in either seven and eight-year-old children or eleven and twelve-year-old children. P1 was about six times larger in the youngest age group compared to the adult group. P1 latency was shorter in the adult group compared to both groups of children, but children did not differ in latency between ages seven and twelve. The N2 component also tended to decrease in both latency and amplitude with age, although this effect was only significant in seven and eight-year-old children as compared to nine- to twelve-year-old children. Latency for P3 was also shorter in adults than children, but amplitude decreased only slightly with age in cases of target stimuli. The authors found that P1 seems to mature soonest, from about seven years, but continues to develop throughout childhood, while later ERP components such as N2 and P3 begin to decrease only around age 12. Latency also tends to mature at an accelerated rate

compared to amplitude, indicating that speed of cortical processing reaches adult-level first, and only then do the resources allocated to the task decrease along with cortical activation.

Of note, the categorization task was easy for even the youngest children to complete, and while younger children tended to have longer reaction times, all age groups performed the task well. However, ERP data differed drastically between age groups. This indicates that even though task performance may be comparable at younger ages, associated neural systems may not yet be mature and stimulus processing may occur quite differently. This information is important in the present series of studies because it presents an outline of normal visual processing development. Based on the work of Batty and Taylor (2002), in the current studies (see Chapter Four) we should expect overall larger amplitudes and latencies in the group of typically-developing children as compared to typically-developing adults. Since the sample in the current studies (see Chapter Four) comprises children between the ages of eight and twelve, it is possible that some maturation effects may be observed within this group, particularly in regard to P1 amplitude and P3 latency. However, this sample is generally not old enough for the latency and amplitude differences in later ERP components observed in older age groups by Batty and Taylor.

Unlike the auditory system, the visual system is uniquely associated with two pathways, each providing different information and aiding in associated cognitive responses; this is an important consideration when investigating vMMN, as it is quite different from the auditory system. The “two stream” hypothesis, proposed by Goodale and Milner (1992), describes two distinct streams of information processing in the visual system associated with particular stimulus elements and related brain areas. The dorsal stream, or the “where/how” pathway, emerges in primary visual cortex (V1) in the

occipital lobe with projections to the parietal lobe. The ventral stream, or the "what" pathway, is interconnected with the dorsal stream and runs from V1 into the temporal lobe. Generally, the dorsal stream is associated with spatial awareness and action guidance and contains detail-mapping of the visual field. By contrast, the ventral stream is associated with object recognition and form representation and contains neurons whose receptive fields together represent the entire visual field. The ventral stream is influenced by attention, working memory and stimulus salience, and is important for determining the significance of stimulus elements. It is important to consider the types of stimuli that each stream of visual processing is uniquely suited to when investigating vMMN. This is emphasized by Pazo-Alvarez et al. (2003) in their review of early studies investigating vMMN. The authors hypothesize that optimal visual stimulation in the correct location within the visual field relates to obtaining positive results in vMMN studies. The magnocellular pathway (associated with the dorsal stream) is primarily responsible for orienting and spatial attention, preparation of movement and target selection, however, they emphasize that input from the ventral stream, associated with the geniculostriate pathway, should also be considered. As both of these pathways may be involved in visual orienting, each should be appropriately considered when designing vMMN studies or determining its neural mechanisms (Pazo-Alvarez et al. 2003). Both pathways are likely involved in this complicated process, as demonstrated by recent research, and the developmental trajectory of each pathway should be considered in any vMMN studies investigating children or infants.

Recent theories (McIntosh and Schenk 2009) have encouraged viewing these two information pathways as highly interconnected rather than separate streams of information that do not interact, and it is likely that both play an important role in visual mismatch negativity. The development of these streams in healthy humans has been a

subject of investigation in several studies. In a behavioral study of visual discrimination, Parrish et al (2005) examined visual performance on a series of tasks designed to investigate the dorsal and ventral pathways, including texture- and motion-defined forms and global dot patterns. They found that neither pathway is mature in school-age children, specifically that the dorsal pathway matures by age seven to eight while some elements of the ventral pathway do not mature until age eleven or twelve. It is important to note that Batty and Taylor (2002) found similar levels of task performance but very different expressions of ERP components in the various age groups in their study, so it would be worthwhile to see results for concurrent ERP data collected during these tasks. Parrish et al concluded that both the dorsal and ventral pathways appear to be maturing in school-age children and did not note clear differences between the two.

These results are interesting in the context of work by Clery et al (2012), who found that while adults utilized the dorsal and ventral pathways equally in processing form and motion changes, children seemed to experience delayed recruitment of the dorsal pathway (see discussion of vMMN). However, while results show that the dorsal pathway matures later in development, additional research has uncovered evidence that the ventral stream may mature more slowly in children. In another behavioral study investigating spatial integration of contours in children ages five to fourteen, Kovacs et al (1999) found that spatial integration was not yet mature in school age children. The authors hypothesize that intrinsic horizontal connections of V1 may be responsible for these performance differences, and that such ability to discriminate between contextual effects may be related to maturation of the ventral stream. It is difficult to confirm this theory due to the lack of imaging results in this study, however.

4.3: Development of vMMN and the presence of multiple negativities in the visual difference wave

While recent research has characterized vMMN relatively well in adults, there are comparatively few studies investigating vMMN in children. In one recent study, Clery et al (2012) used dynamic deformations via a circle slowly becoming an ellipse to examine vMMN in healthy adults, as well as healthy children ages eight to fourteen. Participants were asked to respond to the disappearance of a crosshair with a button press in order to ensure inattention to the circle stimuli. The vMMN in children was very different to that of adults in this study: in adults, the vMMN was observed as an occipital-parietal negativity occurring around 210ms post-stimulus, but in children, three successive negativities originating over fronto-central electrodes were observed between 150 and 330ms. In addition, a larger late positivity mismatch was observed in children around 450ms post-stimulus. The authors conclude that not only is vMMN immature in children up to fourteen years of age, but the successive negative potentials may reflect a sequential visual processing of deviancy that is not present in the mature brain. Processing of visual deviancy during development may require several distinct steps that are not necessary for healthy adults and may be related to immature selective attention processes. Scalp topography maps suggest equal temporal recruitment of the dorsal and ventral pathways in adults, but the involvement of right parietal areas in the late positive potential observed in children suggests that the dorsal pathway may be utilized later in stimulus change detection processing in children.

It is worth noting, however, that the stimuli used in this study featured changes in both form and motion, and the authors hypothesize that these two stimulus properties may be processed separately in children, with maturation of the visual system leading to

better integration of multiple stimulus properties. Currently no studies have investigated the vMMN in children by treating changes in stimulus form and motion as separate deviant events. Studies using static stimuli that compare changes in physical form or dynamic stimuli with constant physical properties would help confirm this theory. Also worth noting is that the age range investigated in this study was rather wide and comprises a good portion of late childhood and adolescence; since many important neurophysiological changes occur during adolescence, vMMN may be vastly different in the younger portion of this sample compared to older participants. The authors also note that developmental changes in vMMN appear more drastic than those in the auditory modality. Developmental changes in aMMN primarily comprise longer latencies at earlier developmental phases, but the appearance of three distinct negative peaks suggests that visual stimulus change detection is much more complicated, implying that perhaps auditory stimulus change detection matures much earlier than visual. However, several studies have noted two negative peaks in the vMMN in healthy adults (e.g. Muller et al 2012; Kecskes-Kovacs et al 2012; Kimura et al 2009; Czigler, Weisz and Winkler 2006). It is thought that the first negative peak reflects changes in stimulus patterns intrinsically, while the second is related to the ability to switch attention to deviant information. This idea is the product of much research and debate, which will be further described below.

Why some paradigms produce a single negative peak in adult subjects while others produce two has yet to be fully resolved. Initial studies (reviewed by Pazo-Alvarez et al. 2003) reported two negativities, suggesting that the earlier negativity (around 100-200ms) might be a more accurate homologue to the auditory MMN. However, more recent research (Czigler et al. 2006; Kimura et al. 2009) indicates that the later negativity is more likely to be a reflection of sensory memory, independent of stimulus features. In

the earlier research, two contrasting hypotheses existed to explain the negativity observed in response to visual deviants: either the vMMN resulted in a genuine memory comparison of current deviant stimuli with previously-seen standards, or it was a simple refractory effect (Pazo-Alvarez et al. 2003). The memory comparison hypothesis is the idea that vMMN results from a detection of change against standard stimuli and is a homologue to the aMMN. The refractory effect refers to the idea that certain populations of afferent neurons specifically activate in response to a particular feature of the deviant stimulus (Kimura et al. 2009). In the refractory hypothesis, vMMN is not a reflection of change-detection per se but of exogenous stimulus effects, and therefore not a true homologue to the aMMN. Previous literature, as discussed below, has attempted to reconcile the memory comparison hypothesis and the refractory hypothesis, as well as examine how these studies may be applicable to developmental populations.

In a paradigm investigating sequence violations versus stimulus color change, Czigler et al. (2006) found two occipito-parietal negativities in response to the change in both stimulus features and pattern regularity. However, the later negativity was only present in the irregularity condition. Because there must be a standard to compare against the deviant in order to be a representation of memory comparison and be a true homologue to aMMN (Pazo-Alvarez et al. 2003), it is more likely that this second negativity can be considered a vMMN. Czigler et al. (2006)'s study was unique in that it was the first vMMN paradigm to investigate vMMN independent of stimulus features. The significance lay not in the color of the checkerboard pattern, but in the violation of the order in which it was presented. This allowed the authors to measure true automatic change-detection response as compared to simple exogenous stimulus feature differences. In another study, Kimura et al. (2009) used the equiprobable paradigm to examine the nature of stimulus effects on vMMN. In this paradigm, two sequences were

presented. In the equiprobable sequence, bar stimuli in five different types of orientations were presented; a control bar stimulus was presented twenty percent of the time, equally as likely to be viewed as any of the other four orientations. This sequence should not activate change-specific neuronal populations. In the oddball sequence, two bar stimuli with the two closest line orientations were presented: the deviant stimulus twenty percent of the time, and the standard stimulus eighty percent of the time. The authors compared deviant/standard, deviant/control, and control/standard pairings, and found two negativities when comparing deviant stimuli to standards; one at 100-150ms and another at 200-250ms. However, when they compared deviant stimuli to controls, only the later negativity was elicited. The authors concluded that the early negativity reflects the refractory effect related to exogenous stimulus features, while the second reflects a memory-based comparison to standards and is analogous to the aMMN.

In addition, even audiovisual studies of vMMN (Froyen et al. 2010) have found what visually appears to be two negativities at some electrode sites, particularly occipito-parietal in their audiovisual paradigm in response to non-letters. They found a primary later window of the second negativity around 238 to 334ms post-stimulus, and also an earlier negativity in some participants around 166 to 198 ms. This peak is slightly later, but generally in line with the latencies of the first negative peak, as observed in other studies where two peaks have been reported (e.g. Kimura et al. 2009; Czigler et al. 2006; Muller et al. 2012). The slightly longer latency in Froyen et al. (2010)'s study could be due to the audiovisual nature of their paradigm and the increasingly complicated nature of dual recruitment of the auditory and visual systems to process the stimuli. Froyen et al. (2012) did not analyze this early negativity because it was not present in enough data points, but it could be interesting to investigate why this earlier negativity is sometimes observed and what it might mean in terms of dual modality

studies. In this study, non-letter deviants resulted in generally smaller amplitudes of vMMN when compared to letter deviants, which Froyen et al. (2012) hypothesized to be a learned efficiency mechanism after stimulus context caused participants to expect letter-sound pairings. The fact that this second, later negativity was only noted in non-letter deviants could be a result of more sequential processing taking place, as participants considered the context in which the stimulus was presented. It would be interesting to see if individuals with language deficits also exhibit the same topography of vMMN to non-letter deviant visual stimuli, or if the earlier negativity is somehow altered.

These studies indicate that the second negativity observed is more likely to be a true homologue of the auditory MMN. What causes vMMN to manifest as multiple negativities in certain paradigms and not others is still unclear. It is possible that these negativities represent two separate processing systems with different neural correlates that meld together in certain paradigms or with certain populations. In this theory, it might be expected that developing populations might have more separation of the two negativities due to a more sequential processing strategy that is not needed in the mature brain. However, additional tasks performed on children would lead to better understanding of the nature of multiple peaks in that age group.

Some recent studies have begun to address the question of multiple negativities in children. In their study, Clery et al (2012) observed three distinct negative deflections in school-age (8-14) children in response to visual deviance, whereas only one negative deflection was observed in adults. This could be due to a wide variety of factors, including polarity shifts in the difference waves created with respect to each ERP component inside the given window for MMN computation. For example, if a particular subject has a larger N1 to standard stimuli than deviants, this could cause the resulting difference wave to be reversed in polarity. Indeed, Clery et al (2012) reported stimulus

grand averages showing that P1, occurring around the first window of negativities when the subtraction was preformed, was more positive to standards compared to deviants in children only. Adults did not show this difference in P1, which could result in one less negative deflection when computing the difference waves. This finding could be consistent with previous reports (e.g. see Czigler et al. 2006; Kimura et al. 2009) that the earlier observed negativity is due to differences in exogenous stimulus features, while the second is due to memory comparison between deviants and standards and the resulting expectancy violation that occurs. Clery et al. (2012) hypothesize that children may be more likely than adults to process these two aspects of change sequentially and separately, with the connectivity of the two processes being incomplete in this stage of development as compared to mature adults. Clery et al. (2012) also observed in scalp topography that recruitment of the dorsal pathway may be underutilized in children, and that this pathway is often associated with shifts of attention (Pazo-Alvarez et al. 2003). Given this, it is possible that the presence of two negativities observed in children when only one is observed in adults reflects immature selective attention and deviance memory in the younger age group, resulting in a 'separation' of the two processes not seen in adults.

However, it is not clear if the negativity observed around 150ms is a stable difference in this age group. Interestingly, in a more recent study comparing vMMN in typically-developing children to children with autism, Clery et al (2013) observed only one negativity in typically-developing children and multiple positivities in children with autism. A close examination of stimulus grand averages in this study reveals that the typically-developing children showed no difference in P1 amplitude to standards versus deviants in this sample, much like the typical adults in their 2012 study. There appears to be a discrepancy between the 2012 and 2013 studies regarding the order of number of

negatitivies observed in typically-developing children, despite the fact that both studies used the same paradigm and ages of the typically-developing children were the consistent as well. It is possible that deviations in the earlier negativity are less stable in children, which, together with the idea that deviance detection as a comparison to standards occurs at the later negativity, supports the idea that this later negativity is a better indication of deviance processing in children. The lack of comparable difference wave elements made analysis of differences in latency and amplitude of vMMN in children versus adults very difficult for Clery et al. (2012). However, unpaired Student's *t*-tests revealed periods of statistically significant differences associated with the differing polarities in the two age groups. Using the idea that the later negativity may be comparable to the single negativity observed in adults, it may be possible to analyze results more completely in future studies.

In another recent study, Tomio et al. (2012) used images of a ball with a varying black/white pattern to examine the developmental latency of the vMMN from age two to age twenty-seven. They found that vMMN latency decreases with age up to about age sixteen, at which time it is not statistically different from that of adults. The authors did not report the effects of development on vMMN amplitude, but the latency differences observed may indicate improved cognitive processing until the late teenage years. In particular, the authors conclude that increasing age affords increasing ability to discriminate pre-attentive stimulus properties. They hypothesize that difficulty of stimulus property discrimination may affect latency differences. It should be noted, however, that the authors did not provide details in terms of how vMMN was calculated, other than nonlinear regression analysis being used to obtain a model. A visual inspection of their presented data indicates that multiple negativities may be present in the children in their sample, particularly in younger ages e.g. five-year-olds. In this case, the authors use an

arrow to indicate vMMN at the later negativity, although they do not discuss the apparent earlier negativity in some of the children. This paper does lend credence to the idea that vMMN can be compared in adults versus children by choosing the later negativity if multiple negativities are present at younger ages; however, differences in analysis procedures between this study and that of Clery et al. (2012, 2013) must be kept in mind. It is currently unclear how differing vMMN topography in adults versus children should be analyzed.

These differences are seen in other studies that have investigated developmental vMMN using different stimuli, such as color differences (Horimoto et al. 2002), which appear to be developmentally mature at seven to thirteen years of age and can even be observed in mentally retarded (MR) children. Therefore, color modality may be easier to discriminate than the black and white stimulus pattern used by Tomio et al., and may require less advanced stimulus discrimination ability. However, it is worth noting that Horimoto et al found a trend for larger amplitudes of the vMMN in school-aged children when compared to adults, though this finding did not reach significance. The children in this study also appeared to exhibit two peaks, as discussed by Horimoto et al. (2002); the authors hypothesized that the later negativity they observed could be similar to the N2b. In their figures, it does appear that a third negativity is present earlier than the other two reported, around 150ms. As this is not outside the accepted window for vMMN studies and was indeed reported on by Clery et al. (2012), it is possible that this first early negativity should also be considered as a possible representation of differences in exogenous stimulus features. In addition, children with MR displayed an inverted pattern compared to control children, resulting in a positive difference when the deviant color stimulus was subtracted from the standard color stimulus. This indicates that both age and disorders in cognitive functioning could impact vMMN.

In summary, many previous studies have observed multiple negativities in the visual difference wave, and some recent studies have begun to investigate this phenomenon in children. Typically-developing children appear to display multiple (two or possibly three) negativities in vMMN experiments, and this finding has also been reported in adults. This may be a result of developmental immaturity and incomplete synthesis of two different processing systems, one focused on differences in exogenous stimulus features and one on stimulus deviance as compared to standards. It is possible that in the paradigms used in previous studies comparing adults and children, these two processes overlapped in adults to produce one smooth negativity, while in children they were expressed sequentially. This may also be related to the nature of the stimuli used in a particular paradigm, especially whether they activate the dorsal or ventral pathway of the visual system. It is possible that stimuli that activate one of these pathways are more likely to produce overlap of processes primed for exogenous stimulus effects and orienting to deviance; given the dorsal pathway's strong association with attentional shifting (Pazo-Alvarez et al. 2003), one might guess that stimuli activating the magnocellular system are more strongly associated with two negativities. These stimuli, such as differences in spatial frequency, peripheral location, or line orientation, might produce a stronger disassociation between orienting to deviance and exogenous stimulus effects. Regardless, more research is necessary to explore this hypothesis, as well as how this process changes throughout development to explain why children (versus adults) are more likely to display multiple negativities in vMMN studies.

4.4: vMMN in autism

Currently there is very little research on vMMN in individuals with autism.

However, one study (Gayle et al 2012) found that amplitudes in response to happy emotional deviants were smaller in adults without an autism diagnosis who scored high on the Adult Autism Spectrum Quotient (AQ). The authors used images of neutral faces as the standard stimulus and images of happy or sad faces as deviant stimuli. While a vMMN was observed in both conditions, the amplitude was larger in response to sad deviants. However, only happy deviants were associated with AQ scores. This finding is supported by low levels of approach motivation and diminished positive affect (Garon et al 2009) in individuals with autism, and decreased activation of the fusiform gyrus (Spencer et al 2011) in response to positive (versus negative) emotions in both individuals with autism and their unaffected siblings. The authors conclude that reduced vMMN amplitudes in the happy deviant condition is related to the overall negative experiences of social interaction that are often reported by individuals with autism, whereas decreased response to negative emotions might result in a positive social interaction experience. However, it is worth noting that none of the subjects in this study had a diagnosis of autism, nor were they first-degree relatives of individuals with autism. It is also unclear whether paradigms with simpler visual stimuli could also elicit differences in the vMMN in individuals with autism as compared to controls.

As of the writing of this dissertation, only one other study has investigated vMMN in children with autism (Clery et al. 2013). In an identical paradigm to one used in a previous study (Clery et a. 2012), typically-developing children and children with autism viewed deformations of a circle into an ellipse in horizontal and vertical directions. While typically-developing children showed an occipital negativity around 330ms post-stimulus, the children with autism showed three successive positivities observed between 50-300ms post-stimulus. Children with autism also had significantly shorter latencies than typically-developing controls, a finding consistent with the literature on aMMN in children

with autism (e.g. Gomot et al. 2002). As discussed in section 2.3, however, Clery et al. (2012) found multiple negativities in their typically-developing children in a previous study, which used the same paradigm and the same ages of participants. It is possible that these earlier elements of the visual difference wave are less stable in developing populations, and replication is needed in children with autism to confirm if this theory is also true outside of typical development.

It is interesting to note that the children with autism in the 2013 study displayed the reverse effect of deviance at P1 found in the typically-developing children in Clery et al. (2012)'s other study: deviant stimuli elicited a more positive amplitude at this element than standard stimuli. This could explain the multiple positivities observed when the subtraction was performed. In addition to P1, N1 was also more positive (i.e., less negative) in children with autism; this reversal of polarity in the autism group as compared to the control is likely responsible for the multiple positivities observed. In addition, Horimoto et al. (2002) also found multiple positivities in their study on children with mental retardation, which indicates that this topography could be a result of general cognitive decline and not autism per se. More research is needed to further explain these findings, as well as to clarify the consistency of the earlier elements of the vMMN difference wave in both typically-developing children and children with autism.

4.5: vMMN as a clinical investigative tool

There is evidence that the well-documented auditory MMN paradigms for investigating clinical populations may also be useful in the visual modality. For example, numerous studies (reviewed by Umbricht and Krljes 2005) have found decreased auditory MMN in individuals with schizophrenia compared to healthy controls, and this

deficit has been associated with lower functioning. A similar phenomenon appears to be present in visual MMN. Individuals with schizophrenia exhibit reduced amplitudes of visual MMN when compared to healthy controls (Urban et al 2008). Furthermore, reduced visual MMN amplitude is also associated with lower levels of functioning in schizophrenia, as well as higher levels of medication dosage. In another study, Qui et al (2011) found decreased visual MMN amplitudes in individuals with major depressive disorder, although this difference did not correlate with depression severity. Finally, Tales at el (2008) found that individuals with mild cognitive impairment (MCI) and Alzheimer's disease showed increased visual MMN amplitude around 140-250ms poststimulus presentation, although this effect was absent in the later elements of the difference wave (250-400ms poststimulus). Taken together, these findings suggest that deficits in early stages of visual sensory processing may be important in clinical populations with respect to visual MMN studies.

Visual MMN may be useful in examining other clinical populations, particularly children with autism. This would allow other sensory modalities to be tested other than auditory (for a more complete discussion, see Chapter Two), as sensory features in autism occur across all sensory modalities and cannot be fully understood with the examination of only auditory stimuli. One recent study (Clery et al. 2013), despite its limitations, found profound differences in vMMN with respect to children with autism, as these children displayed several positivities instead of a single negativity, and the peak latencies of these positivities were also shorter than those of typically-developing children. Studies of other clinical populations indicate that altered vMMN may be useful as a clinical tool investigating neurological disorders. Given the unique core deficits associated with autism and their strong relation to sensory processing, vMMN may be useful in understanding the unusual sensory features that often co-present in children

with autism (see Chapter Two for detailed discussion).

4.6: Unanswered questions and future directions of vMMN

While recent research (Kimura et al. 2009; Muller et al. 2012; Czigler et al. 2006; Kecskes-Kovacs et al. 2012) has provided convincing evidence for the presence of an adequate homologue to the auditory mismatch negativity in the visual modality, independent of stimulus features and requiring a memory comparison to standard events, many unanswered questions remain. It is still unclear why some studies report multiple negativities of the vMMN while others do not, and the lack of standardization with regard to what these additional negativities mean requires many additional explanations and research. It is hypothesized in other research studies (Kimura et al. 2009; Muller et al. 2012) that the earlier negativity often observed may be the representation of exogenous stimulus features or the refractory effect, while the later negativity represents a memory-based comparison to standards, i.e. a true vMMN. However, not all studies have reported multiple peaks, especially in adult populations (Clery et al. 2012). Chapter Four, hypothesizes that this inconsistency may be the result of different visual streams being activated by different tasks, and the varying associations with the dorsal and ventral stream and attentional processes. Because the dorsal stream is more likely to be associated with attentional shifting, orienting, target selection and planning of movements (Pazo-Alvarez et al. 2003), it is possible that paradigms specifically designed to target the dorsal stream are more sensitive to measures of attention. This would include stimuli presented in the periphery, which are highly associated with temporal movement and less associated with form and color. More research is also needed to help clarify these hypotheses and what differences, if

any, underlie stimuli activating the dorsal stream versus the ventral stream in typically-developing populations. Although more work should be done in typically-developing populations with regard to stimuli types, associated vMMN latencies and number of peaks, these paradigms in particular could also be useful to examine clinical populations such as autism where selective attention deficits are present,

vMMN provides a promising clinical tool to investigate visual processing deviance in disordered populations (Kimura et al. 2011; Czigler 2007). A number of previous studies have reported abnormalities in vMMN in various clinical populations when compared to typically developing controls, including Major Depressive Disorder (Qui et al 2011, Chang et al. 2010), schizophrenia (Urban et al. 2008), Mild Cognitive Impairment and Alzheimer's Disease (Tales et al. 2008), autism spectrum personality traits in sub-clinical populations (Gayle et al. 2012) and autism spectrum disorder (Clery et al. 2013). vMMN may serve as a marker for such clinical conditions with future research. For example, there is evidence that vMMN is altered when normal aging is disrupted: while vMMN is reduced in amplitude in typical elderly populations (Tales et al. 2002), its amplitude is increased in patients with Mild Cognitive Impairment and Alzheimer's Disease (Tales et al. 2008). It is important to understand the underlying mechanisms of these alterations of vMMN in order to determine what we can learn about sensory processing that will be helpful in intervention strategies. Scalp current density (SCD) mapping would be useful for this purpose because it allows for better localization of signals to different neural areas and has been used in many studies of clinical and typical populations (e.g. Clery et al. 2012, 2013).

Given vMMN's potential relationships to language development (Froyer et al. 2010) and its strong association with attentional shifting and orienting (Pazo-Alvarez et al. 2003), it makes sense to investigate vMMN in children with autism in order to better

understand visual sensory processing deficits in this population. Only one study has investigated vMMN in children with autism (Clery et al. 2013), and the findings may be affected by inconsistent earlier negativities in the visual difference wave as discussed in section 2.3. In further studies, differences in vMMN in children with autism and those with typical development should be further characterized. It would be particularly beneficial to relate vMMN differences in children with autism with behavioral, self- and parent-report measures of core symptom severity or sensory processing, as several studies have begun to do this using aMMN (Gomot et al 2011; Donkers et al., in review). Finally, a multi-modality approach would help to address the holistic sensory deficits often seen in autism across multiple modalities. Audiovisual MMN studies have been conducted with aMMN (Stekelenburg 2004) and vMMN (Froyer et al. 2010) and could be useful to perform in children with autism to probe sensory features, which are by nature complex and often expressed in multiple modalities. For a more detailed discussion of the usefulness of MMN in investigating sensory features, see Chapter Two.

In summary, research has shown that a homologue to aMMN exists in the visual modality. This visual difference wave is not dependent on the refractory effect of stimulus features and necessitates comparison to standard stimuli. Many studies have been conducted using widely varying stimulus parameters and paradigms that probe both the dorsal and ventral stream of visual processing, but it is still unclear why certain paradigms produce different negativity windows and number of peaks. vMMN may be a useful clinical tool because an adequate visual mismatch response reflects the ability to recognize which stimuli are important and allocate cognitive resources accordingly, and this process may be impaired in a number of clinical conditions. Research on vMMN in children has been sparse, and it is necessary to better understand vMMN both in typical

development and in disordered development. Future research should focus on building connections between number and timing of negativities observed and functional outcomes, as well as more investigation of vMMN in development.

CHAPTER FIVE: METHOD[2]

5.1 STUDY ONE:

Investigating Developmental Changes in Sensory Processing: Visual Mismatch Negativity in Healthy Children

5.1.1. Introduction

The human brain is constantly responding to changes in sensory stimuli, even if these changes do not pass into conscious awareness. Mismatch negativity (MMN), or the brain's response to infrequent changes in a series of repetitive stimuli (Näätänen and Escera 2000), is an element of the Event Related Potential (ERP) that allows for the investigation of the neural correlates of change in the environment. MMN is typically measured when the subject's attention is directed away from the stimulus, and corresponds to a difference wave computed by subtracting a frequently-occurring standard stimulus ERP from a rarely-occurring deviant stimulus ERP. The MMN can be measured relatively early in development and is generally viewed as the outcome of a

[2] *The following studies have been submitted to Frontiers in Human Neuroscience and are currently under review. For a detailed discussion of the associated aims and hypotheses of these studies, please see Chapter Two, section 2.6: Summary and Specific Aims.*

mechanism that compares the current sensory input to memory traces formed by previous repetitive inputs, and signals a mismatch between them (e.g. Naatanen and Escera 2000; Duncan et al. 2009).

MMN has mainly been investigated in the auditory modality, but recent studies have characterized this difference wave in the visual modality as well (see Pazo-Alvarez et al. 2003; Czigler et al. 2007 for reviews). Recent research (reviewed by Pazo-Alvarez, Cadaveira and Amenedo, 2003 and Czigler, 2007) has provided convincing evidence that the brain can unconsciously detect small changes in visual environment. Visual MMN (vMMN) is an occipital-parietal negativity computed by subtracting a frequent standard stimulus from a deviant stimulus in the visual modality, usually occurring around 100-250ms post-stimulus presentation. Visual MMN has been primarily studied in typically-developing adults, and has been observed in response to changes in color (Czigler, Balazs and Winkler 2002; Czigler, Weisz and Winkler 2006; Berti 2009), line orientation (Kimura et al. 2009; Czigler and Sulykos 2010); stimulus position in the visual field (Berti 2009; Muller et al. 2012), emotional faces (Chang et al. 2010; Stefanics et al. 2012; Gayle et al. 2012), and spatial frequency (Heslenfeld 2003; Fu et al. 2003). For a detailed discussion of auditory and visual MMN and its relationship to sensory processing, see Chapters 1-3. The studies described in previous chapters have contributed significantly to the understanding of visual MMN in adult populations; however, there is comparatively little research on the visual MMN in children.

Like the more frequently studied auditory MMN, differences in the specific paradigms employed and, in some cases, differences in populations studied, may yield different patterns of vMMN. In early vMMN studies, there has been some debate as to whether this negativity represents refractory effect of the visual stimulus or a true detection of change based on building up of a memory trace for the repeated stimulus

and a ‘comparison’ of the deviant stimulus features against this trace. Kimura et al. (2009) addressed this question by presenting healthy subjects with two paradigms, the equiprobable (all types of stimuli presented at equal frequencies) and the oddball (standard stimuli 80% of presentations and deviant stimuli 20%). In the equiprobable sequence, bar stimuli in five different types of orientations were presented; a control bar stimulus was presented twenty percent of the time, equally as likely to be viewed as any of the other four orientations. This sequence should not activate change-specific neuronal populations. In the oddball sequence, two bar stimuli with the two closest line orientations were presented: the deviant stimulus twenty percent of the time, and the standard stimulus eighty percent of the time. The authors compared deviant/standard, deviant/control, and control/standard pairings, and found two negativities when comparing deviant stimuli to standards; one at 100-150ms and another at 200-250ms. However, when they compared deviant stimuli to controls, only the later negativity was elicited. The authors concluded that the early negativity is related to the refractory effect while the later one is related to the memory component of stimulus change detection. Similarly, Czigler, Weisz, and Winkler (2006) found two occipital/centro-parietal negativities in healthy adults viewing a set order of color grids that was periodically displaced. One negativity occurred at 100-140ms poststimulus and another at 210-280ms poststimulus. The purpose of the set pattern of alternating colors was to determine if the visual MMN was related to change in stimuli themselves or a detection of deviance from a pre-established pattern of change in stimuli. Only the second later negativity at 210-280ms was elicited when the pattern of color grids was violated, indicating that this later waveform reflects comparison to the established response (pattern) for the repeated stimulus and not stimulus change per se. These findings indicate that, in the visual modality, change detection may involve a 2-step process: a

first “sensory” change detection, occurring earlier, and possibly processed at a more “local” level i.e. in primary sensory cortices; and a second, occurring slightly later, and possibly depending upon the contrasting of the current stimulus with an established “contextual memory trace” through interactions betw

een visual sensory and higher order associated cortical regions.

Despite a growing number of vMMN studies in adults, there is comparatively little research on the visual MMN in children. A recent study (Clery et al. 2012) used dynamic deformations in a circle slowly becoming an ellipse to examine vMMN in healthy adults, as well as in healthy children ages eight to fourteen. While in adults the vMMN was observed as an occipital-parietal negativity occurring around 210ms post-stimulus, in children, three successive negativities originating over fronto-central electrode positions were observed between 150 and 330ms. In addition, a larger late *positive* mismatch response was observed in children around 450ms post-stimulus. The authors conclude that not only is vMMN immature in children up to fourteen years of age, but the successive negative potentials may reflect a sequential visual processing of deviancy that is not present in the mature brain. Processing of visual deviancy during development may require several distinct steps that are not necessary for adults, and may be related to immature selective attention processes or underdeveloped connectivity across cortical regions. Scalp topography maps suggest equal temporal recruitment of the dorsal and ventral pathways in adults, but the involvement of right parietal areas in the late positive potential observed in children may indicate that the dorsal pathway is engaged later in stimulus change detection processing in children. It is worth noting, however, that the stimuli used in this study featured changes in both form and motion, and the authors hypothesize that these two stimulus properties may be processed separately in children, with maturation of the visual system leading to better

integration of multiple stimulus properties.

Currently no studies have investigated the vMMN in children treating changes in stimulus form and motion as separate deviant events. Studies using static stimuli that probe changes in physical form or dynamic stimuli with constant physical properties would help confirm this theory. Also worth noting is that the age range investigated in this study was significantly larger and comprises a good portion of late childhood and adolescence; since many important neurophysiological changes occur during adolescence, vMMN may be vastly different in the younger portion of this sample compared to the older participants. The authors also note that developmental changes in vMMN appear more drastic than those in the auditory modality. Other studies have also reported latency decreases in vMMN with age up to approximately age sixteen (Tomio et al. 2012). This latency differences may indicate improved cognitive processing until the late teenage years, possibly associated with improved connectivity resulting from brain maturation. In particular, the authors conclude that increasing age affords increasing ability to pre-attentively discriminate stimulus properties, and hypothesize that difficulty of stimulus property discrimination may affect latency differences. These differences are seen in other studies that have investigated vMMN across development using different stimuli, such as color differences (Horimoto et al. 2002), which appear to be developmentally mature at seven to thirteen years of age and can even be observed in children with intellectual disabilities (MR). Therefore, color modality may be easier to discriminate than the black and white stimulus pattern used by Tomio et al., and may require less advanced stimulus discrimination ability.

While a small number of recent studies, described above, have investigated vMMN in children, specific differences in the vMMN at various stages in development and across different paradigms are still unclear. In addition, understanding of the

neurobiology of developmental differences in vMMN is still in its infancy. In the current study, we aim to further characterize the vMMN in a sample of eight to twelve-year-old children. We compared the vMMN response to task-irrelevant deviant stimuli in children to the vMMN of adults while both groups performed a simple target detection task.

5.1.2. Materials and Methods

Participants:

We collected EEG data from 20 healthy adults between the ages of 18 and 42 (mean age = 26.6, 10 female) and 22 typically-developing children between the ages of 8 and 12 (mean age = 10.4, 13 female). All participants reported no current, past, or family history of substance abuse, no neurological/neuropsychiatric disorders, no seizure disorder with evidence of seizure activity within the past twelve months, no significant physical impairments or limitations, no history of head trauma or loss of consciousness, and were not currently taking any antipsychotic medications. Participants reported normal or corrected-to-normal vision. One child was excluded from further analysis due to excessive sleepiness during recording, resulting in noisy data.

Participants were recruited from multiple venues, including a university-based mass email system and local community and parent groups. Participants received $30 for taking part in the study and a certificate with a graphical image of their brain waves to take home. Adult participants gave informed consent, and minor participants provided written assent while their parents provided parental permission as approved by the UNC Institutional Review Board.

Experimental Procedure:

Visual MMN Paradigm: Continuous EEG data was recorded while participants performed a simple visual target detection task of responding to images of stars (15%)

with a right finger button press. Participants were presented with target (*) and nontarget (+) images displayed at fixation in front of two types of task irrelevant background images of gratings. Four different stimulus conditions were created (see Figure 6): high spatial frequency (HSF) background with target image placed in center, low spatial frequency (LSF) background with target image placed in center, HSF background with nontarget image placed in the center and LSF background with nontarget image place in the center. All stimuli were 960x720 pixels and consisted of gray and black bars in a repeating pattern with 75% contrast. HSF images consisted of ten cycles of gray and white bars while LSF images consisted of four cycles. The target was a blue star presented in the center of the grating while the nontarget was a blue crosshair in the same location. Our primary stimuli of interest were the standard nontarget images and the deviant nontarget images. LSF images served as deviants while HSF images served as standards. Therefore, standard nontarget images consisted of HSF images with a blue crosshair in the center (HFNT), while deviant nontarget images consisted of LSF images with a blue crosshair in the center (LFNT).

Electrophysiological Recording:

Participants were seated comfortably in a sound-attenuated, dimly lit booth, 80cm away from the stimulus monitor, adjusted to be at eye level with each subject. Stimulus presentation was controlled by CIGAL software, version 17.2 (Voyvodic, 1999). Continuous EEG data were collected using an elastic cap containing 18 electrodes, with only 13 electrodes used to collect data: at frontal (F3, Fz, F4), central (T7, C3, Cz, C4, T8), parietal (P3, Pz, P4) and occipital (O1, O2) scalp locations. The right mastoid served as the reference electrode and AFz as the ground. Bipolar recordings of the vertical and horizontal electro-oculogram (EOG) were obtained by electrodes placed

above and below the right eye and on the outer canthus of each eye, respectively. EEG and EOG data were sampled at a rate of 500 Hz and bandpass filtered online between 0.05 and 100 Hz, with a narrow 60Hz notch filter used to reduce main power frequency interference. Continuous data were analyzed off-line using NeuroScan 4.4 software (Neurosoft, Inc., Sterling, VA, USA). Participants were instructed to avoid excessive movement, tension of facial muscles, horizontal eye movements, or speaking. Participants were told that they would view a series of pictures and that their task was to ignore the background gratings and press a button each time an image of a star appeared at the center of the screen. Images were displayed at eye level on a 19-inch Dell flat panel monitor. Targets were presented in a pseudorandom order (no target was followed by another target). Five runs of five minutes each were presented, with 160 images per run and 800 images total. Images were presented for 750ms duration, with an interstimulus interval of 1000ms offset to onset, and all images were presented mixed within blocks. Total experiment time lasted approximately 90 minutes, including 25 minutes of experiment time and approximately 65 minutes of lab acclamation for child participants, electrode set-up, breaks and instructions.

Data Processing:

Response latencies and percentage of correct responses were calculated for each subject. All incorrect trials or trials containing responses less than 200 ms and greater than 1000ms from onset of the target were excluded from further analyses. Continuous EEG data was filtered offline with a 30 Hz (24 dB/octave) low-pass filter and visually inspected for movement artifacts, and incorrect behavioral responses were removed from the analyses. EEG data sets from each participant were corrected for eye-movements using regression analysis as implemented in Neuroscan Edit 4.4

(Semlitsch et al., 1986). Continuous EEG data from all channels were epoched using a 100ms prestimulus baseline period and a 500ms poststimulus period. Individual epochs were passed through an automatic artifact detection algorithm to remove epochs with EEG activity in excess of -100uV or +100uV. ERPs were obtained by averaging the baseline corrected EEG epochs for each stimulus category and for each participant. The P1, N1 and MMN were identified by an automatic peak detection procedure, defined as the most positive and negative peak (as appropriate) within a specified window after stimulus onset. For P1 and N1, peak windows were determined based on the relevant peak in a visual inspection of grand averages at occipital electrodes.

For children, peak windows were defined as follows: P1 windows were defined as 100-160ms for standard nontarget stimuli, and 110-160ms deviant nontarget stimuli. N1 windows were defined as 190-290ms for standard nontarget and 190-280ms for deviant nontarget stimuli. For adults, peak windows were defined as follows: P1 windows were defined as 100-160ms for standard nontarget stimuli and 100-170ms for deviant nontarget. N1 windows were defined as 150-240ms for standard nontarget 130-230ms for deviant nontarget.

MMN was computed by subtracting the standard nontarget stimulus (HFNT) from the deviant nontarget stimulus (LFNT) and defined as the most negative peak in a specified window. Visual inspection of both grand averages and individual subject data indicated that adult subjects displayed a single negative peak around 150ms post-stimulus. Thus, in this group we detected the most negative peak within a 100-200ms post-stimulus window. By contrast, the children displayed two negative peaks, the first around 150ms post-stimulus and the second around 250ms post-stimulus. Since all

children displayed this second negativity, we defined the first as the most negative peak within 100-200ms post-stimulus and the second as the most negative peak within 200-300ms post-stimulus.

Given prior research's reports of vMMN as an occipito-parietal negativity, data were analyzed primarily at occipital sites (O1, O2) and also at midline frontal, central and parietal sites (Fz, Cz, Pz). P1 was assessed at the occipital sites only (O1, O2) and N1 was assessed at midline frontal, central and parietal sites.

Statistical Analyses

All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). For behavioral analyses, independent samples T-tests were performed. For between-groups comparisons of P1 and of MMN a preliminary model was fit which considered occipital electrode channels simultaneously using a repeated measures mixed model ANOVA, with the between subject factors of Group (child, adult) and the within-subject factors of electrode location (O1, O2). If group effects or interactions were significant, follow-up repeated measures ANOVAs were fit for each group separately. For the N1, we also performed single channel (Fz, Cz, Pz) one-way ANOVAs, with Group as the between-subject factor. All above analyses were performed for both deviant and standard nontarget conditions. In the difference wave, we separately compared both windows for the MMN in children to the single MMN in adults.

Pearson's product moment correlations were computed to determine the relationship between age and P1, N1 and vMMN amplitude in the group of children.

5.1.3. Results

Behavioral Data

Mean response rates (i.e. correct responses) and response latencies for standard and deviant target conditions are indicated in Table 1. There was a significant difference in the response accuracy between the children (M=96%) and the adults (M=100%) for the deviant target condition (t =2.38, p = .022); response rates for standard targets did not differ (p>.08). All groups performed the task with at least 95% accuracy. There were no significant differences in mean response latency between the children and the adults (p > .1 for both conditions).

Between-Group Differences

P1:

The mixed procedure ANOVA demonstrated a main effect of Group for P1 amplitude to standard nontargets (F (1, 39) = 81.34, p < .001) and a significant Electrode x Group interaction (F (1, 39) = 7.00, p = .012) for P1. Post-hoc within-group tests revealed a significant main effect of Electrode in the children with amplitude being larger at electrode O2 (F (1, 20) = 5.99, p = .024) than electrode O1. This effect was absent in the adults. There were no significant differences in P1 latency.

For P1 amplitude to deviant nontargets, we also found a main effect of Group and a significant Electrode x Group interaction (F (1, 39) = 5.90, p = .020). Post-hoc comparisons revealed that in the children P1 amplitude was significantly larger at

electrode O2 (F (1, 20) = 4.98, p = .037). This effect was absent in the adults. There were no significant differences in P1 latency.

N1:

The mixed procedure ANOVA demonstrated no significant differences between groups or a laterality effect for the N1 amplitude to standard nontargets. However, additional between-group tests at electrode position Fz, Cz and Pz demonstrated that in children, the amplitude of N1 to standard nontargets was significantly larger at Fz (F (1, 39) = 37.73, p < .001), at Cz (F (1, 39) = 64.76, p < .001), and at Pz (F (1,39) = 6.00, p = .019).

For N1 amplitude to deviant nontargets, no significant differences between groups or an effect of occipital electrode position was observed. However, additional between group tests at electrode positions Fz, Cz, and Pz demonstrated that the amplitude of N1 to deviant nontargets was significantly larger in children at Fz (F (1, 39 = 19.31, p < .001) and at Cz (F (1, 39 = 35.73, p < .001), but not at Pz.

In terms of latency, for standard nontargets there was a main effect of group with children showing longer latencies to standard nontargets (F (1,39) = 38.29, p < .001). For deviant nontargets there was also a main effect of group with longer latencies of N1 in children (F 1, 39) = 42.12, p < .001).

ERPs to standard and deviant nontargets at electrode positions Fz, Cz, Pz, O1, and O2 are shown in figure 7. A close-up of channels O1 and O2 is shown in figure 8.

Difference wave (MMN):

The mixed procedure ANOVA demonstrated no significant differences between groups or an effect of occipital electrode position on the MMN amplitude. This was the case for the amplitude of the second negativity of the difference wave in the children, as

compared to the single negativity in the adults as well as for the amplitude of the first negativity of the difference wave in the children as compared to the single negativity in the adults.

In terms of latency, the first negativity in the children compared to the only negativity in the adults was significantly earlier (main effect of group ($F (1, 39) = 117.433$, $p < .001$)). Besides this, there was a marginally significant Group x Electrode interaction for the latency of the second negativity in the children compared to the only negativity in the adults ($F (1, 39) = 4.17$, $p = .048$) but post-hoc pairwise comparisons indicated no significant effect of electrode position within groups. There were no other significant differences in terms of latency.

Mean values for latency and amplitude of both negativities in the children and the only negativity in the adults are presented in Table 2. VMMNs for adults and children on channel O1 and O2 are presented in figure 9.

Age Correlations

Age correlations for the group of children are presented in Study Two, since this study used the same typically-developing children. All correlations were significant at the $p < .05$ level. In the group of 8-12-year-old children, the amplitude of P1 in the deviant nontarget condition decreased with increasing age at electrode O2 ($r = -.447$) (see Figure 13). Removing the outlier in this condition did not change the significance of this correlation ($r = -.423$). In addition, the latency of the deviant nontarget N1 also decreased with increasing age at electrode O2 ($r = -.655$) (see Figure 14). Finally, the amplitude of the second negativity of the difference wave decreased with age at electrode O1 ($r= .457$) (see Figure 15). No other significant age correlations were found in the children.

5.1.4 Discussion

This study investigated visual mismatch negativity in healthy children as compared to healthy adults using a simple visual target detection task, during which task irrelevant gratings of high and low spatial frequencies were presented in the background. We found a robust vMMN occurring around 150-170ms post-stimulus in the adult group, and two negativities in the children, the first one occurring at around 150 ms and a second one at around 210-230ms. This study confirms previous research investigating vMMN in healthy adults and is one of the first to investigate this difference wave in children aged 8-12 years old. These results indicate that both children and adults respond to rare task irrelevant visually deviant stimuli as compared to frequent (standard) task irrelevant visual stimuli, but this response is still developing in healthy children ages eight to twelve and may be quite different in this age group in terms of number of negative peaks compared to typically-developing adults.

We primarily noted differences in vMMN latency versus amplitude, which may indicate that efficient recruitment of (automatic) deviance-processing resources is not yet mature in children between the ages of 8 and 12. Our results differ from previous work by Clery et al. (2012), in which changes in form and motion resulted in three sequential negativities in eleven-year-old children while only one was observed in adults. We observed two negativities in our study; however, in a subsequent study comparing typically-developing children to children with autism, Clery et al. (2013) found only one negativity in same-age typically-developing children using the same paradigm from their 2012 study. The authors argue that multiple peaks may be due to a sequential visual processing of deviancy necessary in the developing brain but not in the mature brain. Our results generally support this hypothesis, however, the inconsistent findings

concerning number of early negativities may indicate that these earlier peaks are more dependent on individual differences, or are undergoing developmental changes in this age range. The differences between our results and those of Clery et al. (2012, 2013) may also be due to the different nature of the stimuli used and the properties each investigates: Clery et al. point out that it is difficult to determine whether their results were driven by changes in form, motion or both. Perhaps less dynamic stimuli such as the ones used in our study impose reduced processing demands, insufficient to activate the third waveform observed by Clery et al. It would be interesting to determine if multiple peaks can be elicited with static stimuli of increasing complexity, or if this is due to the dynamism of a stimulus alone.

It could be argued that stimulus effects from the use of low frequency gratings as deviant stimuli may account for the visual mismatch seen here. Spatial frequency deviance has been previously studied by Heslenfeld (2003), where differences in ERPs were indeed observed based on spatial frequencies. Some behavioral differences were also observed: e.g. that task-irrelevant stimuli of low spatial frequencies were more likely to interfere with performance than high spatial frequency stimuli, but only in difficult tasks. Our task was not demanding and all subjects performed it easily and accurately, including the youngest children. In the previous study by Heslenfeld (2003), ERP effects were observed in different components of the ERP and different electrode sites than are studied here, such as larger early C1 components (60-100ms) in high spatial frequency gratings versus low, as well as larger responses at frontal and central scalp sites at 120-180ms in low spatial frequency stimuli versus high. Heslenfeld concluded that this deviance was due to stimulus effects and was congruent with previous literature, which found higher response-interference and attention-capturing properties of low spatial frequencies. However, the effects at occipital sites (120-200 ms) were independent of

task load or spatial frequency, showing that this response was not related to individual stimulus properties. This negativity is likely the true visual analogue of the auditory MMN because it is not related to stimulus features or task difficulty, and our results show negativities at comparable electrode locations and latencies. Similar effects have been observed in other studies using the equiprobable paradigm (Kimura et al. 2009; Czigler et al. 2006), where two negativities were found but only one was attributed to stimulus-independent visual deviance. Therefore we believe that the effect observed in the current study is not related to spatial frequency effects, however, more research may be needed to clarify these findings.

In addition, although many previous studies have included an equiprobable control (e.g. Kimura 2009) stimulus that appears with equal probability to demonstrate the context effect of the repeated standard stimulus, this study did not. While this effect was beyond the scope of this research, future studies that included an equiprobable control would help to further explore the refractory effect suggested here. See Chapter Four for a discussion of the equiprobable paradigm and its importance in previous vMMN research. Finally, it is possible that the negativities observed here could be due to differences in oscillatory activity. Future studies should employ time-frequency analysis to clarify this question.

There were also numerous differences at other ERP components between adults and children: as seen previously in the literature, early components, particularly P1 and (albeit to a lesser extent) N1, were much larger in children and longer in latency. Batty and Taylor (2002) also noted this effect in a simple visual categorization task, finding that the amplitude of P1 seemed to decrease with age throughout adolescence. In our study, latency of P1 was also longer and the peak less sharp, resulting in a much later N1 in children versus adults. It could be that these neural mechanisms are

underdeveloped in children and that they may employ fewer response strategies when performing this particular task, i.e. concerns about speed, accuracy and impulsivity management, and attention devoted to the task's purpose. Behavioral reports on subjects' experience of the task following the ERP experiment might help to answer this question.

This study adds to the limited pool of studies investigating vMMN in children. Due to the preliminary nature of this study, and aware of the changes in ERPs that tend to occur across the lifespan, we chose a limited range to determine initial differences between children and adults. However, future research should examine other age ranges in order to better map the development of vMMN. Our stimuli also probed only one aspect of automatic visual deviancy detection (spatial frequency), and future work should investigate other stimulus properties such as color, luminance and size, to further understand development of the visual deviance response.

Considerations for future studies should also include investigating abnormal development of vMMN. There is evidence that the well-documented auditory MMN paradigms for investigating clinical populations may also be useful in the visual modality. Other studies have demonstrated that the amplitude of the vMMN differs in adult populations with schizophrenia (Urban et al. 2008), major depressive disorder (Qiu et al. 2011) and mild cognitive impairment/Alzheimer's disease (Tales et al. 2008). Numerous studies (reviewed by Umbricht and Krljes 2005) have found decreased auditory MMN in individuals with schizophrenia compared to healthy controls, and this deficit has been associated with lower functioning (Light and Braff 2005). A similar phenomenon appears to be present in visual MMN. Individuals with schizophrenia exhibit reduced amplitudes of visual MMN when compared to healthy controls (Urban et al. 2008). Furthermore, reduced visual MMN amplitude is also associated with lower levels of functioning in

schizophrenia, as well as higher levels of medication dosage. In another study, Qiu et al. (2011) found decreased visual MMN amplitudes in individuals with major depressive disorder, although this difference did not correlate with depression severity. Finally, Tales et at. (2008) found that individuals with mild cognitive impairment (MCI) and Alzheimer's disease showed increased visual MMN amplitude around 140-250ms poststimulus presentation, although this effect was absent in the later elements of the ERP (250-400ms poststimulus). Taken together, these findings suggest that early deficits may be important in clinical populations with respect to visual MMN studies.

Although the above research has demonstrated the usefulness of vMMN as a potential clinical tool, few studies have investigated altered vMMN in disorders affecting children. To our knowledge there has been only one other study of visual MMN in children with neurodevelopmental disorders (Horimoto et al. 2002). This study focused on finding altered vMMNs in children with intellectual disabilities (MR), specifically larger amplitudes that were often difficult to distinguish from other ERP components, as compared to vMMNs observed in typically developing children. Altered vMMN could indicate difficulties with automatic detection of visual change and impair the ability to adapt to a changing environment, and both of these skills have been implicated in childhood disorders such as Attention Deficit Hyperactive Disorder (ADHD) and autism spectrum disorders. Visual MMN could be useful to probe visual information processing deficits in children with neurodevelopmental disabilities, and future work should investigate what differences in vMMN, if any, might occur in atypical neurodevelopment.

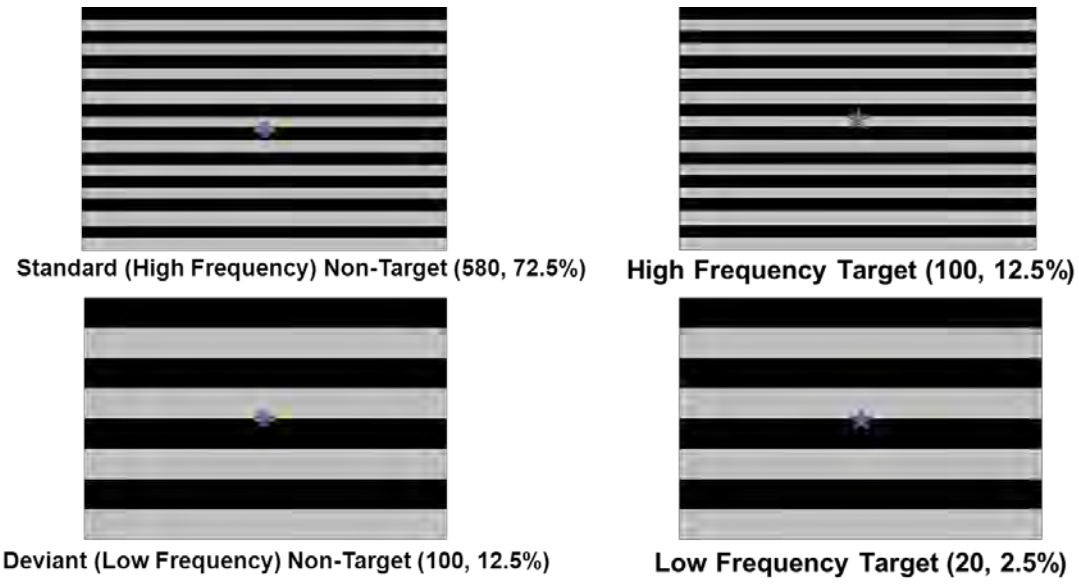

Figure 6: Task design.

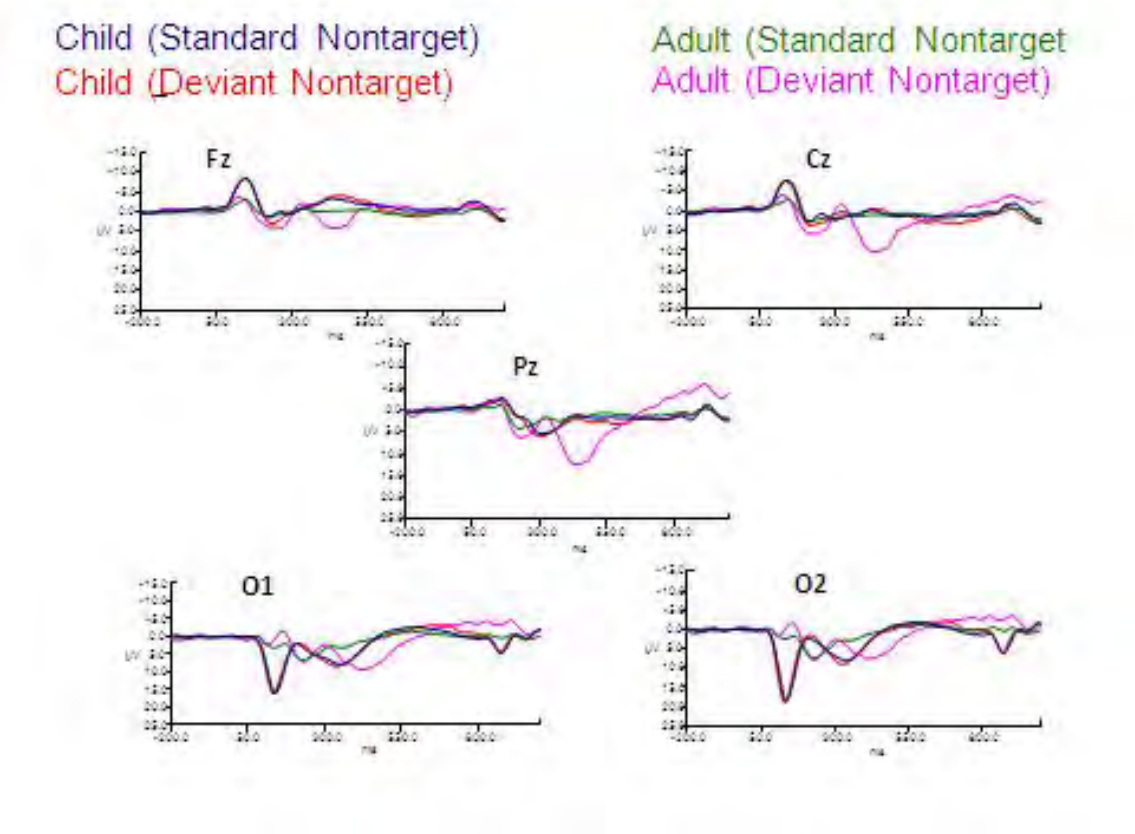

Figure 7: ERPs for both deviant nontarget and deviant target stimulus conditions in children (N=21) and adults (N=20) at electrodes Fz, Cz, Pz, O1 and O2.

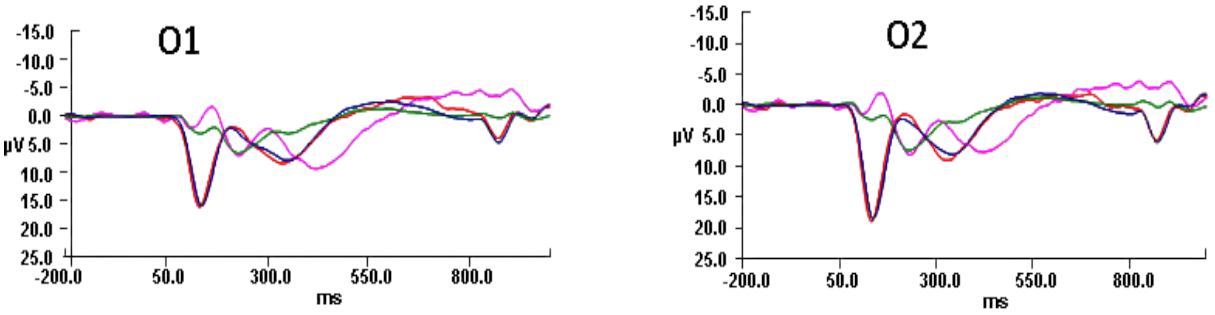

Figure 8: ERPS for both deviant nontarget and deviant target stimulus conditions in children and adults at electrodes O1 and O2 only.

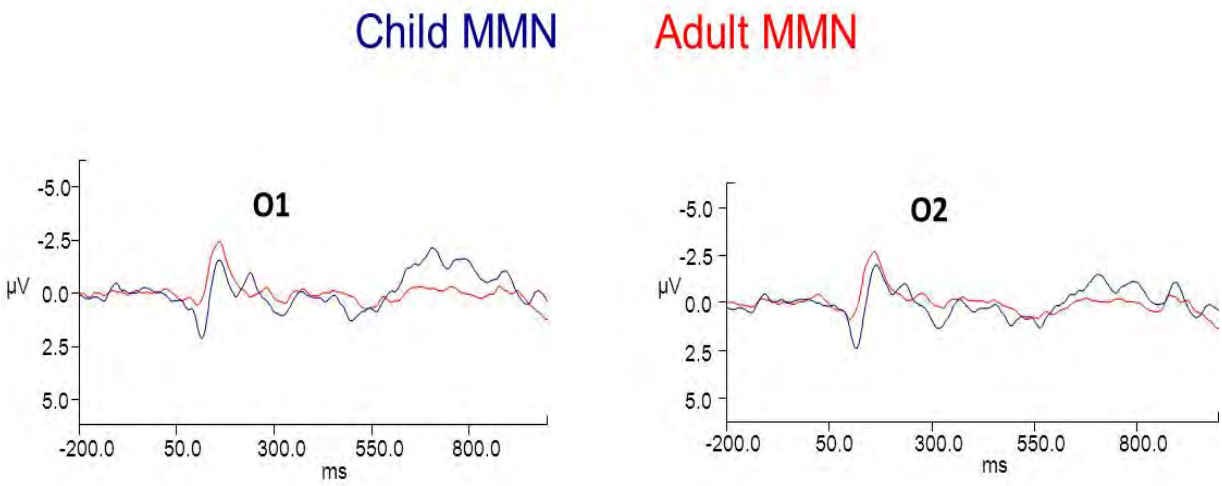

Figure 9: Difference wave (vMMN) computed by subtracting standard nontarget from standard target ERPs for both children and adults at electrodes O1 and O2.

Behavioral Data: Response Rates and Latency for Target Stimuli

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
Rate: Dev Target	Adult	20	1.0000	.00000	.00000
	Child	21	.9690	.05804	.01267
Rate: Std Target	Adult	20	.9890	.03553	.00794
	Child	21	.9548	.05698	.01243
Response Latency (Dev)	Adult	20	498.3400	49.76698	11.12823
	Child	21	589.7594	70.04309	15.28466
Response Latency (Std)	Adult	20	511.7028	50.26686	11.24001
	Child	21	598.3422	57.94139	12.64385

Table 1: Behavioral data for target stimuli in adult and child groups. Indicates percentage of correct targets (rate) and reaction time (latency) for both standard (std) and deviant (dev) target conditions.

GROUP	*TYP CHILDREN*	*TYP ADULTS*
MMN1 AMP O2	-3.26	N/A
MMN2 AMP O2	-3.31	-3.14
MMN1 LAT 02	170MS	N/A
MMN2 LAT O2	251MS	156MS
MMN1 AMP O1	-2.84	N/A
MMN2 AMP O1	-3.18	-3.05
MMN1 LAT 01	163MS	N/A
MMN2 LAT O1	257MS	153MS

Table 2: Mean vMMN latency and amplitude at occipital electrodes O1 and O2 for both negativities observed in the children and the single negativity observed in the adults.

5.2 STUDY TWO

Altered Visual Deviance Processing in Children With Autism: a Visual Mismatch Negativity Study

5.2.1. Introduction:

Autism is a pervasive neurodevelopmental disorder characterized by deficits in language production, social communication, and the presence repetitive behaviors or restricted interests. Repetitive behaviors and restricted interests are sometimes characterized as a preference for "sameness" or an intolerance of change, and pose significant impediments to global functioning and appropriate interactions with one's sensory environment (Gabriels et al. 2005). Preference for sameness and intolerance of change often result in unusual sensory behaviors in autism, which can occur often and have a strong negative impact on individuals with autism and their families (Baranek et al. 2006; Boyd et al. 2010). Recent research has suggested that Event Related Potentials (ERPs) may be used to explain intolerance of change through the investigation of an automatic measure of sensory change detection called mismatch negativity (MMN). Until recently, MMN has mainly been researched in the auditory modality, but recent studies have characterized this stimulus difference wave in the visual modality as well (see Pazo-Alvarez et al. 2003; Czigler et al. 2007 for reviews). Visual MMN is an occipital-parietal negativity computed by subtracting a frequent standard stimulus from a deviant stimulus in the visual modality, usually occurring around 100-250ms post-stimulus presentation. For a detailed discussion of mismatch negativity in the auditory and visual modalities as it relates to autism, see Chapters 1-3. Visual MMN (vMMN) has been primarily studied in typically-developing adults, but some recent studies have begun to investigate vMMN in children as well as clinical

populations.

Several studies have investigated vMMN in various clinical populations when compared to typically developing controls, including Major Depressive Disorder (Qiu et al 2011, Chang et al. 2010), schizophrenia (Urban et al. 2008), Mild Cognitive Impairment and Alzheimer's Disease (Tales et al. 2008), autism spectrum personality traits in sub-clinical populations (Gayle et al. 2012) and autism spectrum disorders (Clery et al. 2013). Currently, little is known about how children with autism process sensory deviance in the visual modality, as only two studies have investigated vMMN in autism, and one of these primarily concerned typically-developing adults. In their study, Clery et al. (2013) used horizontal and vertical deformations in a circle to examine vMMN in a sample of eight-to-fourteen-year-old typically-developing children and children with autism. They found that, while typically-developing children displayed only one prominent occipital negativity around 330ms post-stimulus, children with autism displayed a series of positivities occurring between 50 to 300ms post-stimulus. Clery et al. (2013) found that these latencies were significantly earlier in children with autism, concluding that these children may detect visual changes in their environment more rapidly due to higher cerebral reactivity to sensory deviance.

Investigating the neurobiology of stimulus change in autism may be relevant to behavioral measures of intolerance of change and other symptoms associated with repetitive behaviors. Gomot et al. (2011) found shorter latencies of auditory MMN in children with autism who scored higher on measures of intolerance of change. The authors noted that this latency shortening of MMN seems to be specific to autism relative to other developmental delays, concluding that MMN may be a useful endophenotype for behaviors observed in autism that are related to preference for sameness and

intolerance of change. Previous work in our lab (Donkers et al. 2013, in review) also found relationships between sensory seeking behaviors and early ERP components, particularly P1 and N2, components that are associated with basic sensory detection and discrimination respectively. Related results have been found in other studies outside of ERP research. Perry et al. (2007) also observed a decrease in pre-pulse inhibition in adults with autism with increased repetitive behaviors; these authors hypothesized that inhibitory failure may lead to cognitive and behavioral effects observed in the form of increased repetitive behaviors in autism. Finally, Jones et al. (2009) identified a subset of adolescents with autism with superior performance on auditory duration discrimination tests, and this sample self-reported more auditory sensory behaviors. These studies indicate that intolerance of change may relate to biological measures of sensory deviance processing in the auditory modality. Few studies, however, have investigated these relationships in the visual modality in children with autism, likely because vMMN in autism is not yet well-characterized.

The above studies support the idea of unusual deviance processing in autism; however, questions remain about how vMMN is characterized in these children compared to their typically-developing peers. In a previous study using the same paradigm and same age children, Clery et al. (2012) found multiple negativities in typically-developing children. In addition, a previous study (Horimoto et al. 2002) found similarly unusual peak topography in children with mental retardation, reporting a series of positivities in these children relative to typically-developing controls. More research is needed to characterize the nature of these changes and to understand how they relate to neural processes underlying visual stimulus change processing. In the current study, we used a previously-established auditory oddball paradigm (Cleary et al. 2013, submitted) to investigate vMMN in a sample of children with autism and typically-

developing children, ages eight to twelve.

5.2.2. Materials and Methods

Participants:

We collected EEG data from 22 typically-developing children between the ages of 8 and 12 years (mean age = 10.4, 13 female) and 13 children with autism between the ages of 8 and 12 years (mean age = 10.6, 2 female). Participants with autism had previously received a diagnosis of an autism spectrum disorder from a licensed physician or psychologist. All participants reported no current, past, or family history of substance abuse, no family history of neurological/neuropsychiatric disorders, no seizure disorder with evidence of seizure activity within the past twelve months, no significant physical impairments or limitations, and no history of head trauma or loss of consciousness. All participants reported normal or corrected-to-normal vision. Typically-developing participants had no current, past or family history of any developmental disorder or learning disability and no current or history of antipsychotic use. One typically-developing child was excluded from further analysis due to excessive sleepiness during recording resulting in defective data.

Participants were recruited from multiple venues, including a university-based mass email system and local community and parent groups. Participants received $30 for taking part in the study and a certificate with a graphical image of their brain waves to take home. Minor participants provided written assent while their parents provided parental permission as approved by the UNC Institutional Review Board.

Experimental Procedure:

Task design and electrophysiological recording were identical to that described in Study One (see Study One, section 4.1.2).

Data Processing:

Response latencies and percentage of correct responses were calculated for each subject. All incorrect trials or trials containing responses less than 200 ms and greater than 1000ms from onset of the target were excluded from further analyses. Continuous EEG data was filtered offline with a 30 Hz (24 dB/octave) low-pass filter and visually inspected for movement artifacts, and incorrect behavioral responses were removed from the analyses. EEG data sets from each participant were corrected for eye-movements using regression analysis as implemented in Neuroscan Edit 4.4 (Semlitsch et al., 1986). Continuous EEG data from all channels were epoched using a 100ms prestimulus baseline period and a 500ms poststimulus period. Individual epochs were passed through an automatic artifact detection algorithm to remove epochs with EEG activity in excess of -100uV or +100uV. ERPs were obtained by averaging the baseline corrected EEG epochs for each stimulus category and for each participant. The P1, N1 and MMN were identified by an automatic peak detection procedure, defined as the most positive and negative peak (as appropriate) within a specified window after stimulus onset. For P1 and N1, peak windows were determined based on the relevant peak in a visual inspection of grand averages.

MMN was computed by subtracting the standard nontarget stimulus (HFNT) from the deviant nontarget stimulus (LFNT) and defined as the most negative peak in a specified window. A visual inspection of both grand averages and individual subject data indicated that both groups of children displayed two negative peaks, the first around

150ms post-stimulus and the second around 250ms post-stimulus. Since all children displayed both negativities, we therefore selected both for further analysis, defining the first as the most negative peak within 100-200ms post-stimulus and the second as the most negative peak within 200-300ms post-stimulus.

Given prior research's reports of vMMN as an occipito-parietal negativity, data were analyzed primarily at occipital sites (O1, O2) and also at midline frontal, central and parietal sites (Fz, Cz, Pz).

Statistical Analyses

All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). For behavioral analyses, independent samples T-tests were performed. For between-groups comparisons of P1 and of MMN a preliminary model was fit which considered occipital electrode channels simultaneously using a repeated measures mixed model ANOVA, with the between subject factors of Group (TYP, AUT) and the within-subject factors of electrode location (O1, O2). If group effects or interactions were significant, follow-up repeated measures ANOVAs were fit for each group separately. For the N1, we also performed single channel (Fz, Cz, Pz) one-way ANOVAs, with Group as the between-subject. Analyses were performed for both deviant and standard nontarget conditions. We separately compared both windows for the MMN.

Pearson's product moment correlations were computed to determine the relationship between age and P1, N1 and vMMN amplitude.

5.2.3. Results

Behavioral Data

Mean response rates and response latencies for standard and deviant target

conditions are indicated in Table 3. There was a trend toward shorter response latencies in the autism group (M = 590ms) in the deviant target condition versus the typical group (M = 541ms), but this effect did not reach significance (t = 2.02, p = .052). There were no other significant differences for either standard target response latency or standard/deviant target response accuracy (p > .2 for all conditions).

Between-Group Differences

P1:

For standard nontargets, the mixed procedure ANOVA demonstrated no main effects of Group in terms of either latency or amplitude. However, there was a significant effect of Electrode (F (1, 32) = 7.01, p < .009). Post-hoc within-group tests revealed a significant main effect of Electrode in the typical group with amplitude being larger at electrode O2 (F (1, 20) = 5.99, p = .024). This effect was absent in the children with autism. However, post-hoc within-group tests revealed a trend towards a significant main effect of Electrode in the children with autism with latency being longer at O1 (F (1, 12) = 4.20, p < .063). This effect was absent in the typical children.

For deviant nontargets, the mixed procedure ANOVA demonstrated a trend toward a main effect of Group for P1 latency to deviant nontargets (F (1, 32) = 3.63, p < .066) and a trend toward a significant effect of Electrode (F (1, 32) = 3.86, p < .058). Post-hoc within group tests indicated a trend toward an effect of Electrode in the children with autism in terms of latency, with latencies being longer at O1 (F (1, 12) = 4.18, p < .063). This effect was absent in the typical children.

N1:

The mixed procedure ANOVA demonstrated no significant differences between

groups in either standard or deviant nontargets. However, there was a main effect of electrode for the amplitude of the N1 to deviant nontargets in the children with autism, with O2 being more negative ($F (1, 12) = 5.63$, $P < .035$). Additional between-groups tests at electrodes Fz, Cz and Pz revealed that the latency of N1 was significantly shorter in children with autism at electrode Fz ($F (1, 32) = 11.60$, $p = .002$) and Cz ($F (1, 31) = 5.95$, $p = .020$) for standard nontargets, and was not significant in terms of deviant nontargets.

ERPs to standard and deviant nontargets at electrode positions Fz, Cz, Pz, O1, and O2 are shown in figure 10. A close-up of channels O1 and O2 is shown in figure 11.

Difference wave (MMN):

The mixed procedure ANOVA demonstrated a main effect of Group with respect to the latency of the first negativity of the difference wave, with children with autism displaying shorter latencies at this peak ($F (1, 32) = 4.66$, $p < .038$). No other significant main effects of group were found and no effects of Electrode or Electrode x Group interaction were observed. Additional between-groups tests at revealed that the latency of the first negativity was shorter in children with autism at electrode O2 ($F (1, 32) = 6.74$, $p = .014$). Additional between-groups tests at electrodes Fz, Cz and Pz revealed that the latency of the second negativity was shorter in children with autism at electrode Fz ($F (1, 32) = 5.25$, $p = .029$).

VMMNs for both groups on channel O1 and O2 are presented in figure 12.

Age Correlations

In the typical children, the amplitude of P1 in the deviant nontarget condition decreased with increasing age at electrode O2 ($r = -.447$) (see figure 13). In addition,

the latency of the deviant nontarget N1 also decreased with increasing age at electrode O2 (r = -.655) (see figure 14). Finally, the amplitude of the second negativity of the difference wave decreased with age at electrode O1 (r= .457) (see figure 15). No other significant age correlations were found, including none in the children with autism for any ERP component.

5.2.*4. Discussion*

This study is one of the first to examine visual mismatch negativity in children with autism. One other study (Clery et al. 2013) has investigated vMMN in this demographic, and one study (Gayle et al. 2012) has also investigated vMMN using typically-developing adults who completed the Adult Autism Spectrum Quotient (AQ), a questionnaire measuring autism spectrum personality traits. Gayle et al. (2012) used emotional faces as their stimuli, hypothesizing that the amplitude of vMMN would be increased for emotionally-salient stimuli, and furthermore that this effect would be modulated by the presence of autism spectrum personality traits. They found that higher AQ scores were associated with less sensitivity (i.e. less amplitude increase) to happy faces only, a finding consistent with the idea that individuals with autism tend to have a negative experience of social interaction. Although this study's participants were all typically-developing adults, these findings indicate a possible association with vMMN, affective processing, and severity of autism spectrum personality traits, and is informative for future research that may correlate measures of autism severity with vMMN using populations with an autism diagnosis. This study only found one negativity around 250ms, but the participants were typically-developing adults and the stimuli used were quite complex in comparison to our stimuli, which might account for the differences in peak topography. Indeed, a previous study in our lab (Cleary et al. 2013, submitted)

also found only one negativity of the vMMN difference in typically-developing adults around 150ms post-stimulus. This study used the same stimuli as the current study, so the longer latency compared to Gayle et al. (2012) is likely due to the simpler nature of our stimuli used here. This finding supports the idea of more sequential processing in children compared to adults.

In children with autism ages eight to fourteen, Clery et al. (2013) found a sequence of positivities occurring between 50 and 300ms as compared to typically-developing children, who displayed only one negativity around 330ms. Our results are somewhat congruent with this study, with the main difference being that we found two negativities present in both groups at roughly the same temporal presentation (around 150ms and 250ms). This effect could be due to the relatively simpler nature of our stimuli in comparison to Clery et al. (2013) or differences in our study sample; further research is needed to understand these differences. However, like Clery et al. (2013), we found a trend towards longer latencies of one of the sensory conditions (deviant nontarget) and shorter latencies in the difference wave in children with autism. These shorter latencies varied by electrode location depending on whether the first or second negativity was considered: children with autism processed the first negativity faster at O2, and the second faster at Fz. These results are consistent with the idea that children with autism may be hypersensitive to stimulus deviance in the auditory modality (Gomot et al. 2002, 2011). In addition, although a visual inspection revealed that children with autism appear to have larger amplitudes for the first negativity and smaller ones for the second, this effect was not significant. It is possible that our sample size and the degree of variability obscured this effect. However, it is also possible that differences in visual deviance processing between children with autism and typical development are more focused on latency, indicating that it is speed of processing and not degree of response

that causes visual deviance processing deficits in these children.

Of note, we found that the amplitude of the second negativity decreased with age at electrode O2 in the typically-developing children, but not the children with autism. Other studies have noted maturation of MMN in the auditory modality (e.g. Gomot et al. 2000, Shafer et al. 2000), although these studies typically find either no effect of amplitude or decreasing amplitudes with increasing age; age correlations with auditory MMN are primarily focused on decreasing latency with increasing age (Shafer et al. 2000). Identical effects on latency have also been reported in the visual modality (Tomio et al. 2012). It is unclear why a lateralized, positive age correlation was found here in terms of amplitude, but the fact that this correlation was only present in the typically-developing children may indicate aberrant maturation of visual deviance processing in autism during this age range. Speed of processing (i.e. latency) has been reported to mature more slowly than resources allocated to the processing task (i.e. amplitude) in terms of early ERP components such as P1 and N1 (Batty and Taylor 2002). Interestingly, we found that both the amplitude of P1 and the latency N1 in deviant nontarget conditions mature with age in the typical children, but not in the children with autism. It is possible that our age range results in different observed effects than those of other studies, as Tomio et al. (2012) used a wide range of typically-developing individuals, from preschool children to adults. How developmental maturation affects vMMN in autism merits further study.

We must also consider possible implications for the presence of two peaks in both groups, and what the associated group differences might mean for the processing of visual stimulus deviance in autism. Several previous studies have noted a second, earlier negativity in studies of vMMN in typically-developing adults (e.g. Kimura et al. 2009; Muller et al. 2012; Czigler et al. 2006). These studies hypothesized that the first

negativity may be dependent on exogenous stimulus features, while the second may be more related to a memory-based comparison between the deviant and the standard stimulus. In this view, the second negativity is a true reflection of vMMN and is independent of stimulus features, while the first is a refractory effect of the types of stimuli used (see Kimura et al. 2009; Pazo-Alvarez et al. 2003 for a review). The idea of two negativities and possible implications thereof is discussed more thoroughly in Chapter Four.

It is possible that this process is more incomplete in children, and therefore stimulus feature effects and memory comparison effects are more likely to be represented sequentially (Clery et al. 2012), whereas in adults these two processes are more likely to "fuse" into a single negativity. To this end, we may theorize that children with autism are hypersensitive to visual stimulus features, as evidenced by faster latencies at this first negativity compared to typically-developing children. Although the visually-observed amplitude differences in our sample did not reach significance, it is also possible that children with autism may exhibit greater processing of visual stimulus features and attenuated processing of memory comparison, as evidenced by visually larger first negativities and visually smaller second negativities in this group. This theory may contribute to difficulties in children with autism interacting with their sensory environments (e.g. Baranek 2006), as a preoccupation with features of visual stimuli without developed mechanisms of integrating these stimuli into a comparison with previously-presented stimuli might cause a disturbance in efficient sensory processing. However, more research is needed to further explore this hypothesis.

Some limitations of this study must be considered, particularly the modest sample size, which could obscure effects of vMMN amplitude. The lack of counterbalancing of our visual stimuli also could contribute to effects observed, although

previous research (e.g. Heslenfeld et al. 2002) has suggested that the negativity observed in occipital regions in response to deviance of spatial frequency is independent of stimulus features. Due to the preliminary nature of this study and the difficulty of successfully collecting ERP data in children with autism, we also did not analyze data regarding IQ or autism severity (e.g. ADOS severity scores) in our children with autism, and effects related to mental age differences or overall cognitive functioning cannot be ruled out. Future research should consider these variables to rule out this possibility. Our findings reached significance despite our small and diverse sample, which suggests that further visual sensory deviance studies could significantly inform future autism research. Future work should also consider the relationship between sensory processing deficits and vMMN, as previous work (Gomot et al. 2011; Donkers et al., in review) has shown that ERP components may be related to measures of sensory deficits in autism in the auditory modality.

Despite these limitations, this study is one of the first to examine unconscious processing of rare stimulus deviance in the visual modality (vMMN) in children with autism. Our results confirmed generally shorter latencies of vMMN in children with autism, at least in the first observed negativity in the difference wave, and also added to the small body of literature observing multiple peaks of the vMMN difference wave in children. These results support the idea of sequential visual processing occurring in children that may not yet be mature, and may be altered in children with autism. Specifically, children with autism may be hypersensitive to earlier peaks of this difference wave, and also exhibit attenuated responses to the later components. Future research will confirm if this is the case and, if so, how these components relate to functional aspects of visual deviance processing. With additional research, these findings may help explain sensory processing deficits in children with autism.

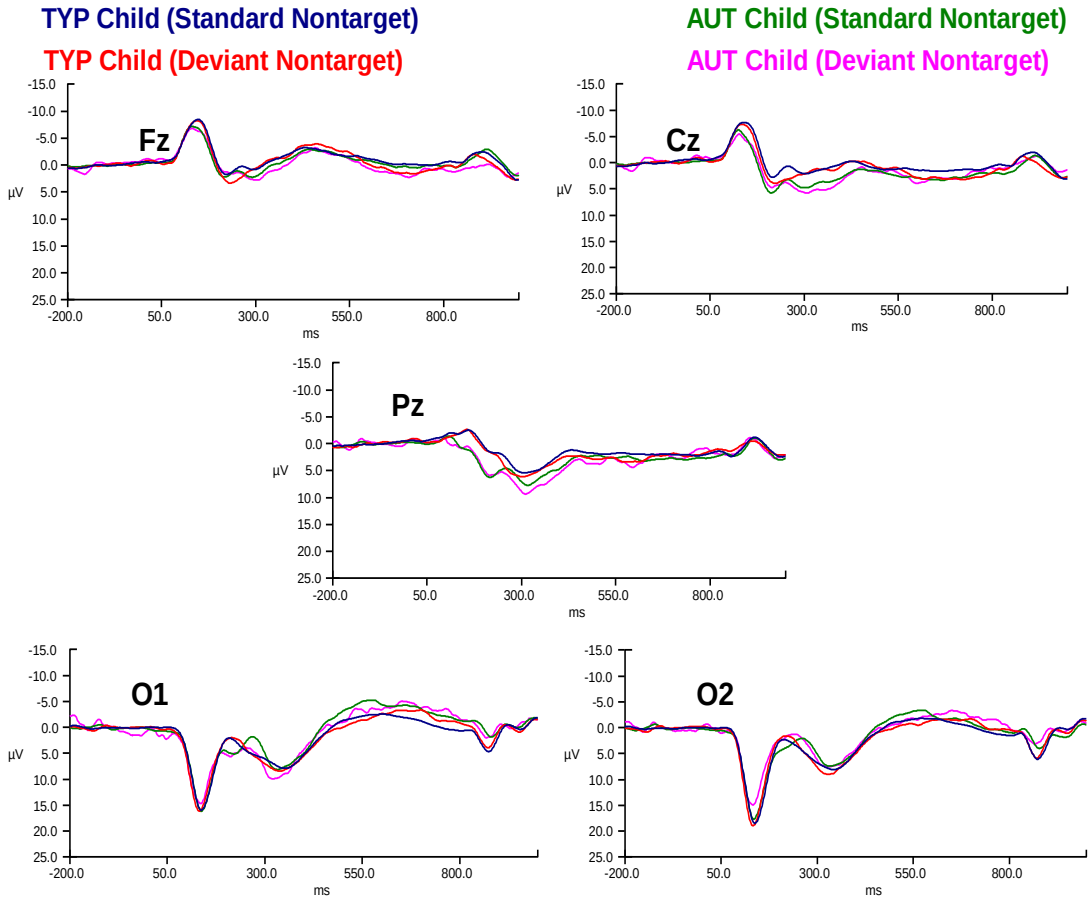

Figure 10: ERPs for both deviant nontarget and deviant target stimulus conditions in typically-developing children (N=21) and children with autism (N=13) at electrodes Fz, Cz, Pz, O1 and O2.

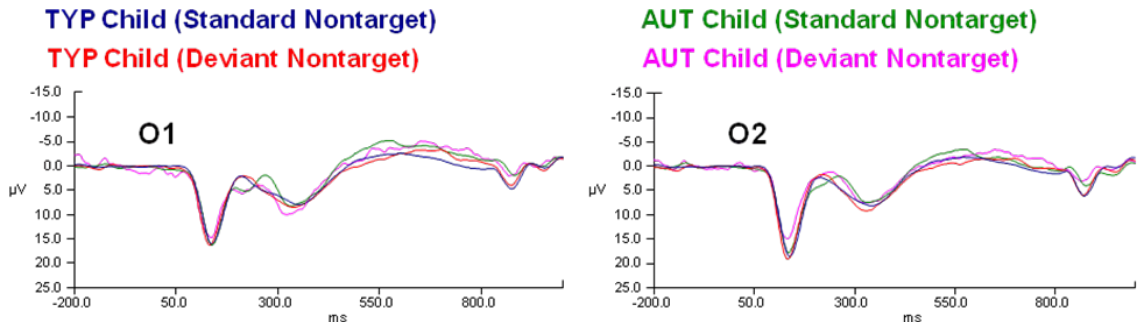

Figure 11: ERPs for both deviant nontarget and deviant target stimulus conditions in typically-developing children and children with autism at electrodes O1 and O2 only.

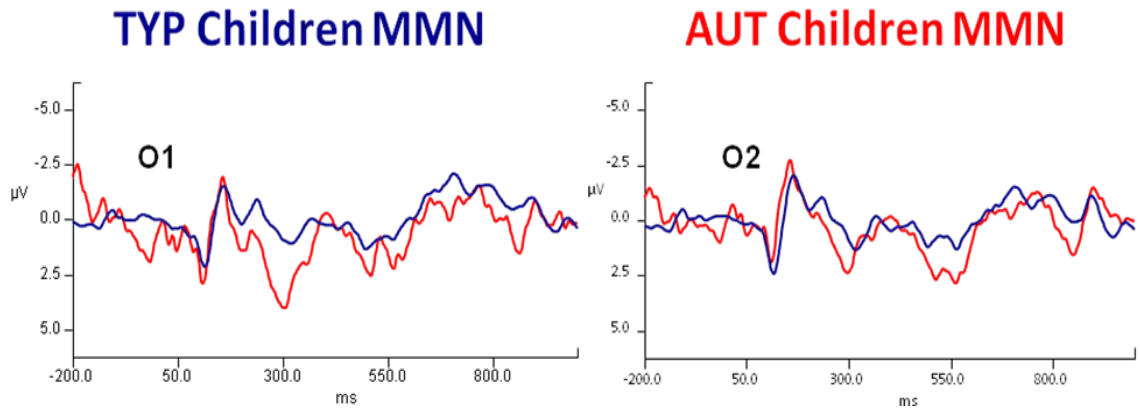

Figure 12: Difference wave (vMMN) computed by subtracting standard nontarget from standard target ERPs for typically-developing children and children with autism at electrodes O1 and O2.

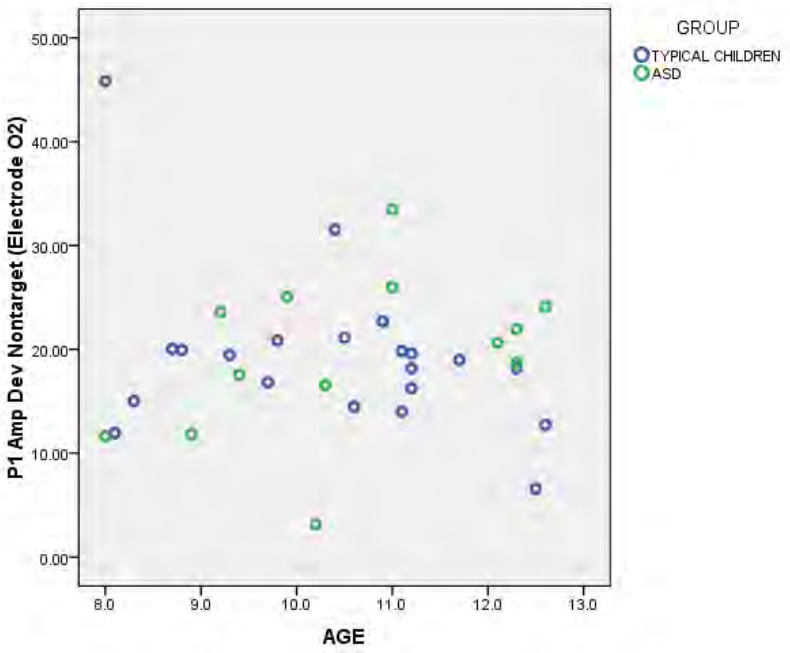

Figure 13: Scatterplot of decreasing P1 amplitude in deviant nontarget condition with increasing age in the typically-developing children at electrode O2.

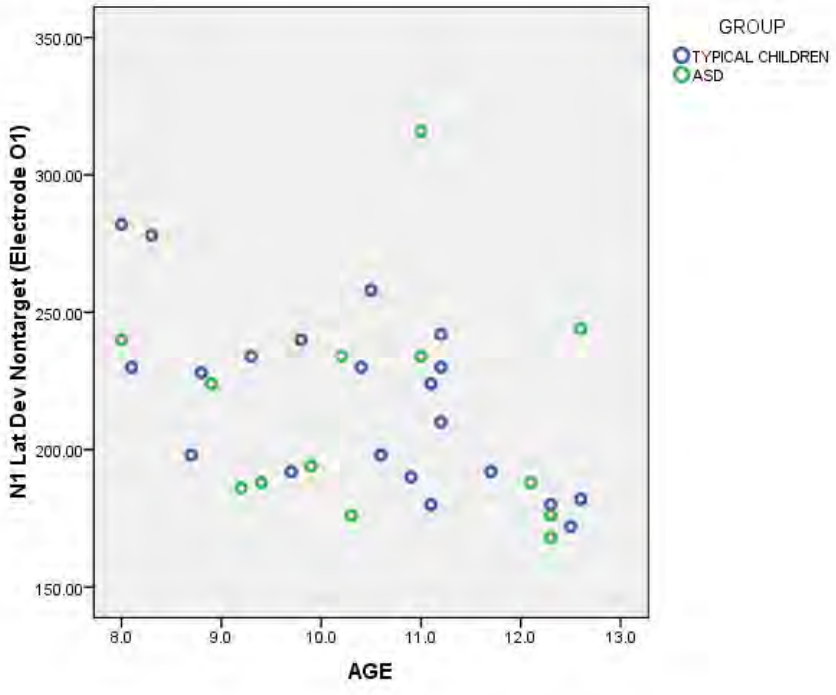

Figure 14: Scatterplot of decreasing N1 latency in the deviant nontarget condition with increasing age in the typically-developing children at electrode O2.

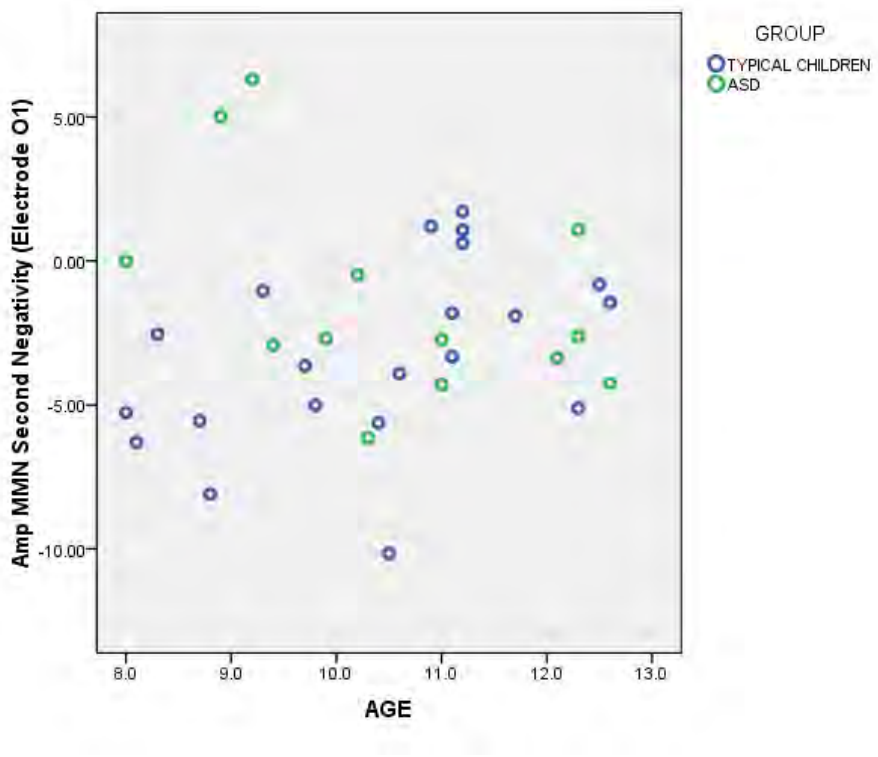

Figure 15: Scatterplot of decreasing amplitude of the second negativity in the difference wave with increasing age in the typically-developing children at electrode O1.

Behavioral Data: Response Rates and Latency for Target Stimuli

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
Rate: Dev Target	2.00	21	.9690	.05804	.01267
	3.00	13	.9538	.07489	.02077
Rate: Std Target	2.00	21	.9548	.05698	.01243
	3.00	13	.9400	.05323	.01476
Response Latency (Dev)	2.00	21	589.7594	70.04309	15.28466
	3.00	13	541.7442	62.87417	17.43816
Response Latency (Std)	2.00	21	598.3422	57.94139	12.64385
	3.00	13	571.0427	73.89141	20.49379

Table 3: Behavioral data for target stimuli in typically-developing children and children with autism. Indicates percentage of correct targets (rate) and reaction time (latency) for both standard (std) and deviant (dev) target conditions.

CHAPTER SIX: DISCUSSION AND CONCLUSIONS

6.1: Novelty of current studies and significance to literature

The previously-discussed series of studies has investigated sensory deviance processing of the auditory and visual modality in typically developing children, typically developing adults and children with autism using ERP. These studies are unique in several ways. First, Study One is one of the first studies to investigate development of the visual MMN in children. A small number of previous studies (Tomio et al. 2012; Clery et al. 2012) have investigated vMMN in this population, but this study is the first to use spatial frequency as visual stimuli while also probing only a single stimulus dimension (i.e. form and not motion). This allows us to answer a question posed by Clery et al. (2012) concerning whether the separate neural correlates of form and motion processing led to multiple negativities observed in their study. We found multiple negativities in the children in our study using manipulation of form (spatial frequency) alone, indicating that manipulations in both form and motion simultaneously cannot fully explain this apparent sequential visual processing in children. Our typically-developing children participants were also nearly exactly the same age as those in Clery et al. (2012)'s study (i.e. mean age of 10.4 years in the current study versus 11 years in Clery et al.), reducing the possibility of different developmental periods affecting the results. It is worth noting that Clery et al. (2012) had a slightly broader age range (8-14 years) than in the current study (8-12 years). However, given that the adults tended to express a single negativity, the addition of slightly older subjects likely did not contribute to the observation of these multiple negativities. This study also adds to the growing literature

concerning the development of the ventral and dorsal visual pathways in young children, and suggests that the dorsal pathway matures more slowly in typical development. This confirms previous study findings (Clery et al. 2012; Kovacs et al. 1999) on the immaturity of the dorsal pathway, but also has implications for previous research (e.g. Batty and Taylor 2002) that indicates the ventral pathway may mature more slowly in school-age children. It will be important to consider carefully the stimuli used in developmental visual MMN studies, and paradigms that probe both pathways will be necessary to fully answer this question.

Second, Study Two is one of the first studies to investigate visual MMN in children with autism. Only one previous study has investigated vMMN in this population (Clery et al. 2013), and this previous study also used both form and motion as stimulus deviants. This again poses the question of whether these two deviants in the standard visual stimulus influenced the sequential nature of processing implied by the appearance of multiple peaks in the autism group. Furthermore, in this study the typically-developing children only displayed a single negativity, which has implications for Clery et al.'s (2012) previous study in which multiple negativities were found in this group. In our study, we found two negativities in both typically-developing children and children with autism, and furthermore these negativities followed generally similar peak topography in terms of latency and amplitude. This could indicate that changes in form are more constant in this age group in general and therefore more likely to be expressed consistently, as Clery et al. (2012) hypothesized that perhaps changes in motion are associated with a separate neural generator that matures later in typical development. We also found that, while there was no statistically significant amplitude difference in either negativity, children with autism had shorter latencies in terms of the first negativity. This result agrees with Clery et al. (2013)'s findings that children with autism had generally faster

processing of form and motion deviance, and also agrees with the literature in terms of auditory MMN studies in children with autism (e.g. Gomot et al. 2002; 2011). This has implications for multisensory studies of MMN in children with autism, as the shortened latency of the MMN seems to be a unique trait to this population and can be found in at least two sensory modalities. Furthermore, shortened latency of the auditory MMN has been associated with increased intolerance of change (Gomot et al. 2011), indicating that repetitive behaviors might be probed using this aspect of the auditory difference wave. It remains to be seen whether this concept applies to visual MMN, but future research should focus on measures of repetitive behaviors, perhaps especially linked to the visual modality, to answer this question. Finally, we found significant positive age correlations in the amplitude of the second negativity of vMMN in typically-developing children, but not in children with autism. To our knowledge this is the first study to investigate age correlations of the vMMN in children with autism, and the presence of this correlation in the typically-developing children only suggests possible maturation dysfunction in children with autism of primary visual areas. Other studies have observed a decrease in vMMN latency in typically-developing children with an increase in age, but this is the first study to both report on amplitude correlations of the vMMN in children and to note the lack of this correlation in a clinical population. It is unclear what biological mechanisms underlie this maturation effect, and this study should inform future research probing age-related changes in visual processing in children with autism. In any case, we have noted some form of abnormal development in terms of strength of response to visual deviancy in children with autism. If this second negativity is indeed a measure of memory comparison (see Chapter Five, section 2.4, discussion), this could imply underdeveloped mechanisms of sensory memory and supports the idea of Weak Central Coherence theory (Frith 1989, see section 6.3).

Third, findings presented in the Preliminary Data are the first to compare aggregate scores of sensory features across three different response patterns (e.g. hyporesponsive, hyperresponsive and sensory seeking behaviors) with early components of the ERP in children with autism. While one other study (Gomot et al. 2011) has correlated behavioral measures with ERP, in this previous study only a single questionnaire was used and only certain items related to the study's hypotheses were included in correlational analyses. It is possible that our study provides a more complete model for measuring sensory features in autism. Hyporesponsive, hyperresponsive and sensory seeking behaviors often co-occur and can be paradoxical in nature (Boyd et al. 2010); for example, a child could have high levels of hyporesponsiveness and also high levels of hyperresponsiveness, either in two different modalities or in the same modality. The methods presented here included both observational and parent report measures of sensory features that provide more detailed information about a particular child's sensory processing deficit severity than studies using a single questionnaire as the sole predictor. In addition, we also found that parent reports were not correlated with any ERP components and had much weaker associations in all comparisons; this calls into question using reported measures in place of observational measures in studies seeking to draw correlations with ERP components. It is possible that our model is too complex to probe individual questions of specific sensory dimensions, such as our simple auditory tones presented in Preliminary Data (see 6.2, limitations). In this case it might be instructive to parse out individual measures such as the SPA for purposes of correlations with ERP components in future studies; items on a particular observational measure could even be separately compared based on their similarity to the sensory modality probed in a particular ERP paradigm (e.g., auditory items). The fact that our study found no significant correlations between parent report measures and ERP components

suggests that these behavioral measures of sensory features may not be sufficiently sensitive for ERP research or that power was insufficient to detect more subtle effects. This has implications for future research that intends to draw connections between observed behavior and ERP components.

6.2: Limitations of current studies and potential solutions for future work

There are also several limitations to this work. First, Studies One and Two did not counterbalance the sensory deviant conditions, so stimulus effects of differing spatial frequencies cannot be entirely ruled out. Although previous research has indicated that the change observed in occipital regions to spatial frequency deviations in our given latency range was independent of stimulus features (Heslenfeld 2002), it is still possible that an exogenous sensory effect exists. This question could be answered by varying whether the low or high spatial frequency would serve as the deviant condition by trial. The reasons for choosing not to counterbalance these deviant stimuli, and why it is likely that this contribution did not significantly alter our results, are detailed in Chapter Five, section 1.4, Discussion.

There are also some remaining questions regarding differences in processing of different spatial frequencies in children with autism as a group. Previous research (Koh et al. 2010) has found no differences in spatial frequency processing between adolescents with autism and their typically-developing peers in terms of visual acuity, contrast sensitivity, the spatial frequency producing the peak contrast sensitivity, and the contrast sensitivity at that peak. There is behavioral evidence that children with autism process high spatial frequencies differently (Deruelle et al. 2004) and are superior at matching faces based on high spatial frequency versus low, but this research is mostly

focused on face processing in the central visual field and therefore likely activates different neural generators. Finally, there is ERP evidence that children with pervasive developmental disorders display atypical processing of high frequencies, leading to attenuated differences between high and low spatial frequency processing (Boeschoten et al. 2007). Our deviants were low spatial frequencies, making it less likely that we would observe amplitude differences between groups and even less likely that atypical high spatial frequency processing confounded our results. The "high" spatial frequencies used in Boeschoten et al. (2007)'s study were also much higher than our stimuli (six cycles per degree), which could have strengthened the effect observed in their results. While ERP processing of different spatial frequencies in autism was beyond the scope of this research, future research counterbalancing the two stimulus conditions and investigating the level of stimulus contrast necessary to elicit vMMN in both typically-developing children and children with autism would definitively answer this question.

Another limitation concerns the lack of behavioral and autism severity data with respect to our autism population in Study Two. While all subjects had previously received a diagnosis of an autism spectrum disorder by a licensed clinician, these diagnoses varied in type and severity, and it is not possible to determine whether our effects are due to general cognitive deficits or autism per se. Future studies should consider measures of IQ and mental age as well as autism severity and co-vary for these measures. It is important for future studies to answer this question, as previous work (Naatanen et al. 2012) has hypothesized that changes in the auditory MMN could be related to general cognitive decline rather than certain deficits (i.e. deficits of language) associated with a particular disorder. Whether this applies to the visual modality remains to be seen. We did not obtain this data due to the preliminary nature

of our study, but our findings open the door to future studies relating autism severity and symptom presentation to vMMN abnormalities. Preliminary Data, discussed below, provide a framework for future research of this nature in the visual modality.

Limitations of our Preliminary Data (Chapter 3) consist mainly of the stimulus parameters chosen, inevitable selection effects of our population, and the applicability of our observational and parent report measures to the auditory ERP paradigm. It is possible that group differences in the frequency deviant condition were not found due to the small (100Hz) difference between the two tones. While other studies have been successful obtaining auditory MMN from similar populations with this frequency deviance (e.g. Gomot et al. 2000, 2002), some other studies have used 1000Hz as the standard and 1200Hz as the deviant (e.g. Dunn et al. 2008). In addition, although the video played during the task was at a low volume (>60dB) and lower than all tones presented (80dB) it is possible that the video's sound interfered with auditory processing of the stimulus tones, especially since self-chosen videos are highly salient in this population. A potential solution to this might be to play a silent cartoon that would still maintain the subjects' attention. We hypothesized that video noise may have interfered with our ability to obtain and measure the auditory MMN (Mahajan and McArthur 2011), so this strategy might allow for future research to investigate this difference waveform.

In addition, as reported in Chapter Three, children with more severe sensory scores were less likely to enroll in the auditory ERP study (see Preliminary Data; Chapter 3), and these children who did enroll were more likely to elect either to stop the study before enough data was collected, or to complete the study but with unusable data. This is due to the high sensory demands the ERP procedure requires, including the capping process, placement of VEOG and HEOG recording electrodes, insertion of electrogel and mild abrasion of the scalp, and the necessity to remain very still and

relaxed during EEG recording. Solutions to this limitation include behavioral management practices and training of ERP technicians to complete the experimental setup while minimizing stress on the child. We used strategies including social stories read to the children prior to the experiment, a "practice" nonfunctioning EEG cap mailed to the child's family 1-2 weeks prior to their appointment, and in-lab practice with the materials including role-play with parents and experimenters. It is possible that, with this continued training, we will be more successful at collecting data from children with more severe sensory scores. We began data collection for Preliminary Data in 2006 and continued through 2012, so an analysis of successful data collection by sensory score severity and year of EEG would be helpful to assess our improvement in this area.

Finally, it is possible that the observational and parent report measures used in this study are too complex to detect discernable relationships using a simple auditory ERP paradigm. Our ERP paradigm probed only a few types of auditory stimuli, all of them only 200ms in duration and mostly consisting of tones. By contrast, our observational and parent report measures reflect complex behavioral constructs that probed a variety of sensory modalities, each in several different ways. For example, parents are asked about a child's behavior in response to loud noises (e.g. ambulance, vacuum cleaner) and children are exposed to noisy toys in the laboratory. There are also a large number of items that probe other sensory modalities, such as tactile stimulation (e.g. lotion on the hands) and visual stimulation (e.g. flashing lights). It is possible that correlating only certain items that are most relevant to our ERP task may produce different results. Such a strategy was employed by Gomot et al. (2011) in their comparison of auditory MMN and autism symptoms, in which they considered only the most relevant items such as bizarre responses to auditory stimuli and intolerance of change. Finally, it should be noted that many items, particularly on parent report

measures, reflect aversive responses to stimuli, either in the auditory modality or others. The sounds used in the ERP paradigm were not aversive, and no child failed to complete the experiment due to a negative reaction to the auditory stimuli. It is possible that the behavioral auditory measures probe a different or more salient type of sensory processing deficit than does a parent report measure. This question could, again, be answered by more selective comparisons of items to ERP components, or perhaps by introducing auditory stimuli more similar to those that traditionally provoke a negative response in these children.

6.3: Potential clinical impact of current and previous studies

The results of Study Two are relevant in terms of the Weak Central Coherence theory of autism (Frith 1989), which states that individuals with autism tend to focus on smaller details of their environments rather than a cohesive whole. We have hypothesized that the two negativities displayed in both child groups represent different aspects of sensory perception that are sequentially processed in 8-12-year-old children in comparison to more uniform, streamlined processing in adults. In this view, the first negativity may represent differences in exogenous stimulus features while the second represents a memory-based comparison of previously-presented standard stimuli and currently-presented deviant stimuli (Kimura et al. 2009). If this is the case, it appears that children with autism display greater speed of processing only in the case of the first negativity, and therefore have enhanced perception of sensory details of spatial frequency. However, this was not the case in the second negativity. There were no significant differences in latency or amplitude of this peak, but a visual inspection of grand averages reveals that the amplitude of this second negativity appears smaller in

the children with autism. There are several reasons why this finding may not have reached significance, including low statistical power due to a small sample size, and high levels of variance in the children with autism. However, in the second negativity there was a difference of 1.8uV in the case of electrode O1 and 1.0uV in the case of electrode O2, and this finding may merit further exploration with different sample sizes and measures of severity. While also not significant, the first negativity was visually smaller in amplitude in children with autism only at O1 (0.9uV difference), but nearly the same at O2. This seems to suggest somewhat more responsive processing of the first negativity in the children with autism; a significantly faster latency at this negativity suggests that, if anything, these children process this first negative peak more quickly than typically-developing children. If the second negativity does indeed represent memory-based comparison as hypothesized by Kimura et al. (2009), it seems that children with autism are less efficient at comparing a previously-presented standard with currently-presented deviants.

Regardless of the visual amplitude differences implied by the grand averages, it is clear that children with autism display faster latencies of the first negativity, which may imply greater processing of smaller environmental details and a stronger "refractory effect" (Pazo-Alvarez et al. 2003). Such ability would strengthen the idea that children with autism display enhanced local stimulus processing, which is a re-structuring of Weak Central Coherence theory that is less focused on global processing weaknesses and more focused on local processing strengths (Mottron et al. 2006). This idea proposes that the "default setting" of perception in individuals with autism is more oriented toward local stimuli than that of typically-developing individuals, an ability demonstrated by superior performance on tasks where global processing conflicts with local analysis, such as hierarchical tasks, e.g. the arrangement of blocks into possible

and impossible figures (Mottron et al. 2006). Indeed, young children with autism are more likely to engage in lateral eye movement toward peripheral objects, which is associated with the dorsal pathway's perception of fine visual details and movement, and may reflect a need to filter unnecessary details and better focus on a task (Mottron et al. 2006). It is possible that the results of Study Two point primarily to an enhancement of local processing of visual stimulus features rather than an attenuation of global processing in terms of memory comparison. The fact that these shorter latencies in the first negativity reached significance when the large visual amplitude differences found in both occipital electrodes for the second negativity did not further supports this hypothesis. Furthermore, children with autism may be able to process global information with increased effort or different strategies despite a bias toward local processing (Rajendran and Mitchell 2007). Early primary sensory areas may be more enhanced in children with autism (Mottron et al. 2006), and vMMN is hypothesized to have neural correlates in right occipital visual extrastriate cortex, right medial and, in the case of memory-based comparisons, right lateral prefrontal areas (Kimura et al. 2009; 2011). It seems most likely that generators in prefrontal areas would be affected by this second negativity, which could help explain differences in visual deviance processing in children with autism. It is possible that while functioning of primary visual areas are intact or even enhanced in children with autism, medial and lateral prefrontal areas may be altered either per se or in terms of connectivity (Just et al. 2004). Previous fMRI data in our lab (Carpenter 2011) indicates that increased arousal facilitates target detection in individuals with autism, but impairs their ability to discriminate between target and non-target events. Carpenter (2011) hypothesized that this occurred due to attenuated engagement of frontal cognitive control and selective attention circuitry in individuals with autism. This could suggest impaired frontal circuitry in visual discrimination associated

with earlier processing such as vMMN.

It is also possible that stimulus type may play a role in the results of Study Two. Our stimuli were designed to probe the dorsal pathway of visual information processing, but many other studies have probed the ventral pathway using deviations of color (e.g. Czigler et al. 2006) and facial emotions (e.g. Stefanics et al. 2011). Of the few studies that have examined vMMN in typically-developing children or children with autism, none have yet used stimuli that activate the ventral pathway. There is evidence that these types of stimuli are processed differently, and some studies differ on which pathway matures first in typical development (Batty and Taylor 2002; Kovacs 1999; Clery et al. 2012). Paradigms that utilize both dorsal- and ventral-oriented stimuli (e.g. Berti 2009) in these populations may help to answer this question. Based on previous research, it is most likely that children with autism will have more typical or even enhanced responses at the early, stimulus-features negativity using stimuli that probe the dorsal pathway in vMMN paradigms compared to those that probe the ventral pathway. Concerning the ventral pathway, there is also evidence in sub-clinical adult populations that a lessened response to certain deviant face emotion stimuli is associated with more autism spectrum personality traits (Gayle et al. 2012). Future studies should investigate this possibility in children with autism to test our hypotheses concerning multiple negativities of vMMN in these groups, and the possible underlying neural and functional deficits.

Findings from our Preliminary Data (Chapter 3) demonstrated that observed sensory seeking behaviors are related to amplitudes of N2 and P3a in children with autism, and further that these amplitudes are modulated by the early P1 component. Specifically, attenuated N2 amplitudes predicted more severe sensory seeking behaviors, given lower amplitudes of P1, and attenuated amplitudes of P3a predicted more severe sensory seeking behaviors given higher amplitudes of P1. This

demonstrates that both bottom-up and top-down processing have effects on behavioral characteristics related to observed sensory seeking behaviors. Particularly, the relationship of P3a with P1 and sensory seeking behaviors implies that disruptions in neural attentional orienting responses are associated with more severe sensory processing deficits. Disrupted attentional mechanisms may diminish responses to novel stimuli, and therefore some children with autism may appear preoccupied with intense and repetitive sensory activities because they are unable to disengage and refocus on other environmental events. This could also occur due to a disruption in reward pathways, whereby disrupted attentional mechanisms lead to hyper-engagement on existing stimuli, especially in the case of sensory-driven activities. P1's modulation of both of these effects demonstrates the potential influence of early sensory deficits with later, higher-order aspects of sensory processing such as orienting to novel stimuli.

Overall, findings from Preliminary Data indicate that there appears to be a subgroup of children with autism who are particularly vulnerable to sensory seeking behaviors, identified by both early (i.e. P1) and late (i.e. P3a) neural responses to auditory deviance. It is possible that these children especially may benefit from sensory-based interventions (Baranek 2002). Perhaps, such basic sensory interventions have the potential to improve orienting responses and the ability to disengage from maladaptive sensory seeking experiences. Since P3a was only predictive of sensory seeking severity at higher levels of P1, it is possible that these children detect basic sensory information more saliently and that this impacts their ability to orient to novel stimuli. It has been suggested that early processing in the visual modality indeed affects sensory gain control, which is the amplification of ERP response amplitude when attention is directed toward a stimulus (Hillyard et al. 1998). Future research should focus on both clarifying the findings from Preliminary Data (Chapter 3) by addressing its

limitations (see section 6.2) and testing whether similar findings exist in the visual modality. Regardless, the identification of several complex ways in which ERP components predict sensory seeking behavior severity has clinical implications in the form of addressing more basic sensory detection deficits in children with autism who may be particularly vulnerable to sensory seeking behaviors.

6.4: Future directions in light of current studies

The current studies have provided valuable information about how visual deviance is processed in typical development, as well as how visual deviance processing differs in children with autism. These studies have also provided information on the relationship of auditory ERPs to sensory features, and several aspects of this research could inform future studies in related areas. Specifically, future studies should consider types of deviants in vMMN studies, including letter versus non-letter deviants; investigate the role of early ERP components such as P1 on both sensory features and later ERP components; continue to study the neural correlates of attentional orienting and their relationship to the MMN; and consider the relationships between vMMN and sensory features in autism. Overall, future research in both MMN and sensory processing deficits should take into consideration multimodality approaches; the prospect of combining auditory and visual deviance studies holds the potential to answer more fully how sensory deviance is processed in typical development and in autism. These concepts are discussed in more detail in the following two sections.

6.4.1: Future directions in Visual and Auditory MMN

These studies provide strong evidence for multisensory investigations of MMN as well as continued investigation of visual MMN in children with autism. We know from previous studies that aMMN and vMMN are not the same in language-related audiovisual tasks (Froyen et al. 2010), and that this may be due to the arbitrary value of visual language as opposed to auditory language. However, we also know that non-letter and even meaningless auditory and visual stimuli can alter MMN in healthy subjects (Froyen et al. 2010; Besle et al. 2005). The results from Preliminary Data (Chapter 3) have shown that the sensory deficits underlying sensory seeking behaviors in autism may be much more fundamental than previously thought, with between-groups differences found even in response to standard tones, and a strong influence of P1 on the ERP predictors of sensory seeking severity. Future studies investigating letter and non-letter deviants paired with congruent and incongruent auditory stimuli (see Froyen et al. 2010) in children with language deficits may help to answer how auditory and visual MMN interact in this population.

The P1 is clearly an important component in our auditory paradigm, with its amplitude modulating sensory seeking severity prediction for both N2 and P3a. In Study Two, we found significant differences at P1 only in terms of the latency of deviant non-targets, and did not find any amplitude group differences. However, this does not necessarily mean that P1 does not play a role in vMMN. Indeed, we hypothesized that the large differences in the amplitude and latency of P1 in Study One contributed to the multiple negativities observed in children, compared to the single negativity observed in adults, in terms of the difference wave obtained. In the case of Study One, it would be interesting to determine the interaction of P1 on the MMN in either dataset by separating

out high and low amplitudes of P1 in the children and comparing them to the adults. A similar goal could also be accomplished in Study Two by separating children with autism with higher amplitudes of P1 and those with lower amplitudes of P1, and comparing them to typically-developing children. It is possible that this earlier sensory component modulates the relationship of vMMN in children with autism, given that the study presented in Preliminary Data (Chapter 3) found relationships between P1, N2 (occurring around the window where aMMN would normally be obtained) and sensory seeking severity. Relating P1 amplitudes to auditory MMN in a future study where the limitations discussed in section 6.2 are accounted for could also further explain the relationship of this early component to later measures of stimulus deviance, as well as determine if such relationships are similar across modalities. Finally, the question of latency's influence on vMMN versus aMMN should be further investigated, as at first glance it appears to be much more relevant to vMMN group differences in children with autism and typically-developing children. However, other studies (Gomot et al. 2000; 2002; 2011) have indeed found differences in aMMN latency in children with autism and typically-developing children, so this concept merits further study at the level of ERP components per se, as well as comparison with sensory features. Limitations of Preliminary Data as discussed in section 6.2 could also account for this lack of effect, and the results of Study Two as well as previous aMMN research indicate that it should be further investigated in the auditory modality.

Overall, more research is needed concerning developmental MMN in the visual modality to determine the topography of this difference wave in children, especially in terms of number of negativities. Our results are somewhat similar to Clery et al. (2012)'s report of multiple negativities in typically-developing children, implying sequential processing of deviant visual stimuli; however, we only observed two negativities at rather

standardized timepoints and locations (i.e. occipital negativities around 150 and 250ms). Differences in stimuli and paradigm may account for these discrepancies; as hypothesized in Chapter Four (section 1.4, discussion), deviations in motion in Clery et al. (2012)'s paradigm may have probed different neural generators versus static stimuli that only deviate in form. However, further research is needed to test this hypothesis. Similarly, more research is needed to determine the nature of vMMN in children with autism, as our findings differed from Clery et al. (2013). The fact that this later paper found different results for same-aged typically-developing children may imply that the early negativity observed in this group is less stable across recording sessions, even in similar age groups. Moreover, our children with autism displayed a difference wave very topographically similar to typically-developing children in terms of number of peaks and peak latency windows; however, Clery et al. (2013) found sequential positivities at very different timepoints in this group of children in their study. This may, again, be due to the nature of stimuli chosen, as Clery et al. (2012, 2013) used deviations in both motion and form, and our stimuli were not dynamic. Future research examining dynamic stimuli may help to answer this question.

Finally, stimulus type may play a role in terms of visual pathway activated; our stimuli (and that of other papers investigating vMMN in children) primarily activated the dorsal pathway, which is known to be more concerned with peripheral stimuli and motion detection. It is possible that our hypotheses concerning the functional relevance of the two negativities observed in Study One and Study Two could be further tested by using paradigms that activate the dorsal and ventral pathways separately. Deficits in dorsal stream functioning have been reported in autism, while the ventral stream is either relatively intact or is often accompanied by ventral stream dysfunction (Macintyre-Beon et al. 2010), although these deficits seem especially apparent in terms of motion

processing (Spencer et al. 2000). These principles could explain both the differences found in Study Two and Clery et al. (2013) and the functional relevance of the two negativities observed in Study One and Study Two. It is possible that using stimuli that probe the ventral pathway (i.e. deviations in shape or color in the central visual field), as well as varying static and dynamic stimuli, could reveal specific stimulus conditions under which children with autism differ in one of these negativities with respect to typically-developing children. Based on previous work, dynamic stimuli activating the dorsal pathway are likely to produce the most deficits in the second, memory-comparison negativity, with these deficits less apparent in static stimuli activating either the ventral or dorsal pathway. Future studies varying the deviant stimulus on two conditions (i.e. static vs dynamic and dorsal vs ventral) would help answer these questions and clarify the stimulus features/memory-comparison hypothesis.

6.4.2: Future directions in investigation of sensory features

Through the current research and the findings of previous studies, we have a stronger knowledge base of underlying neural mechanisms of sensory deficits in autism, particularly sensory seeking behaviors. It is now clear that the relationships between auditory ERP components and sensory seeking behaviors is complex and involves P1's early sensory detection modulation of the later components N2 and P3a. We still do not know how, if at all, hyporesponsive and hyperresponsive behaviors relate to ERP components in the auditory modality, nor do we know how these findings may apply to the visual modality. In addition, it is unclear if simpler measures of sensory features, such as single items related to the modality and stimulus types of interest, might provide a more complete picture of the neurobiology of sensory processing. Other research has

drawn parallels between repetitive behaviors and superior auditory discrimination (Jones et al. 2009), repetitive behaviors and decreased PPI response (Perry et al. 2007) and intolerance of change and reduced latency of auditory MMN (Gomot et al. 2011). Future research in auditory ERP should focus on auditory items that may reflect sensory seeking behaviors in particular, such as failure to disengage with a toy that makes a musical sound. The current studies have demonstrated that neural correlates of sensory seeking behavior may focus on deficits in attentional orienting, reward circuitry, and early sensory detection mechanisms. Tasks that probe these specific constructs will help to further answer which types of sensory seeking behaviors are most relevant to ERP components. Addressing the limitations discussed in section 6.2 will also make it more likely that sensory features can be correlated with the auditory MMN, which has been demonstrated to be behaviorally relevant in autism in at least one previous study (Gomot et al. 2011). For this reason, future work should also focus on latency differences of both individual ERP components and their resulting difference waves. This is especially in light of the results of Study Two, which found several latency differences between typically-developing children and children with autism. Speed of processing may play a role in auditory sensory processing that the paradigm used in Preliminary Data (Chapter 3) perhaps was not sensitive enough to measure.

It is also unknown what relationship, if any, ERP studies in the visual modality may have to sensory features. Sensory features in the visual modality may manifest in discomfort with lights, particularly bright lights, and children with autism who have low auditory threshold sensitivity also tend to have low visual threshold sensitivity (Kern et al. 2006). Children with sensory features in the visual modality may display atypical, increased, or decreased orienting or attention to novel visual stimuli, may exhibit atypical responsiveness or fixation on visual stimuli, or may show abnormally high levels of

aversion to visual stimuli (Baranek 1999). These children may have unusual fascination with shiny objects, get unusually excited at seeing objects spin, may twist or flick their hands near their eyes, or become unusually fascinated by looking at objects from many different angles (Leekam et al. 2007). Like sensory features in other modalities, these unusual behaviors tend to decrease in frequency with increasing age (Kern et al. 2006). Previous research has found differences in visual sensory features between children with autism and typically-developing children (Leekam et al. 2007). In addition, it is known from retrospective video analysis that infants with autism tend to exhibit less orientation to novel nonsocial visual events than either typically-developing children or children with other non-autism developmental delays; however, infants with autism tend to exhibit less visual fixation on objects than infants with other developmental delays (Baranek 1999). This is especially relevant in light of the results from our Preliminary Data (Chapter 3), which showed that more severe sensory seeking behaviors are associated with attenuated amplitudes of P3a, given high amplitudes of P1. It is possible that a similar mechanism could be taking place in the visual modality, with early sensitivity to basic sensory detection mechanisms (i.e. larger P1 amplitudes) modulating P3a response levels' prediction of visual sensory seeking behavior severity. Because target stimuli were beyond the scope of Studies One and Two, we did not report on P3a data in this particular study, but future research could attempt to uncover relationships between this component and visual sensory seeking behaviors. In particular, association with specific items on behavioral measures of sensory seeking that are most relevant to visual processing would allow for a more direct examination of this modality, similar to Gomot et al. (2011)'s approach in the auditory modality.

Finally, the relationship between sensory features in the auditory and visual modality, as well as their relationships with associated ERP correlates, should be

considered. Mechanisms of shifting attention between auditory and visual modalities may have similar neural sources in the cerebellum, and the neural response to these types of stimuli can greatly exceed that of a visual or auditory stimulus alone (Iarocci and McDonald 2006). The recent audiovisual MMN studies (e.g. Froyen et al. 2010) are uniquely positioned to examine how these two modalities interact in the vein of sensory processing. In the future, MMN studies could move beyond the auditory and visual modalities into somatosensory investigations, as previous research (Restuccia et al. 2009) has indicated it is possible to obtain an MMN to tactile stimulation differences in typically-developing children. Sensory features in the tactile modality are more likely to persist into adulthood than even those in the auditory or visual modalities (Kern et al. 2006), so research into this area has the potential to better understand sensory processing deficits across the lifespan.

6.5: Conclusions

Although sensory features negatively impact children with autism and their families, the neural correlates of sensory processing deficits in autism are poorly understood, and little research exists investigating visual sensory deviance processing in children with autism or children with typical development. The current series of studies has completed a preliminary investigation of both of these concepts, using a visual oddball paradigm to characterize visual mismatch negativity in children with typical development and children with autism, and an auditory oddball paradigm to characterize the relationships of measured or reported sensory features and recorded ERP components. We found that both groups of children in the visual oddball paradigm displayed a difference wave to nontarget events consisting of two occipital negativities,

one early around 150ms and another late around 250ms. This finding confers with previous research where two negativities were reported in some tasks with adult participants. In these studies it was found that the first negativity was associated with exogenous stimulus features while the second was associated with a memory-based comparison of previously-presented events. We also found that the severity of observed sensory seeking behaviors was related to P3a and P1 amplitudes in the auditory oddball paradigm, specifically such that attenuated P3a amplitudes were associated with more severe sensory seeking behaviors at high amplitudes of P1 only.

The results of these studies provide a more complete picture of the neurobiology of auditory and visual sensory processing in typical development and in autism. We have seen that processing of visual stimulus deviance in children ages eight to twelve is not yet mature, and this age group may employ sequential processing reflective of an immature dorsal pathway of the visual system. We have also seen that this process seems to be altered in children with autism, particularly with what appears to be a heightened speed of processing of exogenous visual stimulus features. Children with autism also do not appear to have the same increasing response to memory-comparison of standards to deviants as age progresses, as seen in typically-developing children. This could reflect maturational deficits of global visual processing, and in particular deficits in connectivity of frontal brain areas with primary visual areas, in these children. Finally, early sensory processing elements of stimulus detection, corresponding to the ERP component P1, appear to be particularly important in both visual and auditory deviance processing. Early components appear to have an effect on the topography of the visual difference wave in both typically-developing children and in children with autism, and children with autism seem to be particularly sensitive to deviant stimuli at

this component. Early sensory processing also appears to modulate relationships between ERP components and severity of observed sensory seeking behaviors. This indicates that sensory deficits may have roots at very early, bottom-up levels of processing, which has implications for intervention therapies that target these early deficits in order to improve higher-order functions such as attentional orienting.

Further research is needed to unravel outstanding questions in this field, especially considering that these studies are some of the first to investigate both sensory processing in the visual modality in these populations, and the neurobiology of sensory features in any modality. We do not know why early ERP components influence later components' relationships with behavioral measures of sensory processing deficits, nor how these relationships may carry over into the visual modality. It remains to be seen how the two modalities may interact in audiovisual studies of stimulus deviance, and whether combining these modalities could provide a more complete picture of the neurobiology of sensory deviance. With future work, these studies may help identify subsets of the population of children with autism who may be particularly vulnerable to sensory deficits of particular types or modalities, allowing for more individualized interventions and better treatment outcomes. One day, neurobiological measures of sensory deviance may even be used as a diagnostic tool for assessing vulnerability to sensory features in young children with autism. To this end, we will continue to work to create a world where untroubled navigation of the ever-changing sensory environment is accessible to all.

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