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Audiovisual sensory processing in autism spectrum condition.

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AUDIOVISUAL SENSORY PROCESSING

IN AUTISM SPECTRUM CONDITION

by

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ABSTRACT

AUDIOVISUAL SENSORY PROCESSING

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RYAN MIKEL BURDETTE KISER

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Autism spectrum condition (ASC) consists of a set of pervasive developmental problems marked by measurable deficits in social interaction and communication, often coupled with specific and repetitive patterns of behavior. Featured restrictions in the capability to communicate and remain attentive can directly relate to the individual's ability to interact with others within societal norms. Evidence has suggested that the deficits commonly demonstrated by individuals with autism may arise from a disconnect between neural processes governing sensory inputs. Comparing ASC subjects to controls, previous investigations had shown that electroencephalogram (EEG) recordings and event-related potentials (ERPs) evoked via separate auditory and visual stimuli do not display aberrations in latency or amplitude in the ASC individuals. However, the findings reported here suggest decreased latencies in early-evoked potentials. Additionally, during the combined audiovisual task, electrophysiological recordings revealed significant cortical activity differences between ASC subjects and controls. To investigate the aforementioned phenomena this study employed EEG recording technology while subjects participated in an oddball-paradigm reaction time test. This project reports on the differences behavioral reactions as well as variances in amplitude and latency in twelve autistic individuals and twelve matched controls. Subjects were evaluated using the event related potentials, N100, N200, and P300, as well as dipole source coherence and power of EEG gamma oscillations recorded at fronto-central and

parietal sites in both hemispheres. Findings of this study suggest that the irregularities arise from deficits in the integration and combinatorial processing of multiple sensory inputs. Previous research investigating the neuropathology of autism has identified abnormalities in the structure, number and activity of the cortical minicolumns, which are believed to influence excitatory and inhibitory impulses of sensory processing. The minicolumns of ASC individuals appear in greater number coupled with increased neuronal density due to a reduction in the volume of peripheral neuropil space and neuronal cell bodies. Such a cortical and cellular arrangement favors the formation of short intralobular connections between neurons at the expense of longer interlobular fibers. This study proposes that aberrations in sensory processing and functional cortical binding, as evidenced by EEG recordings related to the tasks, further reflect underlying abnormalities of minicolumns in ASC individuals. Thus, the results of this project intuitively suggest that dysfunction of sensory processing by way of minicolumn irregularity may in turn lead to symptoms commonly associated with autism spectrum condition.

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1.1.1 Definition and Diagnosis of Autism Spectrum Condition

Evidence has suggested that the deficits commonly demonstrated by individuals with autism spectrum condition (ASC[1]) may arise from a disconnection between the neural processes governing sensory inputs, such as visual and auditory stimuli. These deficits may govern how ASC individuals process exogenous stimuli, which in turn affects how they interact with their surroundings, including other individuals (23, 24).

Currently, according to the Diagnostic and Statistical Manual (DSM) V (4, appendix A) published in the United States, ASC consists of an established criterion of pervasive developmental disorders marked by measurable deficits in social interaction and communication, often coupled with specific and repetitive patterns of behavior which are often an outward display of hyper- or hypo-sensitivities to sensory stimuli (2, 78, 103).

Autism spectrum condition is found within all socioeconomic, racial, and ethnic classes. Generally, early detection of ASC occurs around thirty-six months of age, however; some reports suggest that ASC traits can be evident to a trained clinician as early as eighteen months.

Clinically, physicians and researchers may also rely on supplemental materials such as the Autism Diagnostic Interview – Revised (ADI-R) (58), or the Autism Diagnostic Observation Schedule (ADOS) (59), which have been combined with the measures of the DSM to evaluate and formally diagnose individuals.

1.1.2 Epidemiology and Etiology

[1] The terminology according to DSM-V is autism spectrum disorders. The neuro-diversity movement has criticized the use of 'disorder' for its negative connotation and in this regard 'condition' may be more appropriate.

The official frequency and distribution of ASC within the population is often a contentious topic of discussion and point of research. Between the years 2002 through 2010, the Centers for Disease Control (CDC) reported the overall prevalence of ASC increased from 1 in 150 children, as reported in 2007, to 1 in 110, as reported in 2009. In 2011, the CDC proposed that an estimated 1 in 88 children can be classified with a diagnosis of ASC (27), which works out to be roughly 11.3 individuals per 1,000. The changes in prevalence marked an increase in incidence of 78% from 2002 to 2008. More recently in 2013 the CDC reported that the incidence rate of ASC is now 1 out of every 50 children. The increase in prevalence and early age of diagnosis presents an urgent need to identify causes and effective treatments for ASC (27).

The Triple Hit Hypothesis (24) suggests that ASC is a multifactorial disorder, which may give rise to many comorbidities suggesting diverse heterogeneity between ASC individuals. The hypothesis intimates that the threshold of three criteria must be surpassed to initiate the development of pathology related to ASC, in which an exogenous insult from the environment agitates a genetically vulnerable fetus during a critical period of cortical development (24).

1.1.3 Neurobiology and Pathology of Autism Spectrum Condition

The observed neuropathology of ASC cover a broad-spectrum of cortical and cerebellar anomalies. Neuroanatomical abnormalities in the ASC individual may range from minor focal cortical dysplasia, to heterotopias and more severe dysfunctional neural tissue irregularities (32, 78, 103). It has been hypothesized that a variety of neuroanatomical aberrations in cortical organization are the fundamental causes to the outwardly displayed symptoms of ASC (23, 24). The basic functional unit of the neocortex is an alignment of cells deemed a “minicolumn,” which is believed to be negatively affected in ASC individuals (23, 24, 25). The minicolumn is composed of cylindrical arrangements of pyramidal cells radially positioned from their place of origin (19). The core of the minicolumn is surrounded by sets of gamma amino-butyric acid (GABA) releasing interneurons in the peripheral neuropil space, positioned to modulate the

incoming and outgoing signals of pyramidal cells involved in processing regionally-specific information throughout the cortex (22). More precisely, the double-bouquet interneuron is proposed to provide a “vertical curtain of inhibition,” via the arrangement of repeating 15-30 μm wide axon bundles, thus isolating the excitatory projections of the core pyramidal cells (33, 66). The GABAergic surround dictates the volume and significance of excitatory signals produced by each minicolumn (67). The function of other inhibitory interneurons is thought to provide combinatory degrees of lateral inhibition between cell columns via tangential collateral extensions (23, 24). These lateral extensions may in turn influence task specific multiplicity within the signaling properties of the pyramidal cells, thus affecting whole regions of minicolumns (23, 24, 25). A benefit of this cytoarchitectural arrangement is that alignment and activity of inhibitory cells permits for varying degrees of excitatory activity within regions of cortical minicolumns (87).

The minicolumn pyramidal cell template originates from developmental precursors before embryonic day 40 of gestation and provides the milieu for organization of maturing axonal and dendritic processes (83). Interneurons surrounding the pyramidal cells primarily arise from the tangential migration of glial stem cells within the ganglionic eminence (25). Working in tandem, the chains of connected pyramidal cells and their associated interneurons form conical circuits (25). The “assembly line” effect would enhance the efficiency of information processing, bolstered by uniformity within the cortical system (25). Globally, minicolumns allow for the configuration of efficiently organized cortical connectivity (24). However, without signal modulation by the inhibitory interneurons one could expect that a system of increased amplification and hyper-excitability would exist, creating cascades of activity within regions (25).

Histological and stereological evidence has shown that the minicolumns are more narrow in ASC subjects compared with controls, exhibiting an increase in cellular density, decreased nucleolar size and a reduction in neuropil space (23). Researchers have found that deviations in the aforementioned minicolumn morphology deviations varies across cortical regions, with the dorsolateral prefrontal cortex (DLPFC) composed

of Brodmann areas 9 and 46, showing the greatest diminution in minicolumn width (23, 80). This finding was important in regards to the functions associated with the DLPFC: sensory integration, management of discrete information, regulation of intellectual function, as well as having a role in the planning and initiation of movement, (106). Damage to the DLPFC has shown to be associated with impairments in abstract thinking and social activity (39).

Casanova *et al.* (2002) observed that the minicolumns in ASC individuals were more tightly packed within the neocortex, displaying an increase in short connections at the expense of longer connection fibers between differing regions (21). An increase in white matter was associated with previous findings of an increase in the number of short connections between excess numbers of minicolumns (24). Casanova *et al.* (2002) suggested that, because of the metabolic constraints associated with smaller neurons and increased minicolumn density, there is a predisposition to shorter intraregional connection fibers, which creates interregional signaling deficits (21). The loss of interregional connectivity and dysfunction in cortical modular organization would impair the sensory informational processing at higher levels of cognition (23, 25). An additional effect correlated to the bias of increased minicolumns and short association fiber predominance was a reduction in the gyral window of ASC subjects (24). The gyral window has been described as an aperture at the base of cortical gyri, this space allows for the channeling of projection fibers to and from the cortex (24, 25). A constraint on the size of the gyral window would further confer an increase in cortical compartmentalization and a reduction of global trans-cortical interconnectivity, (25).

Functional magnetic resonance imagery has shown a decrease in activity linking prefrontal and posterior cortical areas in ASC individuals (50). This understanding of diminished long-range neuronal connectivity, might explain why the behavioral, cognitive abnormalities observed in ASC are more prominent when an emphasis is placed on higher level informational processing (23).

The combination of increased minicolumn density, neuronal density and short connection fibers, as well as a reduction in the activity of the inhibitory surround leads to cortical regions with exaggerated specialization and hyperactivity to stimuli, underscoring a pattern of selective convergence of adjacent processing modalities (23, 78). The convergence of various sensory stimuli could lead to the stereotypical observation of ASC individuals "not seeing the forest for the trees," because higher order perception and cognitive analysis necessitates interregional connectivity and coherent processing coordination (23).

Various researchers have hypothesized that some symptomology of ASC subjects can be explained by diminished inhibitory GABAergic interneuron activity, specifically those related to aberrant sensory processing, such as visual and auditory hypersensitivities (91). Without an effective system of inhibitory surround, one could expect that a cascade of signal amplification would occur in distinct cortical loci, resulting in a loss of necessary signal transfer to other regions for information integration (91). It could be argued that the enhanced physiological stress and erratic behavioral reactions may be rooted in exaggerated cortical signal amplification and the resultant overreaction to one's environment (91). Increased local interconnectivity coupled with diminished prefrontal trans-cortical connections would cause many cognitive processes to dysfunction in accordance with a defect in modular organization of the cortex. This hypothesis is further highlighted by the underlying pathology of increased number of minicolumns, smaller, more densely packed neurons, and a higher proportion of short, intra-regional connecting fibers in the neocortex of ASC subjects (23, 78).

1.1.4 Event-related potentials

Event-related potentials (ERPs) are small positive or negative inflections imbedded within the recorded electroencephalogram (EEG) (49, 74). Event-related potentials are transient components of oscillatory sinusoidal waves generated by the synchronous activity inherent to volume conduction (49, 68, 98). ERPs are provoked by either an early external event (signal) or late internal cognitive processes, which through

EEG recordings can be assessed with temporal resolution on the order of milliseconds (msec) (68, 74). The ERP voltage deflections are representative of the cortical activity associated with the reaction to and processing of sensory information (34). Event related potentials can be used to expound upon a variety of lower and higher cognitive functions such as the speed of inter-hemispheric transmission or the attention paid to and processing of complex stimuli (74). Evoked potentials are believed to represent the initial, basic processing of stimuli (49, 90). The features of evoked components – spatial distribution, latency, amplitude - appear to be dependent on the properties of the stimuli, such as strength and modality, and may be unaffected by the subject's cognitive operations (61). Induced components reflect perceptual and multimodal associative processing and therefore tend to be affected by the cognitive state of the subject and their subsequent engagement with the presented stimulus (49, 61). Cognitive functions related to attention, information processing, etc., might affect the elicitation of induced potentials (61). Collectively, ERPs are believed to be a representation of the activity of cortical regions related to complex cognitive processes, specifically in the sensory and association cortices (90).

The use of ERP technology in the research of ASC has proven to be adept in interpreting the neural activity at early stages of cortical development and may further prove useful in determining endophenotypes within ASC (49). Most often the literature states that disrupted cortical processes lead to attenuated amplitudes and increased latencies in the ASC population (15, 62). By expanding on the knowledge base concerning ERPs, researchers have begun to examine the principal deficits underlying ASC and correlate electrophysiological findings with the deficiencies associated with autism (49).

This study uses EEG first to establish a baseline of measurements related to single modality processing, and secondly, to analyze any possible differences incurred during multimodal sensory processing.

1.1.5 Cortical Coherence

Cortical coherence is a measurement that can be derived from EEG recordings (93). Cortical coherence is mathematically derived from the cross-spectrum of concurrent signals divided by power spectrum density, generating a correlation coefficient that evaluates the regularity which pairs or groups of electrodes measure the same amplitude and signal phase within a specific frequency band (20, 93, 97). The calculation is based upon the quantifiable synchronization between electrodes and describes the consistency at which the signals are in phase with one another (29, 93). Coherence values range from 0 to 1, or as a percentage of such. A value of 1 from coherence analysis indicates that the activity of two separate sources are perfectly in phase with one another, whereas a value of 0 indicates dyssynchronous firing with random phase differences (29). Electroencephalogram dipole coherence when described in terms of coupling is often used to measure the functional association of synchronous activity between two cortical regions (97). It is believed that due to differences in functional and neuroanatomical connectivity, ASC individuals display atypical cortical coherence as compared to neurotypical individuals (48, 49).

1.1.6 Neuronal Gamma Oscillations

Cognitive models suggest that selectively distributed oscillatory networks promote specific functions through established specialized patterns of activity linking spatially distinct cortical regions (9). It is believed that multifaceted and integrative cognitive functions are the result of an overlay of cortical gamma oscillations within various networks (9). Empirical evidence suggests that the production of gamma frequency oscillations (30-80 Hz) is dependent on the collaborative and balanced network of excitatory pyramidal cells and inhibitory GABAergic interneurons (75). Research found that GABA-facilitated inhibition is required to establish the phasic oscillatory activity found to generate the fluctuations of activity associated with cortical function (5). Gamma frequency oscillatory responses are described based on their post-stimulus temporal relationship (8, 9). Early evoked gamma is correlated with early sensory processing in isolated cortical areas sensitive to the presented stimulus features, typically defined as

occurring within 100-150 msec post stimulus; induced gamma typically arises 250 msec post-stimulus (8, 9). Variations in the increases and decreases of gamma band activity have been defined as event-related synchronization or dys-synchronization, with related fluctuations being specific to the cortical network engaged in processing (26). Neuronal phase-locked gamma oscillations have been observed in various and distinct cortical structures, acting in parallel to one another, indicating that recorded scalp potentials are produced by large numbers of neurons acting synchronously (9). Gamma frequency oscillations have been associated with multiple cognitive processes, e.g. selective attention and sensory integration, and therefore it has been hypothesized that gamma activity synchrony may serve as the basis of cerebral functionality and cortical communication (9). It is believed that due to neuroanatomical differences, ASC individuals display atypical functional connectivity of cortical regions mediated through synchronized gamma oscillations, (18, 76).

1.2 Hypothesis

The purpose of this project is to employ electrophysiological measures to study and provide observable evidence of atypical neurological multimodal sensory processing in the presence ASC. This study uses the cognitive oddball paradigm test and a measure of elicited dense array ERP activity that mirrors the underlying cognitive responses to the processing of presented stimuli. Aberrations of the fundamental cortical structures of ASC subjects create a deficit in essential processing and integration of sensory modalities. We believe that this deficiency results in the observable sensitivities to exogenous stimuli, as well as for the various social, behavioral, and emotional differences typical to ASC.

We believed that ASC subjects would display deficits in the ability to attend to and respond to rare, combined target stimuli. It is hypothesized that because of a dysfunction in cognitive target discrimination in ASC subjects, that ASC subjects would display impaired cognitive inhibition, thus exhibit hyper-excitable responses to non-targets. Furthermore, we believed that decreases in the ability to selectively discriminate

between targets and non-targets would create delayed latency in the ERP components and induced EEG responses of in the ASC subjects.

Based on previously described neuroanatomical differences in ASC subjects compared with controls, if ASC subjects do, in fact, exhibit abnormal regionally-specific hyper-connectivity, then we would expect to see observable differences in EEG recordings in response to tasks involving sensory processing. We hypothesized that ASC subjects will display exaggerated responses to both target and non-target stimuli eliciting early and late stage differences in gamma oscillations.

Furthermore, we expect to see delays and differences in regional cortical functioning and synchronicity between posterior cortical regions responsible for cerebral sensory processing and frontal regions associated with informational integration.

1.2.1 Aim 1: Unimodal Visual Stimuli Only Module: ASC vs. Controls

The first aim is to establish a baseline of similarities or differences in behavioral response and electrophysiological recording between ASC subjects and neurotypical subjects during the visual modality oddball task. Subjects were evaluated via number of response errors, reaction time, event-related potentials, dipole coherence and gamma frequency oscillation.

1.2.1.1 Visual Sensory Processing

After visual information is processed in the primary visual cortex, it is then sent along two parallel pathways to the secondary visual cortices: the prestriate cortex surrounding the primary visual cortex, and the infero-temporal cortex within the inferior portion of the temporal lobe (80). The two visual processing pathways leading to the secondary visual cortices are described as the dorsal, “where,” pathway and the ventral, “what,” pathway (42, 43, 80). The dorsal visual or “where” pathway relays stimulus information from the primary visual cortex to the dorsal portion of the prestriate cortex where the information is then transferred to the posterior parietal cortex for additional

analysis (80). The ventral visual or “what” pathway is thought to be involved in object identification. Its pathway leads from the primary visual cortex, through the ventral prestriate cortex to the infero-temporal cortices (80). The dorsal pathway is linked to control of subject behavior in response to visual stimuli and the ventral stream representing conscious perception of visual stimuli (42, 43, 80). Research has shown that most information from the secondary cortices is transferred to association areas within the posterior parietal cortices (80).

1.2.1.2 Visual stimuli and Event-related Potentials

The visual N100 is an early-evoked component, generally arising between 70-180 msec post-stimulus (31, 96). N100 is most likely generated by the activity of the lateral extrastriate cortices, with regions of the parieto-occipital and occipito-temporal regions adding to the dipole signal (41, 46, 105). The visual N100 is composed of several subcomponents; the earliest begin to show activity in frontal cortical regions with peaks occurring between 70-150 msec. The later N100 subcomponents appear over posterior parietal regions and may arise between 150-200 msec post-stimulus (61). The frontal N100 component will typically show increases in amplitude during target discrimination tasks (61).

1.2.1.3 Visual Sensory Processing: ASC

Atypical visual processing and behavioral responses to visual stimuli have been associated with autism; however, the reports concerning differences in visual processing have been varied (14). Tasks measuring visual ERPs have shown that ASC individuals atypically respond during early stages of visual processing (99). Collectively, studies concerning visual processing appear to suggest complications in integrating visual information to create a perceptual representation (13).

1.2.2 Aim 2: Unimodal Auditory Stimuli Only Module: ASC vs. Controls

The second aim is to establish a baseline of similarities or differences in behavioral response and electrophysiological recording between ASC patients and neurotypical subjects during the auditory modality oddball task. Subjects were evaluated

via number of response errors, reaction time, event-related potentials, dipole coherence and induced gamma frequency oscillations.

1.2.2.1 Auditory Sensory Processing

Recent research suggests that similarly to the dual “what” and “where” pathways of the visual system, the auditory system is also comprised of semi-separate and parallel networks (1). It is believed that selective attention may play a role in the auditory processing networks, in which the nature of the stimulus is processed based upon the stimulus’ characteristics (1). Researchers believed that the “what” pathway associated with hearing travels through a network linking the secondary auditory cortices in the anterior temporal lobe to the inferior frontal lobe, which is specialized for higher cognitive processing (1). The “where” pathway in auditory processing is said to link the parietal regions with the lateral prefrontal cortices (1). Neuroimaging has confirmed the non-primary auditory cortex plays a role in modulating the dissociative pathways through the aforementioned anterior “what” and posterior “where” networks (1). It is believed that these pathways may be activated as soon as 75 msec post-stimulus (1).

1.2.2.2 Auditory Stimuli and Event-Related Potentials

The auditory evoked N100 component, similarly to its visual counterpart, is composed of several subcomponents; the first is found in the fronto-central scalp locations, approximately 75 msec post-stimulus, generated by the auditory cortex of the temporal lobe (61). At 100 msec post stimulus, the second subcomponent emerges in recording sites around the vertex of the skull; the last component occurs more laterally, peaking at approximately 150 msec, possibly being produced by the superior temporal gyrus (61). It has been found that the auditory N100 wave is sensitive to and affected by the amount of attention applied by the subject, possibly leading to increased latency or diminished amplitudes (61).

1.2.2.3 Auditory Sensory Processing: ASC

Abnormalities have been found in the low-level processing auditory networks and converging results from various works suggest that there are significant deficits in

auditory sensory processing (72). Many believed that atypical processing of auditory sensory information at all levels may contribute to and represent a core deficit related to the main overarching symptoms associated with autism (72). After investigating the differences in visual and auditory processing separately, we then wanted to investigate differences between ASC subjects and controls when visual and auditory processing tasks were combined, leading up to the third aim of this study.

1.2.3 Aim 3: Bimodal Audiovisual Stimuli: ASC vs. Controls

The third aim is to assess the behavioral and electrophysiological differences associated with bimodal stimulus presentation to ASC patients and neurotypical controls during concurrent audiovisual stimulation tasks. Subjects were evaluated via number of response errors, reaction time, event-related potentials, dipole coherence and gamma frequency oscillations.

1.2.3.1 Auditory and Visual Sensory Processing

The auditory and visual processing networks operate independently of each other, having cortical regions that are specialized for the hierarchal processing of modality specific stimuli information (80). Communicating with the outputs of both the auditory and visual secondary processing cortices, the association cortices, (e.g. parietal cortices) receive sensory information from both auditory and visual sensory networks (80).

1.2.3.2 Auditory and Visual Stimulus Associated Event-related Potentials

The N200 component can be elicited by both auditory and visual stimuli (30, 61) through the use of the oddball paradigm, which will be discussed in a later section. The presence of the N200 is contingent on the appearance of a stimulus that deviates from the conditioned norm (30, 61). That is, the N200 can be found using a protocol where the subject is presented with a set of probable and improbable stimuli; the rare improbable stimulus will evoke the N200 (30, 61). The elicitation of the N200 is contingent upon the subject attending to the stimuli, which suggests that it is an indicator of processing of observed sensory deviance (30, 61). A task relevant deviant stimulus will elicit a larger

amplitude of the bilateral N200 component, which could be another indication of the potential being related to the categorization process (30). Though the N200 component is produced by both auditory and visual stimuli, the spatial location of the resultant ERP differs (30). An auditory evoked N200 generally appears maximally over central sites, whereas a visual N200 stimulus is evoked more posteriorly (30). If the rare stimulus is consciously attended, as aforementioned, it will be followed by another component classified as the P300, which will be discussed below (30). Furthermore, the N200 component can be used to extract information concerning the temporal processes of discrepancy recognition or through fronto-central regions and identify when there are aberrational response inhibitions (54). Generally, if the attended stimulus is derived from auditory sources, then the N200 is most strongly found over superior temporal cortices (82). During visual attention tasks the N200 can be strongly recorded over the superior parietal and inferior temporal cortical regions (82). Previous research has correlated the N200 with cognitive activities related to formation of modality specific representations for distinct perceptual pathways (82). Overall, the N200 is believed to reflect the processes of target discrimination, recognition, perception and classification of stimuli (100).

The P300 waveform has been reported as having a loci of generation in the association cortices of the parietal lobes with latency between 300 – 600 msec and as such is considered modality non-specific (34, 61, 79). As with the N200, the P300 is most often elicited by the standard oddball paradigm and is a response to an attended rare, task relevant stimulus (30, 34, 61). Variations in P300 amplitude reflect disparities to what degree cognitive resources are allocated in creating internal representation of the experimental variable (74). The latency and amplitude of the P300 potential can be affected via experimental manipulation; the more difficult the discrimination, the longer the latency; the less probable the rare event, the larger the elicited amplitude is when the target appears (30, 61). The amplitude of the P300 potential can be affected by higher cognitive functions associated with the subject's expectancy of stimuli presentation and attention to stimulus (34). It is believed that the P300 represents the cognitive process of

context evaluation and reflects the activity of several neuroanatomical components working in conjunction (30, 61). The production of the potential occurs after cognitive processing within the criteria of the task (30, 34). The P300 component can be affected by changes in cortical integrity (61). Overall, the P300 component characteristics have been linked to cortical responses related to task-relevance and decision making as related to the memory updating process. The P300 is believed to be a reflection of a central, cohesive system with a high degree of connectivity between cortical regions (34, 79).

Polich and Herbst (2000) postulated that the P300 component is useful for delineating subtypes within disorders, or between pathological means of aberrant neuro-electrophysiology. Because P300 is sensitive to fluctuations in the capability of apportioning cognitive resources to tasks, such as attending to stimuli, it is an apt clinical measure of dysfunctional higher cognitive skills associated with abnormal cortical development (81).

1.2.3.3 Audiovisual Sensory Processing: ASC

If there are deficits in single modality stimulus processing, one would naturally expect there to be deficits in tasks when the individual is required to integrate information from multiple modalities. The anticipated deficiencies associated with ASC individuals may be reflections of the failure to successfully attend to and/or process multiple modalities, e.g. visual, auditory, or concurrently (73). It is expected that the multimodal audiovisual tasks will more readily elicit observable processional sensory deficits (62). In accordance with the previously mentioned neuroanatomical observations linked to ASC, it is also likely that abnormal ERPs, coherence and gamma oscillations associated with multimodal sensory processing might be the results of altered minicolumn morphology and decreased inhibition (6, 90, 91).

1.3 Methods and Materials

This study used a cognitive oddball task concurrent with continuous EEG recording of brain potentials in attempt to measure facets related to the cognitive

processing of sensory stimuli within separate and combined audiovisual sensory modalities paradigms. This study attempted to capture data concerning aforesaid processing via ERP components, such as the N100, N200 and P300, as well as levels of gamma frequency oscillation and coherence of said oscillations between cortical regions.

1.3.1 Participants

A total of 24 subjects (12 ASC; 12 control) with no known history of seizures, genetic disorders, or clinically observed neuroanatomical abnormalities participated in this study. Both ASC and control subjects with substantial hearing or visual impairment were excluded from the protocol. The ASC group was comprised of 4 female and 8 male participants while the control group consisted of 3 female and 9 male participants. The ASC subjects were categorized and diagnosed by clinicians at the University of Louisville Weisskopf Child Evaluation Center by means of the previously defined DSM-IV-TR (appendix A) and ADI-R. Having been previously clinically evaluated, all subjects had been categorized as having normal levels of hearing and vision, or wore corrective lenses. All accepted ASC subjects were considered high functioning with an intelligent quotient greater than 80 as gauged by the Wechsler Intelligence Scale, for Children – fourth edition (WISC-IV) (103). Subjects with a history of seizures, known genetic disorders, clinically observed neuroanatomical abnormality, or substantial hearing or visual impairment were excluded from the protocol.

All control subjects were recruited via local media advertisements and, as reported by their parents, were free of any major medical conditions, including but not limited to neurological or psychiatric conditions, or learning disabilities. Additionally, all control subjects had normal levels of audition and no significant visual impairments. To confirm parental reports, subjects were evaluated for a history of any cognitive deficits via the structured clinical interview DSM-IV, non-patient edition (SCID-NP) (37). Furthermore, control subjects were closely matched to ASC subjects by age, IQ and socioeconomic status – as determined by parental level of education and household income. All subjects had an IQ greater than 80. The age range of the ASC group was 8 –

23 years of age, and the control group was 8 – 26 years of age. There were no significant differences in age between the two groups [Control, 16.8 years (±5.1)[2]; ASC, 15.2 years (±4.8); F = 0.7; p = 0.4].

All accepted subjects, as well as their parents or legal guardians were fully briefed and provided a complete overview of the study, including information regarding the local Institutional Review Board (IRB) study purpose, participatory requirements and responsibilities, as well as risks, benefits, and reimbursement schedule. Previously, the IRB had reviewed and approved all consent and assent forms, which were fully explained to all participants that were willing to be or accepted as participants. All participants were given the opportunity to ask questions, and posed questions were answered before the participant was asked to sign consent forms. Upon agreeing to participate, subjects signed and dated all required documentation and were given a copy countersigned by the researcher obtaining their consent.

Factors related to individual subject recording reliability and subsequent extraction of associated data necessitated that for some calculations the formation of subject subgroups was required; these changes are noted in results section.

1.3.2 Oddball paradigm

Oddball paradigms demand multiple stages of cognitive processing from the tested individual; therefore it represents a keen methodology to elicit measureable ERPs. The oddball paradigm has been used widely in clinical research recently because of its proven consistency, and has been established in the literature as a well-reviewed and repeated method. Oddball protocols have been shown to elicit vigorous ERP responses and have displayed particular efficacy in elucidating processes of cognitive sensory discrimination and target probability.

Each participant performed 5 target detection tasks during a single ERP recording session. Total task time lasted approximately 20 minutes. Each task consisted of a block of (100) trials with a break every (50) trials. Students were instructed to press a

[2] Values in parenthesis represent standard deviation values.

key for the specific target in each block. Stimuli were presented pseudo randomly with a target to standard ratio of (20:80). Stimuli had (150 msec) duration with a random inter-stimulus interval between 1000 – 1250 msec.

The program software for oddball paradigm was E-prime (Psychology Software Tools Inc., PA) operated through a desktop computer; additionally, E-prime was the program through which manual responses to stimuli were collected. Manual responses to targets were collected via a five-button keypad (Serial Box, Psychology Software Tools, Inc., PA) (90). Visual stimuli were presented on a 15" monitor, the stimuli were presented as white letters and the background was solid black. Auditory stimuli were presented through un-modulated Logitech Z-5500 THX speakers in an isolated room with external sound dampening.

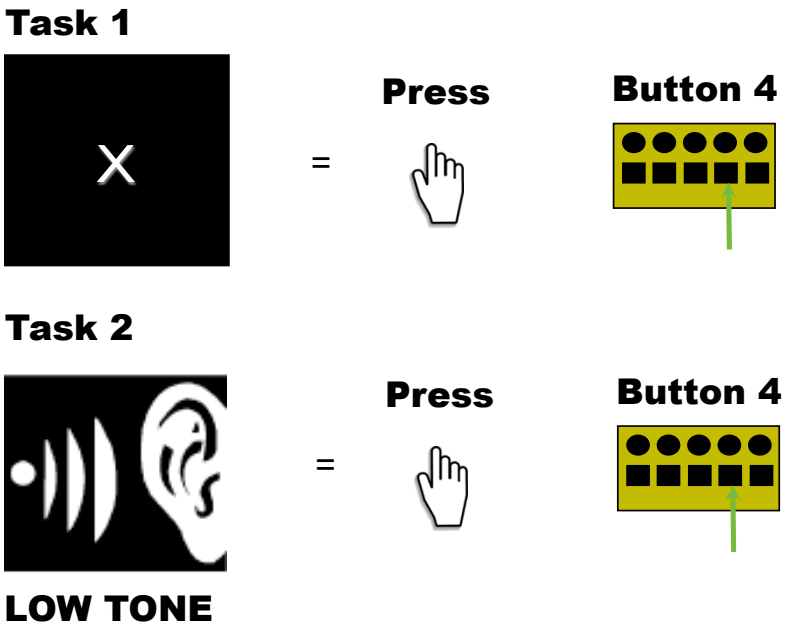


Figure 1.1 Pictographic instructions for tasks 1 and 2.

1.3.2.1 Task 1: Visual Only

Visual only oddball task: Single visual stimulus – either a letter "T" standard non-target or a letter "X" target – appear on the center of the screen; Student presses the button when the target X presents itself [Figure 1.1 (top)].

1.3.2.2 Task 2: Auditory Only

Auditory only oddball task: Single auditory stimulus – either a high (1.5 kHz) non-target tone or a low (0.75 kHz) target tone; Student presses the button when the low tone target sounds [Figure 1.1 (bottom)].

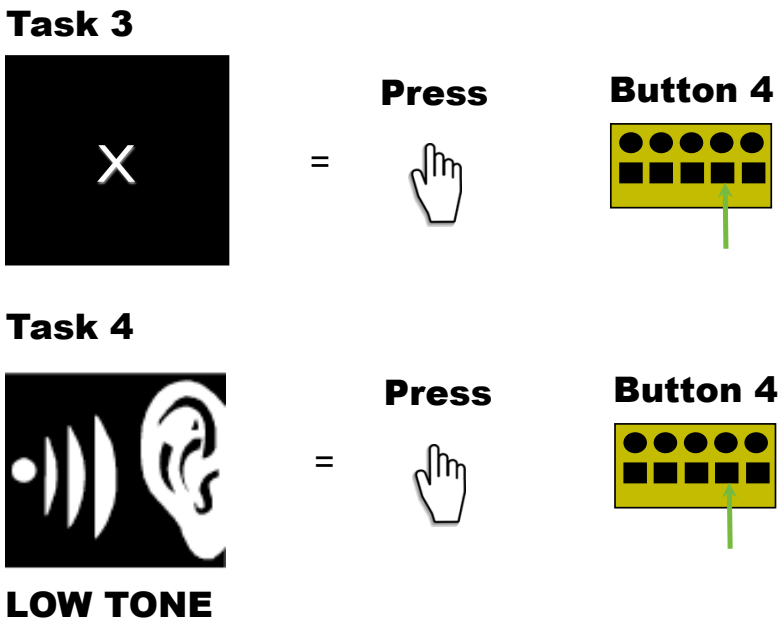


Figure 1.2 Pictographic instructions for tasks 3 and 4

1.3.2.3 Task 3: Audiovisual – Visual target

Combined audiovisual oddball task: Subjects were presented with simultaneous visual and auditory stimuli, but were instructed to ignore the auditory tones and only respond to the visual target, “X” [Figure 1.2 (top)].

1.3.2.4 Task 4: Audiovisual – Auditory Target

Combined audiovisual oddball task: Subjects were presented with simultaneous visual and auditory stimuli, but were instructed to ignore the visual stimuli and only respond to the auditory target, “low tone” [Figure 1.2 (bottom)].

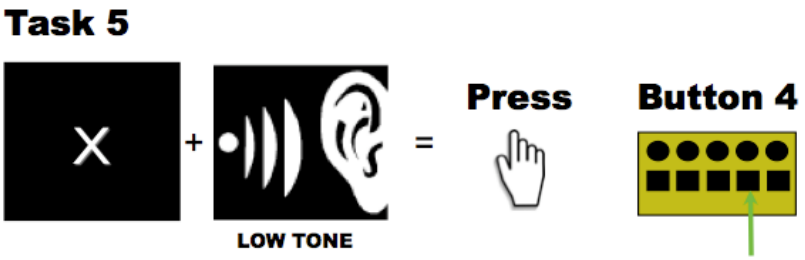


Figure 1.3 Pictographic instructions of task 5

1.3.2.5 Task 5: Audiovisual – Combined Target

Combined audiovisual oddball task: Subjects were presented with concurrent visual and auditory stimuli, and were instructed to only respond when the visual target "X" and auditory target "low tone" were presented simultaneously (Figure 1.3).

1.3.3 Electroencephalogram and event-related potential data acquisition and analysis

The EEG measurements were acquired via a 129-electrode channel Electrical Geodesics Inc. (EGI) system (v. 200) net (90). The net is composed of a thin elastic thread meshwork holding Geodesic Sensor Ag/AgCl composite electrodes held by plastic encasing and an artificial sponge that is saturated in a potassium-chloride solution to facilitate conductance. The use of a large array net compared to smaller numbered electrode nets allows for greater specificity in spatial investigation of scalp volume conduction (68, 98). Because of smaller inter-electrode distances, one is able to more accurately investigate and differentiate between component differences based on scalp topography, which in turn affords the possibility of generating more precise models concerning source generation (68, 98).

The net electrodes were connected to Net Amps and Net Station software (Electrical Geodesics Inc.) powered via a Macintosh G4 computer. Continuously recorded EEG data underwent 0.1-200 Hertz (Hz) analog filtering after it was sampled and digitized at 500 Hz. Per the Technical Manual of EGI (2003) electrical impedance was kept under 50 kiloohms (KΩ), deemed as sufficient by technical standards and previous research. EEG channels with either visually observable artifacts (e.g. subject movement

or channel drift) were marked as “bad” for eventual offline removal within the Net Station program’s “waveform tools.”

Additionally, during post testing analysis the stimulus-locked EEG measurements for each subject were segmented into 1000 msec time epochs, with the first 200 msec consisting of pre-stimulus recording and the last 800 msec consisting of crucial post-stimulus measurements centered around responses to protocol related events, e.g. rare target or standard non-target. Furthermore, the data was digitally investigated for any remaining artifacts related to eye movement, blinks, or general body movement. Any channels that appeared to be disrupted via extraneous activity were removed by employing artifact rejection tools. Such channels are identified via Net Station Waveform Tools’ Artifact Detection component, which identifies contaminated EEG channels if certain criteria are met: 1) average amplitude exceeds 200 microvolts (μV), 2) differential average exceeds 100 μV, or 3) channel displays zero variance. If circumstances arose with a subject that caused a particular portion of the recording to be irrevocably tainted with artifact, e.g. if the testing segmentation displayed ten or more channels containing artifacts recorded at an amplitude of >70 μV, these channels were substituted via a NSWT function that makes use of spherical splines to reference recordings from unaffected channels.

Low pass settings were introduced with the components of interest in mind; a setting of 100 Hz is used; of note: this setting may be affected by the analog-digital conversion rate as well as the intended offline digital filtering (90). The minimum rate of digitization of EEG data was 200 Hz, within 1000 msec epochs: 200ms pre-stimulus, 800ms post stimulus.

After channel correction, etc., the data was passed through a digital 60 Hz notch filter, with the purpose of attenuating frequency recordings derived from ambient noise. Band-pass filters with a range of 0.3 – 20 Hz were then employed to segment the data by condition, the results of which were then averaged, thus displaying the desired ERPs. A

baseline correction was then applied to the ERP averaged results with additional re-reference processing of the data into an average reference frame.

The ERP signal to noise ratio is often smaller in ASC subjects as compared to controls, which is compounded by a typical increase of general eye movement. Due to the excessive electrophysiological artifact associated with increased eye movement there is often a loss of measurable trials. The loss of trials associated with such biological artifacts often requires the averaging of more trials (90).

1.3.4 Behavioral Analysis

Behavioral measure analysis was achieved by comparing group mean reaction time (msec) to stimulus and response accuracy: number of omissions, commissions, and total number of errors.

1.3.5 Dipole Source Coherence Analysis

Net Station software was used to convert raw data into Brain Electrical Source Analysis (BESA) ready files, (review of BESA program, 45) The BESA program was used to compute and analyze dipole source coherence activity. The data was digitally filtered using a 60 Hz notch filter. Four regions of interest were used to measure coherence of activity between frontal and parietal region electrodes in response to only target stimuli in each modality. Two electrodes from frontal and parietal regions were selected, one from left and right hemispheres (F3/4, P3/4). Frequency and coherence peak measurements were taken with the parietal electrodes individually being selected as reference points for concurrent gamma coherence activity. Coherence peak activity was cataloged within early evoked (100-200 msec) and late-induced (300-600 msec) epochs, between 30 – 45 Hz.

1.3.6 Gamma Frequency Acquisition and Analysis

Tailored algorithms generated in MATLAB were used to extract measures of gamma frequency from the EEG recordings. The extracted data was then processed using SPSS to assess between group differences for power (μV^2) hemispheric activity, response to visual, auditory, and combined audiovisual stimulus conditions (7, 44).

1.3.7 Statistical Analysis

SPSS v.14 was used to analyze between group differences utilizing individual subjects averaged responses as the compared observations. The predominant statistical model employed was a repeated measure of ANOVA. For this project dependent variables were reaction time, response accuracy and error percentage, previously specified ERP component characteristics' of amplitude and latency per region of interest. Additional dependent variables included coherence coefficients measured from all modality target responses as well as amplitudes of evoked gamma frequency to targets and non-targets of each modality. Measures of hemispheric and region of interest comparisons were evaluated for both coherence and gamma activity. Coherence data was analyzed for peak coherence within 30 – 45 Hz between four regions of interest. ANOVA was used to analyze the following factors within all participants: 1) Modality (Visual, Auditory, Combined), 2) Stimulus (target, non-target), 3) Hemisphere (left, right), 4) Group (ASC, control). Statistical significance was deemed as p-values < 0.05.

1.4 Results

1.4.1 Behavioral Measures: Errors and Reaction times

The behavioral measures only identified a few significant differences between controls and ASC participants. The findings that showed true group differences occurred during the visual block (Table 1.1) where there were significant differences in average reaction time to visual targets [Control, 225.1 msec (±48.7 msec); ASC, 282.8 msec (±75.0 msec); p = 0.05]; the percentage of the number of errors related to missed button push responses to targets, [Control, 0.5% (±1.6%); ASC, 6.5% (±6.7%); p = 0.01]; and average total number of errors [Control, 1% (±0.7%); ASC, 11% (±6.5); p = 0.05]. As it will be noted shortly, the ASC subjects displayed significantly faster early evoked potentials responding to visual stimuli; however, the average reaction time to visual targets was significantly slower. This issue will be further expanded on, but one may be able to glean that although early cortical responses to stimuli occurred for the ASC group, there was some type of deficit in communication between early sensory processing

structures and later processing structures that facilitated the physical response. It is possible that the differences in errors are also related to atypical processing of stimuli, not allowing the ASC subjects to classify targets and non-targets as quickly as the control subjects.

There were no significant differences within the reaction times or number of errors in response to the auditory or audiovisual targets (Table 1.2; Table 1.3). Despite that, the reaction times do show that the control group responded an average of approximately 40 msec faster than the ASC group [Control (At), 241.68 msec (±71.8); ASC (At), 282.62 msec, (±70.7)], [Control (AtVt), 250.99 msec, (±60.8); ASC, (AtVt), 296.46 msec, (±82.8)]. These findings, though not statistically significant, suggest that there still may be processing differences in the auditory and audiovisual modalities that may be elucidated by increasing the number of subjects.

In the processing of reaction times and errors, some subjects were excluded due to what appeared to be file conversion errors.

Group	**(Vt) Average Reaction time (msec)**	**% (Vt) Omissions**	**% (Vt) Commissions**	**% (Vt) Total Error**
Control	225.12 (±48.7)	0.5 (±1.6)	0.5 (±0.9)	1.0 (±0.7)
Autism	282.81 (±75.0)	6.5 (±6.7)	4.5 (±7.5)	11.0 (±6.5)
F-value	4.16	7.62	2.65	4.36
p-value	0.05*[3]	0.01*	0.12	0.05*

Table 1.1 Visual block behavioral measures

Group	**(At) Average Reaction time (msec)**	**% (At) Omissions**	**% (At) Commissions**	**% (At) Total Error**
Control	241.68 (±71.8)	1.0 (±2.1)	0.75 (±1.2)	1.75 (±1.1)
Autism	282.61 (±70.7)	4.0 (±5.7)	2.13 (±2.5)	6.13 (±2.5)
F-value	1.65	2.46	2.45	3.82
p-value	0.22	0.14	0.14	0.07

Table 1.2 Auditory block behavioral measures

[3] An "*" denotes values of significance.

Group	(AtVt) Average Reaction time (msec)	% (AtVt) Omissions	% (AtVt) Commissions	% (AtVt) Total Error
Control	250.99 (±60.8)	11.9 (±16.5)	2.18 (±3.0)	14.08 (±4.8)
Autism	296.46 (±82.8)	23.5 (±26.0)	9.33 (±11.8)	32.83 (±13.2)
F-value	1.68	1.20	2.75	2.53
p-value	0.21	0.29	0.17	0.13

Table 1.3 Audiovisual block behavioral measures

1.4.2 ASC vs. Controls: Visual Stimulus Only

1.4.2.1 Visual Event-related Potential Differences

As indicated by the behavioral measures, there were a few significant differences in response to visual targets; this was evident within the event-related potential measures as well.

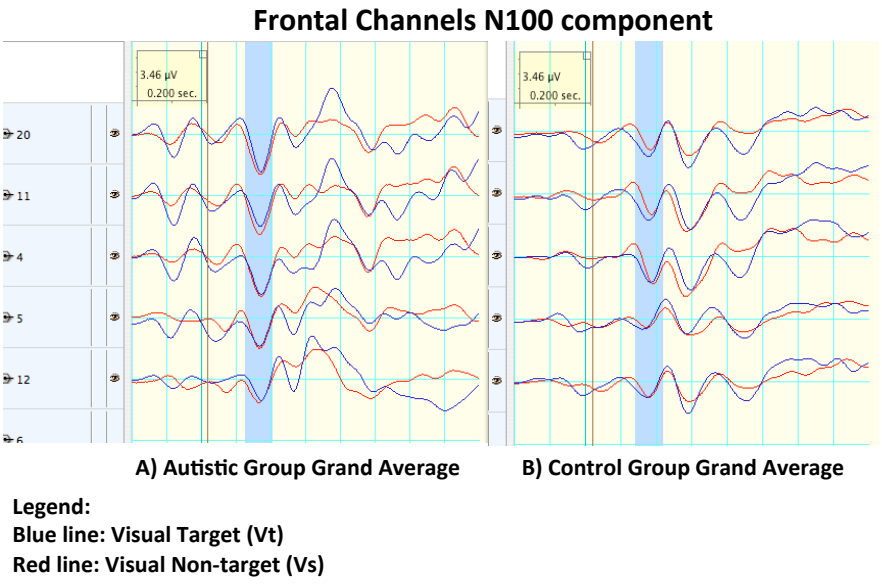


Figure 1.4 Frontal N100 event-related potential. ASC subjects (A) Control subjects (B). Visual target (Vt) blue line. Visual non-target (Vs) red line.

An example of the visual ERP for the frontal N100 (highlighted in light blue) is represented in Figure 1.4. Though there were no significant findings related to this particular potential, increased amplitudes are visible in the responses of the ASC group.

For the early evoked, N100 component, tempo-parietal region (Table 1.4) we observed a significant difference in latencies between groups in response to both visual targets [Control, 163.87 msec (±12.6); ASC, 136.81 msec (±19.8); p = 0.02] and visual non-targets [Controls, 160.22 msec (±7.7); ASC, 137.93 msec (14.4); p < 0.01]. Coupled with the behavioral measure information, and given the previously reported difference in reaction time and error rate, the data could imply that the ASC subjects were cognitively more responsive to visual stimulus features, without regard to the contextual difference between visual targets and non-targets.

Group	**(Vt) Average N100 Latency (msec)**	**(Vnt) Average N100 Latency (msec)**
Control	163.87 (±12.6)	160.22 (±7.7)
Autism	136.81 (±19.8)	137.93 (±14.4)
F-value	7.11	11.71
p-value	0.02*	< 0.01*

Table 1.4 Visual N100, tempo-parietal region latency. Response to Visual Targets = (Vt); Response to Visual Non-targets = (Vnt)

The latency difference for the tempo-parietal N200 response to visual targets and non-targets (Table 1.5) displayed significant temporal differences in response to the visual non-target [Control, 327.78 msec (±20.9); ASC, 290.54 msec (±36.5); p = 0.05], but not the visual target. Such findings could be indicative of downstream effects of earlier sensory discrimination within the control group, having already identified the non-target within the networks of lower level processing, less cognitive resources were allocated for the processing of non-target stimuli. Though the differences were not statistically evaluated for significant difference, when looking at the N200 amplitude associated with response to stimulus, we found that the control groups displayed a negative inflection of 2.60 μV to targets and 1.79 to non-targets, which also could be considered an indicator of less resource allocation to processing non-targets.

Group	(Vt) Average N200 Latency (msec)	(Vnt) Average N200 Latency (msec)
Control	319.57 (±14.4)	327.78 (±20.9)
Autism	293.05 (±46.0)	290.54 (±36.5)
F-value	1.51	4.95
p-value	0.25	0.05*

Table 1.5 Visual N200, tempo-parietal region latency. Response to Visual Targets = (Vt); Response to Visual Non-targets, (Vnt).

1.4.2.2 Dipole Source Coherence and Gamma frequency

There were no significant differences within the unimodal visual task cortical dipole coherence or gamma frequency oscillations; however, significant differences were found between modality and will be discussed below.

1.4.3 ASC vs. Controls: Auditory Stimulus Only

1.4.3.1 Auditory Event-related Potential Differences.

As behavioral measures would indicate, there were no significant differences in the processing of auditory stimuli in regards to the elicitation of event-related potentials.

1.4.3.2 Dipole Source Coherence

During the auditory stimulus task there was a significant difference in hemispheric dipole coherence between groups. Using a P4 electrode as the reference point and collapsing both early evoked and late induced peaks; the ASC group showed almost no hemispheric differences in responding to auditory targets [Left F3, 0.46; Right F4, 0.43], while the control group displayed preferential coherent activity in the left frontal region [Left F3, 0.43; Right F4, 0.32], (Table 1.6). The ASC group's lack of hemispheric difference could be indicative of excess global activity in the use of more cognitive resources to respond accurately to the targets or non-targets. Figure 1.5 displays a pictographic representation of the hemispheric interactions.

Group	(At) Average Coherence P4-F3	(At) Average Coherence P4-F4	Hemisphere x Group
Control	0.43 (±0.2)	0.32 (±0.2)	
Autism	0.46 (±0.2)	0.43 (±0.2)	
F-value			4.48
p-value			0.05*

Table 1.6 Hemispheric coherence interactions: Auditory Target = (At).

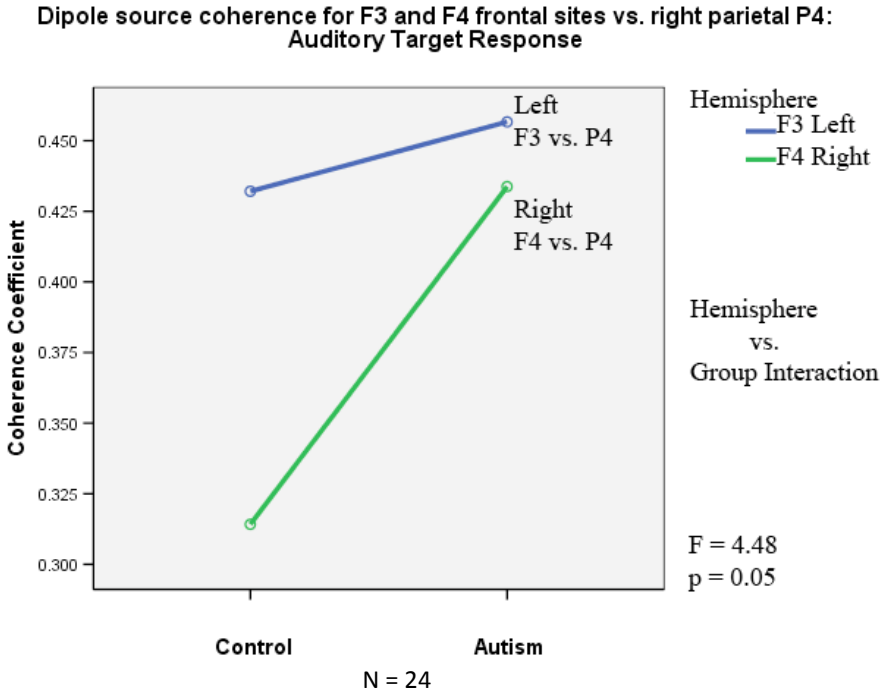


Figure 1.5 Auditory modality coherence interactions

1.4.3.3 Gamma Frequency Oscillations

There were no significant differences in gamma frequency within the auditory modality itself; however, there were differences between sensory modalities that will be discussed below.

1.4.4 ASC vs. Controls: Audiovisual Stimulus

1.4.4.1 Audiovisual Event-related Potential Differences

Statistically significant findings were found in the latency of the N100 in the frontal region of interest in response to the combined audiovisual non-target. Once again,

the ASC group showed significantly shorter N100 latencies to a non-target stimulus [Control, 166.18 msec (±26.9); ASC, 138.60 msec (±17.3); $p < 0.01$], (Table 1.7). The results may further indicate that the ASC individuals are more reactive to stimuli without regard to context. Interestingly, the latency differences were very close to the same for the audiovisual modality as they were for the visual, possibly suggesting vision being the dominant sensory modality.

Group	**(AntVnt) Average N100 Latency (msec)**
Control	166.18 (±26.9)
Autism	138.60 (±17.3)
F-value	8.93
p-value	< 0.01*

Table 1.7 Audiovisual N100 latency: audiovisual non-target = (AntVnt)

In the tempo-parietal region there was a significant difference in the amplitude of the negative deflection for the N200 component in response to the audiovisual non-targets [Control, 0.21 μV (±0.5); ASC, 0.68 μV (±0.6)], (Table 1.8). While the ASC group did show differences between the responses to audiovisual targets and non-targets, the significant difference displayed in amplitude in response to non-targets may be indicative of deficits in cognitive discrimination between targets and non-targets. The statistical difference in latencies of response for the ASC group were insignificant and frankly were close to being the same in the tempo-parietal region (ASC – AtVt, 290.68 msec (±33.0); ASC-AntVnt, 287.99 msec (±34.1); $F = 0.04$, $p = 0.85$).

Group	**(AtVt) Average N200 Amplitude (μV)**	**(AntVnt) Average N200 amplitude (μV)**
Control	1.08 (±1.0)	0.21 (±0.5)
Autism	1.30 (±1.6)	0.68 (±0.6)
F-value	0.13	4.36
p-value	0.73	0.05*

Table 1.8 Audiovisual N200 amplitude. Response audiovisual target = (AtVt); response to audiovisual non-target = (AntVnt).

The parietal P300 showed a significant difference in amplitude response to audiovisual targets over the parietal region of interest [Control, 0.31 μV (±1.5); ASC, 2.77 μV (±2.4); p = 0.01], (Table 1.9). Linking these findings to the behavioral observations, where there were no statistical differences in error or reaction time, one might suggest that this is indicative of hyper-connectivity in the posterior region and possible compensatory mechanisms that will be discussed below. This notion is further indicated in Figures (1.6) and (1.7). Figure 1.6 shows that the ASC group has specific peak fluctuations of gamma activity in the parietal regions through the first 200 msec. As noted it appears that the control group's decreased parietal P3b component in response to targets may coincide with decreased parietal gamma activity. Additionally, it appears that by 200 msec the cortical activity in response to audiovisual targets has moved to the frontal lobes (Figure 1.7).

Group	**(AtVt) Average P3b Amplitude (μV)**
Control	0.31 (±1.5)
Autism	2.77 (±2.4)
F-value	7.66
p-value	0.01*

Table 1.9 Audiovisual P300 amplitude. Response to audiovisual target = (AtVt).

Gamma Frequency Activity in Parietal Region: audiovisual response

A) Autistic Group Grand Average

B) Control Group Grand Average

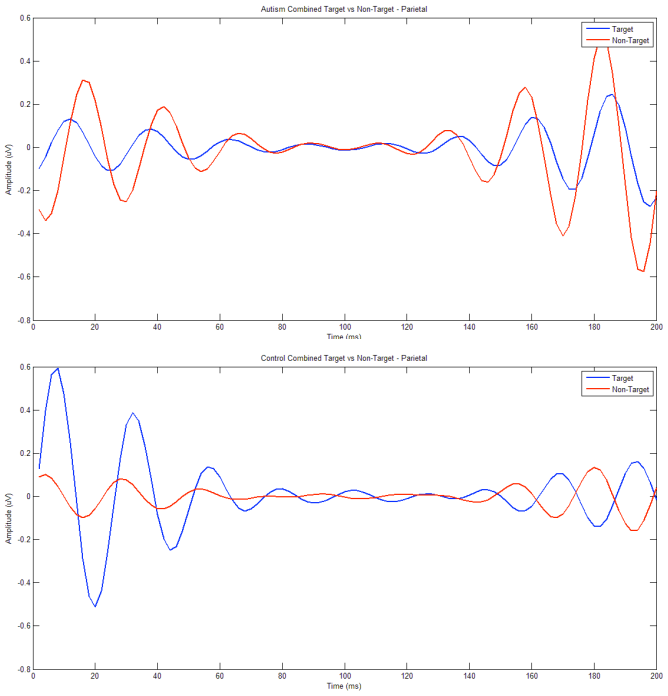


Figure 1.6 Comparison of gamma activity: parietal region response to audiovisual stimuli

Gamma Frequency Activity in Frontal Region: audiovisual response

A) Autistic Group Grand Average

B) Control Group Grand Average

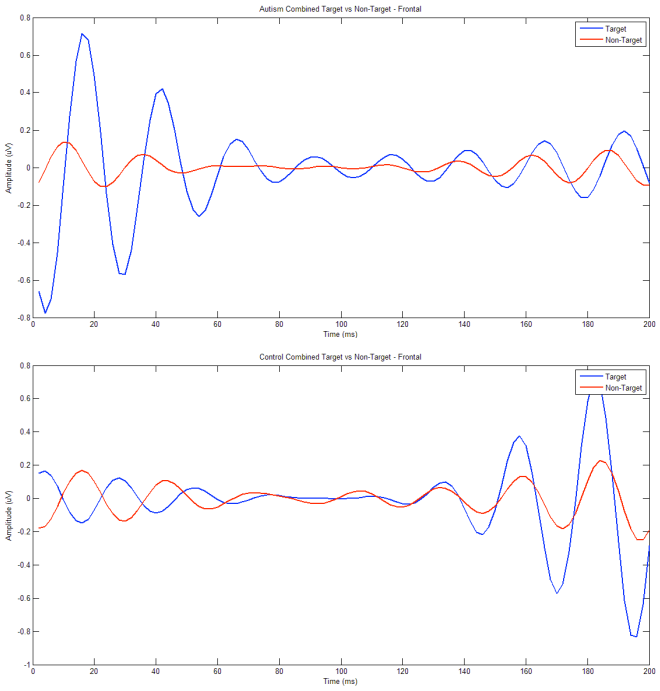


Figure 1.7 Comparison of gamma activity: frontal region response to audiovisual stimuli.

1.4.5 ASC vs. Controls: Various Group Interactions

1.4.5.1 Cross-modality Event-related Potential Group Interactions

Statistically significant between group N100 component amplitude differences were found in the tempo-parietal region in regards to an evaluation of cross-modality stimulus response: targets versus non-targets. Neurotypical control subjects were found to display a significant difference in amplitude response to targets vs. non-targets across modalities as compared to ASC subjects. This finding could also be indicative of deficits in early target discrimination found in autism.

Group	**Target - (Vt, At, AtVt) Average N100 Amplitude (μV)**	**Non-target (Vnt, Ant, AntVnt) Average N100 amplitude (μV)**	**Stimulus x Group**
Control	2.82 (±2.3)	1.02 (±1.0)	
Autism	1.18 (±1.5)	0.76 (±0.8)	
F-value			5.60
p-value			0.04*

Table 1.10 Group amplitude differences: response to targets and non-targets. Response Target: Visual Target (Vt), Auditory Target (At), Audiovisual Target (AtVt). Response to Non-target: Visual non-target (Vnt), Auditory non-target (Ant), Audiovisual Non-target (AntVnt).

1.4.5.2 Dipole Source Coherence

Significant between group differences were found in the coherence coefficient when the target response to all modality targets were evaluated; again a hemispheric difference was displayed with the control group showing preferential left frontal F3 [Control – left frontal F3, 0.50 (±0.2); right frontal F4, 0.37 (±0.2)], activation as compared to the ASC group, which displayed more equal global activation of both right and left [ASC – left frontal F3, 0.48 (±0.2); right frontal F4, 0.43 (±0.2)], (Table 1.11). Figure 1.8 displays the between group differences in hemispheric interaction. Figure 1.9 displays two representative individuals from each group. Of note, the ASC subject shows significantly more global frontal activity than the control subject.

Group	Collapsed: (Vt, At, AtVt) Average Coherence P4-F3	Collapsed: (Vt, At, AtVt) Average Coherence P4-F4	Hemisphere x Group
Control	0.50 (±0.2)	0.37 (±0.2)	
Autism	0.48 (±0.2)	0.43 (±0.2)	
F-value			4.48
p-value			0.05*

Table 1.11 Hemispheric differences in coherence: all modality targets. Response: Visual Target (Vt), Auditory Target (At), Audiovisual Target (AtVt). Response: Visual Non-target (Vnt), Auditory Non-target (Ant), Audiovisual Non-target (AntVnt).

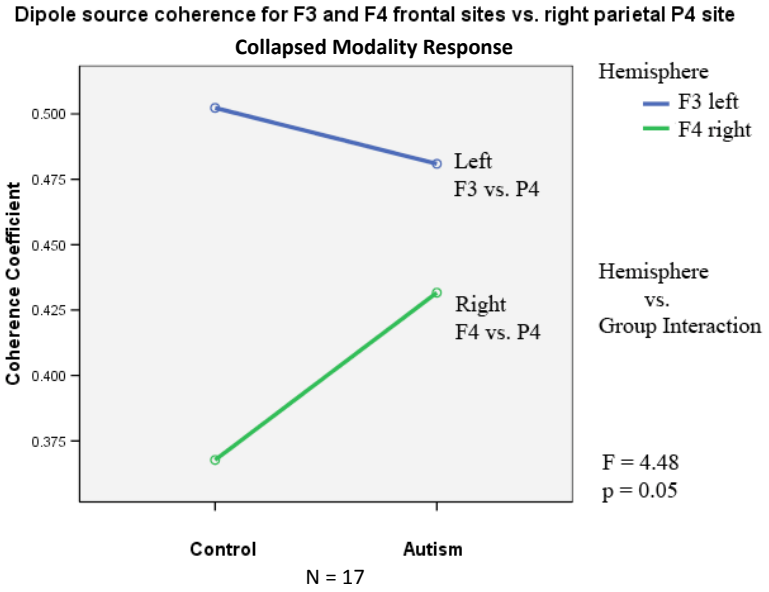


Figure 1.8 Collapsed modalities: hemispheric differences in coherence coefficient.

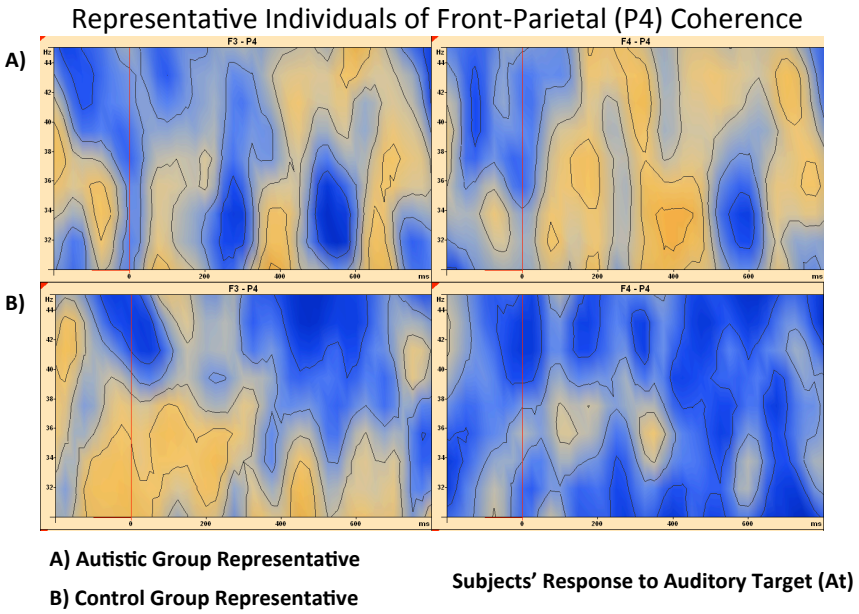


Figure 1.9 Representative individuals for fronto-parietal coherence.

1.4.5.3 Gamma Frequency Oscillations

Upon collapsing the activities measured at frontal left and frontal right as well as the responses to targets and non-targets of the auditory and audiovisual stimuli, a significant hemispheric difference was found in gamma activity between ASC subjects and neurotypical controls (Table 1.12). The individuals with autism displayed a significant bias towards right frontal hemispheric gamma activity [ASC – Left frontal, 13.44; Right Frontal, 58.42]. Figure 1.10 displays the interactive hemispheric differences. Figures 1.11 and 1.12 respectively show parietal and frontal gamma activity across all modalities. Interestingly, the ASC group shows increases in gamma activity within 0 – 50 msec and as well as the 150 msec – 200 msec across all modalities in the parietal region (Figure 1.11a) additionally showing frontal increases in activity for the combined condition (0-50 msec) and the auditory condition (150 – 200 msec) (Figure 1.12a). The control group shows early increases in response to the combined condition in the parietal region and response to visual modality during the 150 – 200 msec span (Figure 1.11b). The frontal

region for controls is rather tempered until the 150 – 200 msec period, where there is a more vigorous response to the combined audiovisual condition (Figure 1.12b).

Group	Collapsed: (At/Ant, AtVt/AntVnt) Average Gamma Left Frontal Region (μV^2)	Collapsed: (At/Ant, AtVt/AntVnt) Average Gamma Right Frontal Region (μV^2)	Hemisphere x Group
Control	26.66 (±40.3)	15.74 (±14.9)	
Autism	13.44 (±11.0)	58.42 (±73.9)	
F-value			4.93
p-value			0.04*

Table 1.12 Frontal hemispheric differences in gamma activity for collapse of Auditory and Audiovisual responses.

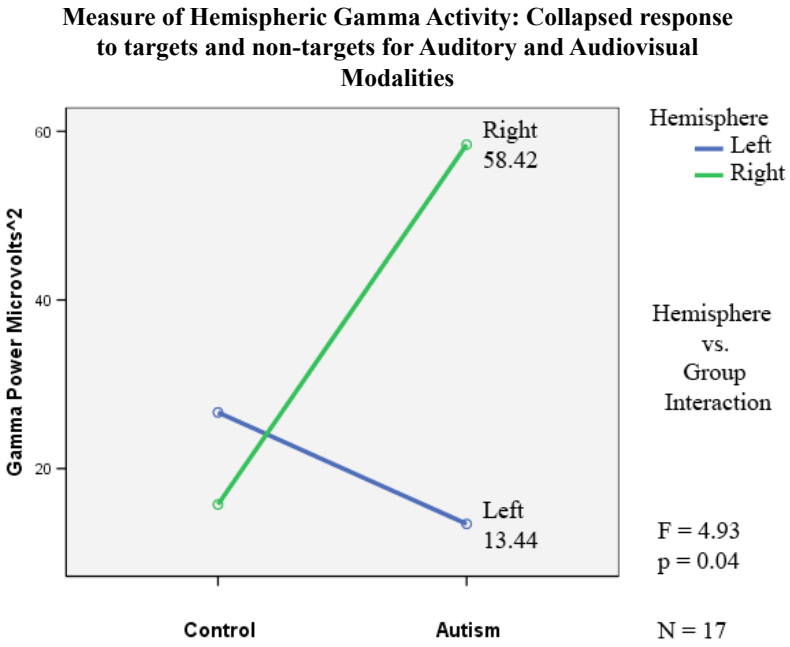
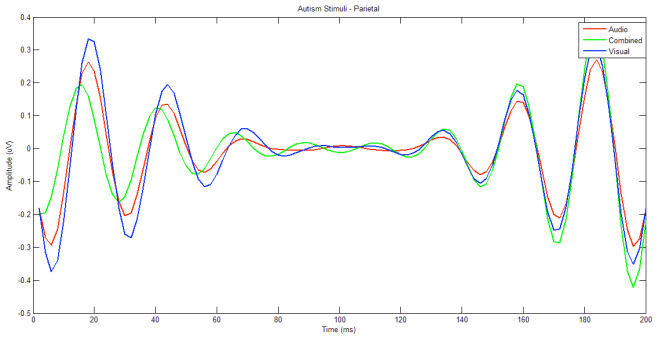
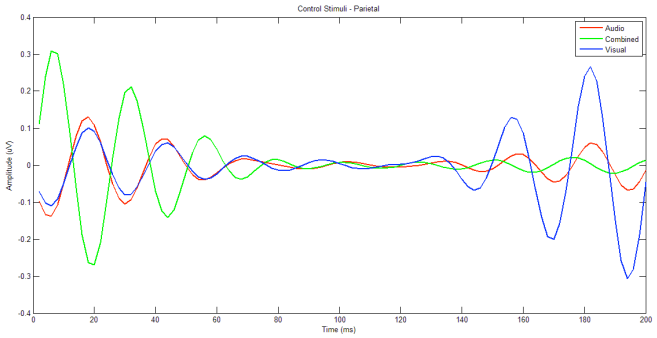


Figure 1.10 Hemispheric differences in gamma activity

Gamma Frequency Activity in Parietal Region, all modalities

A) Autistic Group Grand Average



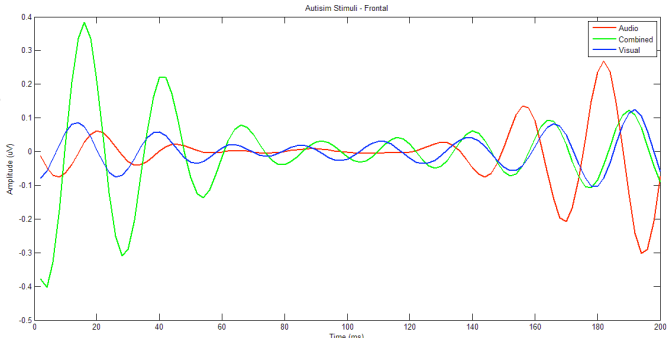


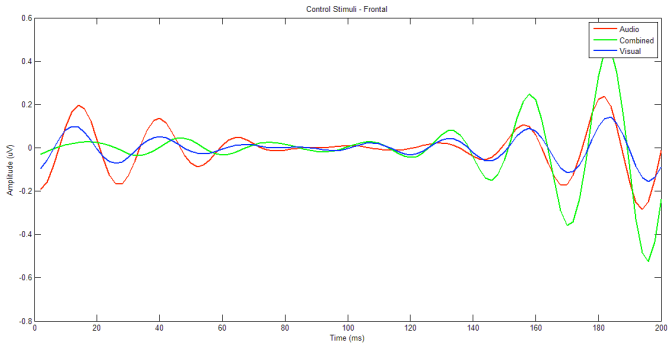
B) Control Group Grand Average

Figure 1.11 Parietal gamma activity: all modalities

Gamma Frequency Activity in Frontal Region, all modalities

A) Autistic Group Grand Average





B) Control Group Grand Average

Figure 1.12 Frontal gamma activity: all modalities.

1.5 Discussion

The purpose of this study was two-fold. First, investigations attempted to link some cognitive and behavioral symptoms of autistic spectrum condition with atypical sensory processing through measureable differences in electrophysiological recordings. Secondly, based on the quantified differences in measured recordings, investigations attempted to provide differences in electrophysiological recordings of ASC subjects and controls that could potentially support our lab's previous postmortem findings of underlying neuroanatomical and cytoarchitectural differences. However, it must be noted that there is limited capacity to what can be inferred concerning more complex behaviors associated with ASC, such as the main overarching deficiencies (appendix A) by which individuals are evaluated.

1.5.1 Behavioral Outcomes

The data from converging studies suggest that differences exist between the sensory processing of audio and visual stimuli between ASC subjects and controls, both in the early and later stages of cognitive processing (49). Previous findings imply that there are atypical neural connections in the cerebrum of ASC subjects, leading to abnormalities in cognitive sensory processing functions – e.g., target discrimination and attention (49). Researchers have hypothesized that because of the shorter early ERP latencies, one could anticipate that the response times would actually be shorter. It is possible that an observation of reaction times actually being delayed may not be due to a dysfunction in the primary cortices, but rather due to a dysfunction in the secondary cortices through the emanating downstream connections to regions of higher cognitive functioning (e.g. parietal and frontal cortices, hippocampus, etc.) (49).

In the present study, significant results were found during the unimodal visual task; however, no significant differences were found during the auditory or audiovisual tasks. We believe that the significant differences in reaction time and error rate observed during the visual modality could be related to visual processing differences associated with the decreased latency measured in the early-evoked visual N100 component.

Individuals with autism uniformly had slower reaction times, though they displayed earlier ERPs related to early sensory processing. Such findings could be founded as indiscriminate responses to stimuli. Because the ASC individuals cortically respond to all incoming stimuli more expeditiously, it may create an overabundance of sensory information waiting to be processed in downstream cognitive processes. The inability to properly filter significant and insignificant information could create the disparity that was observed in reaction times and average number of errors.

While there was no statistical difference between the groups' performance in the auditory and audiovisual modalities, there were observable differences in average number of errors and reaction times. This may be due in part to the level of demand that was required of all subjects. Considering that the subject pool consisted of high functioning ASC individuals, it is possible that the task was not cognitively demanding enough to display significant differences in performance in comparison to controls. However, despite the lack of significant behavioral differences in the auditory and audiovisual modalities, other metrics of measurement showed statistically significant variations between the groups. This could possibly suggest the use of compensatory processing mechanisms in task completion, which will be addressed later, as such behavioral measures will receive additional attention as they relate to the topics of discussion.

1.5.2 Visual Measures

Autistic individuals are often categorized as having abnormal responses to sensory stimulation in the form of hypersensitivities and domineering interest in singular sensations (28). Some reports have suggested that nearly 90% of ASC individuals experience sensory-perceptual abnormalities (40). The cognitive processing of sensory stimuli requires a series of steps, including initial feature translation, target discrimination and eventual allocation of conscious attention functions (49). To date, there is less literature on ERP response to visual stimuli processing in ASC as compared to auditory stimuli, and most visual processing studies are coupled with auditory processing

Atypical visual processing and behavioral responses to visual stimuli have been associated with autism; however, the reports concerning differences in visual processing have been varied, from enhanced detail perception to impairments in processing complex information (14). Tasks measuring visual event-related evoked potentials have shown that ASC individuals atypically respond during early stages of visual processing (99). Research has also indicated that during visual processing tasks, ASC subjects will display an enhanced, exaggerated response to non-target distractors while cortical structures associated with integrative functions display decreases in connectivity (12). Collectively, studies concerning visual processing appear to suggest complications in integrating relevant details into a whole object perceptual representation (13).

In this study, the analysis of event-related potentials associated with subject response to unimodal and bimodal oddball stimuli yielded several statistically significant differences between the individuals with autism and the neurotypical group. It is believed that the decreased latencies for the ASC group, relative to the controls, are indicative of cortical hyper-activity in early sensory processing. The ASC group displayed a significantly faster early-ERP response during the visual unimodal task, e.g., early N100 visual component.

The tempo-parietal N100 component in general has been related to pre-attentive cognitive priming and selective attention (61). In the present study, though the ASC individuals' visual (Vt, Vs) tempo-parietal N100 component (thought to capture processing within the "what" visual pathway) average occurrence was approximately 24 msec earlier than the control group, this did not translate into improved reaction times, or error rates. Interestingly, it was actually the opposite with the ASC group displaying significantly slower reaction times and an increase in the number of errors. The ASC group's reactions to the visual targets were nearly 60 msec slower than the control group, and as a group had committed more than three times the errors in responses. Though neither groups' latency measures were deemed to be abnormal, the faster ERP responses found in the ASC group could be related to cytoarchitectural differences, such

as minicolumnar irregularities, predisposing the individual to hyper-excitable electrophysiological activity (24).

Research published by Sokhadze *et al.* (2009, 2010) found that during a visual oddball protocol, of ASC subjects versus controls, ASC subjects displayed attenuated amplitudes of the N2b (N200) component in response to target stimuli. In our study the N200 latency response to visual non-targets (Vs) was significantly faster in the ASC group, as compared to the control group; however, there were no latency differences between the groups in response to the visual target. The N200 has been associated with attention to stimulus and target recognition. The fact that the N200 latency to visual non-targets in the ASC group occurred much early than the control groups could be indicative of deficits in stimulus discrimination.

Measures of selective attention in autistic individuals utilizing simple visual oddball tasks typically show no differences in behavioral measures; however, when the task becomes more complex – either utilizing spatial changes or multiple modalities – ASC subjects have been found to have attenuated amplitudes to deviant targets (31). More complex visual attention tasks often have the effect of prolonged reaction times and diminished accuracy in the ASC population (62). Such findings suggest that increasing the attention demands of a task has both physiological and subsequent behavioral effects and have been supported by a number of studies, (54, 101).

A visual discrimination task by Baruth *et al.* (2010) found early-exaggerated oscillations of positivity and negativity within the first 200 msec, a time period associated with immediate detection and classification of stimuli. The observation that the aforementioned often occurs with task irrelevant stimuli further suggests atypical task orientation for ASC subjects (6). Baruth *et al.* (2010) suggested that the amplified responses to sensory inputs in the early stages might lead to a large-scale cortical inundation of regions tasked with sensory integration, leading to dysfunction. Additionally, the amplified and delayed early responses to target stimuli may reflect hypersensitivities to stimuli, which could in turn delay processing (6).

Possibly more reflective of such deficits were the behavioral measures that showed ASC subjects had a significantly higher rate of error, presumably indicative of disruptive selective attention and executive functioning (6). Our recent subjects displayed significant differences as well; the ASC group's average number of errors as well as the measured reaction time for the group were noticeably larger in comparison to the control group. Additionally, the ASC subjects of this study also displayed exaggerated activity in the early-evoked periods of sensory processing, as evidenced by more expeditious latencies and in the early ERPs and exaggerated gamma responses that will be discussed later.

The inclusive literature of ERP data hints at the notion that the neural circuitry for early, low level visual sensory processing is unaffected in ASC, yet functions of higher level sensory processing, e.g., attention to and target discrimination of visual data, is impaired (49). Differences in response to traditional oddball tasks observed in autism spectrum condition may be reflective of atypical neural connections specifically affecting working memory (49).

In the present study behavioral measures of reaction time and accuracy within the ASC population showed variation from the controls and several electrophysiological measures of response to stimuli differed as well. This study's findings suggest some aberrations in visual processing in ASC.

Most studies indicate an increase in latencies, attenuated amplitudes and aberrant behavioral measures being associated with enhanced task complexity. Collectively, researchers have suggested that the processing of more complex stimuli requires greater cognitive use of the attentional networks and enhanced allocation of neurological and energetic resources. Thus, any variations in the functioning of lower or higher-level processing networks may have deleterious affects (62). We suggest that the basis for the measured irregularities in electrophysiological activity are related to underlying neuroanatomical differences in the cytoarchitectural arrangement of cortical minicolumns.

1.5.3 Auditory Measures

Children with autism typically display a reduction in the ability to process various modalities of information; generally the effect of modality impairment is greater for auditory stimuli than visual stimuli (34). This effect of impairment may be highlighted by deficiencies in processing novel or rare stimulus information (90). However, because of the heterogeneity of ASC, a general pattern of ERP activity for the condition has not been established (90). Auditory processing measures have consistently displayed early and late stage processing differences. ASC subjects have often displayed early-evoked N100 potentials with dampened amplitudes in response to targets during auditory oddball tasks (60, 71).

In our study event-related early processing responses were inherently faster for the ASC group; however, there were no statistical differences in the early potentials associated with processing. Numerous studies employing simple, pure-tone stimuli, e.g. basic auditory oddball tasks, have reported a decrease in auditory N100 latencies for ASC individuals (36) and in some cases attenuated amplitudes. Some have suggested that quickened N100 responses are representative of more efficient low level processing. This author would believe that early latencies in ASC individuals could be inherently related to hyper-connectivity within the low level processing cortices.

A multitude of research has shown that ASC subjects display abnormal latencies and amplitudes related to early auditory processing, even when there was no measurable difference of reaction time and percent errors (49). One such study found that ASC children had smaller component amplitudes in response to target auditory stimuli deletions (69). Martineau *et al.* (1984) found via an oddball paradigm that ASC subjects displayed decreased latency in regards to the early-evoked ERPs, such as the N100. Our results mirror Martineau's findings in that our ASC subjects displayed decreased latencies in the N100 component as well, but unlike Martineau's findings the differences in our study were not significant.

Electrophysiological studies have been used to measure the cortical activity associated with selective attention and have been successful in demonstrating concepts concerning the cognitive limitations an individual experiences when faced with complex tasks (62). In an auditory study of high functioning autistic adults researchers observed that the ASC individuals displayed both behavioral deficits in correctly attending to target sounds as well as displayed irregularities in ERPs – both early and late (95). The ASC individuals in the aforementioned study displayed more sustained early-evoked N100 peaks.

In the present study there were observed differences in the rate of errors, with ASC subjects committing approximately three times the amount of total errors during the auditory only task. However, the differences were not statistically significant, possibly due to the limited number of subjects analyzed in the measure. In other studies involving the measurement of event-related potentials researchers have observed that the auditory evoked N100 potential subcomponents displayed differences as compared to the neurotypical group (16). The ASC subjects had larger lateral N1a amplitudes, but showed attenuation of the posterior N1 component (16). Developmental age differences were noted in which the youngest children in both cohorts showed larger negativities than the older children (16). Orekhova *et al.* (2009) observed that ASC children had diminished N100 amplitudes over right mid-temporal regions and decreased N200 amplitudes over frontal sites in response to paired acoustic click presentations, which the authors suggested may be indicative of impaired attentional networks. Additionally, Orekhova *et al.* (2009) findings suggested atypical right hemisphere processing.

Cortical hyperexcitability and atypical activity seem to occur across the spectrum of modalities. Kemner *et al.* (1994, 1995) found that there were increases in electrophysiological activity to novel stimuli in the form of larger N200 amplitudes in fronto-central areas.

Though our findings during the auditory task did not yield any significant differences in the behavioral or event-related potential measures, there were some

differences associated with cortical coherence measures. These findings will be discussed more thoroughly in the section below on cortical coherence and gamma frequency oscillations.

1.5.4 Audiovisual Measures and Multimodal Integration

Expectedly, if there are deficits in single modality stimulus processing, one would naturally expect there to be deficits in tasks where the individual is required to integrate information from multiple modalities. The observed deficiencies associated with ASC individuals are believed to be reflections of the inability to successfully filter and/or process multiple modalities, e.g. visual, auditory, concurrently (73). Multimodal audiovisual tasks have found the disconcerted stimulus presentation will often elicit more readily observed processional deficits (62). Some investigators have suggested that deficits in cross-modal sensory integration are at the core of the behavioral symptoms associated with autism (86). Previous works have proposed dysfunction within neuronal physical connections between and associated with pyramidal cells may lead to a failure of integrating sensory information into a context representative of the stimulus event (102).

Individuals with autism appear to have deficits related to early automatic sensory processing, thus causing a reliance on downstream cortical networks, which became overwhelmed, leading to a systemic failure of networks related to higher cognitive functions (10, 35).

In the present study, the N100 component latency for audiovisual non-targets occurred statistically earlier for ASC subjects over fronto-central electrodes. As previously mentioned, the N100 potential may be related to early selection of relevant information (61). As with the other modalities the hastened component latency was not matched with faster reaction times or improved response to target stimuli for the ASC group. The results in this case may also suggest that the ASC subjects are hyper-responsive to stimuli without regard to context. Suggestions of visual processing being dominant over

auditory processing may coincide with latency differences for audiovisual N100 was similar to that of the visual N100.

The N200 component has been associated with higher cognitive functions, e.g. attention and deviant stimulus detection (61). It has been reported that when an ASC subject is passively performing an oddball task, in response to novel stimuli they will display greater amplitudes in the N200 component (54). In the current study it was observed that over the tempo-parietal region there was a significant difference between groups in the amplitude of the negative deflection for the N200 component in response to the audiovisual targets and non-targets. The ASC group did show differences between the responses to audiovisual targets and non-targets; however, the ASC group also displayed a significantly enhanced amplitude in response to non-targets, which may be indicative of deficits in cognitive discrimination between targets and non-targets as insinuated through other measurements.

The P300 component is often associated with measures of cognitive workload and context updating (61). Kemner *et al.* (1994) reported that ASC individuals displayed increases in P300 amplitude over parietal sites in response to novel stimuli during an oddball task. The current study found that the ASC group had enhanced positive deflecting P3b component amplitude while both groups had nearly identical latencies over parietal locations. It is believed that this is related to the ASC group's deficiencies in pre-attentive priming and/or exaggerated responses to stimuli in general with atypical activity associated with target discrimination. One could correlate the increased response in early processing networks with increased parietal activity based on the notion that heightened global activity and processing "congestion" between the processing of targets and non-targets leads to a downstream exaggerated parietal response. Additionally, the findings could be due to increases in baseline cortical activity. Furthermore, It may also be possible that the task was even less difficult for control subjects than it was for the ASC subjects and did not demand the downstream cognitive attentional resources that it did for the ASC subjects. Together the electrophysiological and behavioral observations

are indicative of ASC individuals showing hyper-connectivity in the posterior region and possible compensatory mechanisms such as those suggested with Sokhadze *et al.* (2009) due to the absence of statistical differences between reaction times and error rate.

In an attempt to determine any general stimulus response differences cross modal and stimulus (target versus non-target) comparisons were made. A statistically significant between group difference of the N100 component amplitude difference was found in the tempo-parietal region in regards to collapsed modality stimulus response: targets versus non-targets. The neurotypical subjects showed significant general amplitude increase in response to targets, as compared to non-targets. This is in contrast to what was observed with the ASC individuals. While ASC subjects did have enhanced amplitudes in response to targets over non-targets, the difference was quite small when compared to the difference of the controls. Again, N100 is related to early selective attention and target recognition, the similarities of the ASC group's response to both targets and non-targets are once again suggestive of deficits in early target discrimination.

Evidence has suggested that the mechanics of multimodal sensory integration begins to fail during the stages of processing of 150 – 175 msec post-stimulus, when the formation of a coherent precept is dependent on the coupling of feature information from distinct cortical structures (88). It was reported that ERPs peaking around 175 msec displayed significant differences, suggesting that responses in this time frame may be associated with multimodality sensory processing deficits in individuals with autism (88).

In the present study we found that the ASC subjects generally had shorter latencies for the N100, but as the later N200 and P300 components appeared, then difference in the latencies between the two groups dramatically changed. By the N200 component the difference had changed from approximately 25 msec differences at the N100 to around 13 msec. By the P300 the average difference in response to targets and non-targets latencies had dropped to around 4 msec. Though these changes have not yet been analyzed for significance, they may be indicative of processing deficits during

the aforementioned time frame. As repeatedly stated, shorter latencies in early responses were not indicative of behavioral improvements, but quite the opposite.

The behavioral deficits of ASC individuals may be contextualized as arising from disordered cortical integration of sensory stimuli, that because of developmental abnormalities, there exists a disparity between regions honed for specialized processing and integration between regions (90). This idea is more simply explained by the possibility that specific regions tasked with processing a particular set of stimuli are essentially disconnected from other processing units (90). Several groups of investigators have suggested that in some cases of autism the inherent ability to perceive and process one modality may not be flawed, but the dysfunction of sensory perception lies within the ability to coordinate the integration of the individual modality networks (17, 47, 50). High levels of "cortical noise" related to an increased ratio of excitation to inhibition in cortical regions important to information processing have been suggested as a key irregularity in ASC subjects (90).

For high functioning ASC individuals it generally appears that higher cognitive inhibitory control remains intact, however it also appears that the parietal and frontal regions of these patients display increased activity related to standard and novel stimuli (90). It has been conjectured that there could be two reasons for the observed cortical hyperactivity: ASC subjects may have atypical neuroanatomical development, or ASC subjects may employ unconventional compensatory cognitive processing techniques that require more cortical activity (90). Tannan, *et al.* (2008) found that in a sensory discrimination task, ASC individuals failed to adapt to the changes in the stimulus while controls did, and the authors suggested that the lack of adaptation was indicative of the hyper-excited network based on ineffective GABAergic interneuron network mediation.

Cortical hyperexcitability associated with anatomical minicolumn pathology may be the basic anomaly affecting a subject's attention span as well as the individual's mitigation of sensory arousal (25). The exogenous overstimulation of an ASC individual's

cortex would cause improper functioning due to the excess “cortical noise,” further affecting how the individual relates to stimuli as well as other people (84).

Hypotheses concerning exaggerated responses and local hyper-connectivity are bolstered by neuroanatomical findings of increased numbers of smaller and denser minicolumns – minicolumn cells - within frontal and temporal lobes (23). The GABAergic interneurons are responsible for the inhibitory surround of ASC minicolumns and are found at a decreased ratio to the excitatory pyramidal neurons (23). The coupling of decreased spatial distribution of pyramidal cells and disruption in the balance of excitation/inhibition can promote more localized connections and have a global effect on interregional connectivity (23). The increases in local intraregional excitation would serve to decrease stimuli specificity and functioning of interregional cortical networks (23). The excess accumulation of localized networks in the frontal and parietal regions could create a scenario where those regions are functioning in isolation at the expense of network integration (53). Corroborating evidence has been suggested through displays of the incongruously activated cortices associated with ASC subjects (90). Specifically there have been demonstrations of atypical exaggerated responses to sensory stimuli, coupled with deficits related to attention orientation as well as indices of dysfunction concerning downstream higher cognitive level processing (90).

It is believed that any disruption to the networks associated with “top-down processing” would be observed through markers indicating hampered sensory integration accompanied by a system of disjointed cognitive processing (53). A cortical system affected in such a manner is believed to predispose the ASC individual to processing individual details separately, eventually leading to sensory information overwhelming the regions responsible for higher cognitive processes and an inability to integrate the various details into a coherent whole (53). The observation that ASC individuals are inclined to process the low level minutiae at disproportionate amounts suggest a possible “bottom-up” compensatory mechanism and “hyper-specialization” of distinct cortical regions (53).

1.5.5 Cortical Coherence and Gamma Frequency Activity

It has been found that the co-activity of several cortical regions is needed to enable efficient functional sensory processing and that ASC individuals often show irregularities within the spectrum of aforementioned governing factors (53). Likewise, ASC individuals may have developed compensatory networks or mechanisms to process and respond to sensory information (53).

Several publications have suggested that the frontal lobe is the cortical region at the center of the disrupted connectivity, stemming from dysfunction within the lobe itself as well as the long connecting fibers running to and from the region (53). These reports have been supported by studies reflecting dysfunction within the realms of cognitive inhibition and executive functions (53). A disruption of the network linking the frontal lobe to other cortical regions would impair cognitive processing on a global scale, causing dysfunction in "top-down processing," (53). Converging data suggests dysfunctions in sensory integration associated with ASC most likely arise from asynchronous activity through cortical networks.

In the present study the dipole coherence measures were measured as peaks of coherence occurring in the time blocks of 100 – 200 msec and 300 – 600 msec within the frequency range of 30 – 45 Hz. For coherence measurements only responses to target stimulus were evaluated. During single modality analysis the lone significant difference between groups was found during the auditory modality, in which the ASC group displayed general increases in activity across both left and right frontal regions with respect to the parietal reference. This was in contrast to control subjects who displayed a predominance of activity in the left frontal region as compared to the right.

An analysis of target response across modalities yielded a significant between group differences in the coherence coefficient within the frontal regions. Once again, hemispheric difference was displayed as the control group showed preferential left frontal activation as compared to the ASC group, which displayed more equal global activation of both right and left. Of note, there was only a minute difference in left frontal activity

between the controls and ASC subjects, thus it could be reasoned that the ASC subjects showed significantly more global frontal activity than the control subjects. This notion was visually apparent via Figure 1.9, displaying two age and gender matched group representatives. In Figure 1.9a, the ASC individual visibly displayed more total posterior – frontal activity.

Isler *et al.* (2010) found that during a visual stimulus task ASC subjects showed reductions in inter-hemispheric cortical synchrony compared to controls, though they displayed increases in activity power in both hemispheres. The dysfunctional inter-hemispheric connectivity was associated with hypersensitivity in sensory processing cortices, as evidenced by decreased latencies for early, evoked responses. Findings could suggest that aberrant cortical activity increases cause dysfunction in inter-hemispheric functional connectivity.

It has been previously reported that stimulus mediated increases in spectral power, specifically in the gamma range, is related to enhanced synchrony and degree to which cortical networks are recruited to process sensory information (64). It is believed that reduced or excessive activity within the necessary cortical networks suggests aberrant cortical means of sensory integration, as noted within the ASC population, which in turn would suggest disrupted perceptual binding (64)

In the present study, in order to attain larger group numbers for calculation, measurements of gamma activity during visual tasks were excluded from the cross-modal analysis. Once the data from the auditory and audiovisual tasks were collapsed along with responses to targets and non-targets, hemispheric comparisons of activity were made. Analysis of the frontal left versus frontal right hemispheres found a significant difference in gamma activity between ASC subjects and neurotypical controls. The individuals' with autism displayed a significant bias towards right frontal hemispheric gamma activity. The exaggerated response could be indicative of frontal region hyper-connectivity, such as that explained by the aberrant minicolumn hypothesis and findings of minicolumn pathology within frontal regions in post-mortem tissue.

Interestingly, while gamma activity was found to be exaggerated in the frontal right hemisphere of ASC subjects, coherence values for that region were actually less than the left frontal region in ASC subjects. With that in mind it is plausible to speculate that excessive gamma activity within the right frontal region was deleterious to the establishment of functional connectivity between frontal and parietal regions.

A study by Kana *et al.* (2007) found that reduced functional connectivity did not coincide with reduced cortical activation of the regions of interest, and that under-connectivity between regions occurs despite cortical regions displaying some form of activation. Such findings propose the hypothesis that dysfunctional connectivity is not a result of reduced cortical region activity but a reduction in synchrony (52). In the aforementioned study the largest dissimilarities in cortical connectivity appeared to be between long distance, fronto-posterior regions, especially during tasks of executive function.

However, based upon graphical representations of the data it appeared that ASC subjects experienced increased levels of gamma activity in the posterior parietal regions as well, leading credence to the hypotheses that suggest that the regions can become more functionally isolated due to apparent intrareal hyper-activity. Additional hypotheses centered on decreased corpus callosum volumes could explain intra-hemispheric hyper-activity (89).

Kikuchi *et al.* (2013) recently released a study investigating the laterality of electrophysiological cortical activity in ASC subjects versus controls, finding that ASC subjects displayed significantly high right hemispheric gamma activity levels. In that study they found no differences in measured intra-hemispheric coherence within the gamma band, although the parieto-temporal network showed a significantly decreased laterality index for the left hemisphere in ASC individuals, as aforementioned (57). Other studies have reported either an increase in right hemisphere functional connectivity laterality or decreases in the left hemisphere during rest and working memory tasks (56, 65). Courchesne *et al.* (2008) described aberrant right hemisphere activity and lateralization

during tasks associated with speech in ASC individuals. A study by Orekhova *et al.* (2007) found that EEG measured excesses in gamma frequency activity was significantly related to severity of developmental delays in ASC individuals. Orekhova *et al.* (2008) found that higher levels of frontal gamma activity corresponded with decreased abilities in auditory sensory gating.

As previously mentioned, global comparisons found that the ASC group displayed general increases in gamma activity within 0 – 50 msec and the 150 msec – 200 msec time frames in the parietal region along with frontal increases in activity for the combined condition (0-50 msec) and the auditory condition (150 – 200 msec). The control group displayed early increases in response to the combined condition in the parietal region and response to visual modality during the 150 – 200 msec span. The frontal region for controls is rather tempered until the 150 – 200 msec period, where there is a more vigorous response to the combined audiovisual condition.

Another visual study employing the use of Kaniza illusory figures, test measuring induced gamma oscillations, found significant discrepancies in cortical activity between the ASC group and the controls (18). The individuals with autism showed a global increase in cortical activity, consisting of an early enhancement of gamma activity at 100ms and induced peaks occurred 50 – 70 msec earlier than controls (18). Brown *et al*. (2005) suggested that the atypical gamma oscillations were due to diminished “signal to noise” ratio on account of attenuated inhibitory activity.

Findings in the current study indicate a lack of variation in gamma activity in response to targets and non-targets. Such findings intimate that the indiscriminate activity observed with ASC individuals may be correlated with previously reported exaggerated responses to any presentation of sensory stimulus (90). A hyperactive cortex coupled with diminished inhibition networks may enhance the level of “cortical noise;” irregular cytoarchitectural favoring excitatory synapses at the local level while neglecting more global connectivity may drive dysfunctions in stimulus detection and selection (87).

Electroencephalogram studies have helped elucidate the existence of anatomical differences between local and global cortical networks (17, 85). A model demonstrating the number of active cortical synapses per unit volume has helped explain the interactions between local and global fields and suggests that the individual combinatorial actions of local regions is responsible for the global appearance of synaptic activity (70). Additionally, observations of the aforementioned model have suggested that a bottom-up effect exists where local activity generates the global field, yet in turn, the global field will exert a top down effect upon the local cortical region activity to assist in generating coordinating activity (70). A dysfunction in this feedback loop will result in what is termed as “hypo-coupling”, where the global field activity has little to no effect on the activity of the isolated regional generators (70). If a condition of hypo-coupling exists, then coordinated activity between regions is affected and there is a deficit in comprehensive object processing, each region acting in isolation in response to stimuli (70). It is believed that hypo-coupling may be the result of diminished long-range connection fibers between regions or excessive intraregional activity (70). Altogether, the aforementioned model suggests that irregularities in global field activity and interregional functioning, may lead to atypical sensory information processing in ASC individuals (70).

It has been proposed that multisensory processing and integration deficits are the common theme linking the hypotheses of the core dysfunctions of autism, e.g., weak central coherence, temporal binding, etc., (47). Literature reviews would suggest that sensory processing modalities in autism are not tied to just one specific dysfunctional system, but to several modalities that fail to integrate the processed information from each into a coherent precept (47).

1.6 Conclusions and Summary/Future Implications

1.6.1 Conclusions

It has been proposed that the processes of neural network integration along with regional specialization are imperative for normal anatomical and cognitive development (17). The balance between neural integration, cortico-region function and specialization

development persists through adolescence, yet a disruption of these systems could be tied to ASC cognitive symptoms.

Brock *et al.* (2002) further described their hypothesis as such: the developing cortex of a neurotypical individual delicately balances increased specialization within cortical regions while also enhancing the complex connectivity between the regions. This is in contrast to the development of the ASC individual's cortex, where increased functional specialization within neuro-regions leads to further isolation of activity during cortical maturation (17, 85). The differences in development between neurotypical and autistic individuals can be evidenced by ASC individuals' impaired functioning during tasks that require the co-activation of multiple regions, but normal or enhanced abilities during tasks reliant on the functions of an isolated cortical region (17, 85). Thus, the disparities between the possible endophenotypes of ASC may be related to the extent of the neuro-integration deficit; low functioning individuals would be expected to have more widespread, universal integrative deficits, even between adjacent cortical regions, while high functioning individuals would most likely have greater connectivity between adjacent regions, with deficits between more distant regions (17). Where lower functioning individuals would have greater difficulty with simpler tasks, deficits in higher functioning ASC individuals wouldn't arise until co-activation and integration of incongruent regions was necessitated (17, 85).

Brock *et al.* (2002) additionally suggested a hypothesis concerning the development of ASC that posits aspects of the observable symptoms of ASC are related to atypical cortical coherence and temporal binding. The aforementioned researchers suggest that impairments in the synchrony of cortical activity would influence the individual's cortex to rely on "combination coding," having a downstream effect of diminished automatic sensory integration and result in representations of whole objects as distinct individual pieces. It is believed that the impairment in functional connectivity only exists between regions; however, the intrareal activity of neurons within regions may be intact or even enhanced, increasing local qualitative processing (17, 85).

Collective research suggests that ASC is a condition of neurobiological origin and with a multitude of possible genetic contributors (53). More confounding to understanding the cause is the notion that research has found several brain regions, cortical and subcortical, to be either atypical in their cytoarchitectural arrangement or with their overall functioning (53). Many of the typical demonstrative symptoms of ASC are associated with impairments in social interaction, communication, and repetitive behaviors. It can be reasonably assumed that the governing of such behaviors is reliant on an intact cortical executive function system. Brock *et al.* (2002) suggested that the observable symptoms of autism were related to decreased integrative capabilities between specialized intraregional neural networks, reflected in a decrease in frequency oscillation coupling and coherence, between cortical regions.

Hypotheses based on dysfunctional connectivity in autism attempt to correlate differences in anatomical and functional connectivity to the observable characteristics associated with ASC individuals (89). Previous studies have found a relationship between an ASC individual's ADOS and ADI-R scores and measurable decreases in functional interregional connectivity (89). Just *et al.* (2007) found that the higher the ADOS score the more disrupted the frontal-parietal functional synchronicity: a trend that appeared also to apply to those with poorer social skills and more severe repetitive behaviors in other studies. The findings suggest a correlative trend of diminished fronto-posterior cortical connectivity and severity of ASC behaviors concerning repetitive behaviors, social interaction, and language difficulties.

Findings of increased connectivity within posterior regions in those deemed to display more severe ASC traits could be evidence of the formation of compensatory mechanisms, or possibly evidence of the prevalence of more short connection fibers due to minicolumn pathology (23, 89). Long distance anatomical connections, as evidenced by white matter tracts have suggested that greater behavioral disturbances arise with decreases in anatomical white matter connectivity between regions (89). Converging results from several studies fit the theme of under-connectivity, showing that diminished

white matter integrity and connectivity appear to be underlying many of the observable symptoms of ASC (89).

Because of the wide variety of symptoms associated with a classification of ASC, it is likely that a global manifestation of disruptive cortical connectivity is present (53). This idea is supported, in part, by the myriad of behavioral and neuroanatomical findings across possible endophenotypes (53). It is possible that the severity of ASC symptoms may be correlated with the degree to which the cortical connectivity is disrupted (53).

Superfluous numbers of neurons within regions such as the frontal lobe will have the consequence of distinct intraregional hyper-connectivity at the expense of global connections, further isolating the activity of the frontal cortices (53). Postmortem studies have found that the cortices of ASC individuals have diminished numbers of long interregional fibers paired with an observation of an overload of thin axons making short connections with adjacent regions (107). In one particular study, the researchers found evidence of reduced axon myelination in the frontal cortex (107). Altogether, a system predicated on the aberrant structure and number of individual neurons will have an effect of global proportions: a system wide level of insufficient connectivity and functionality (53).

While many other studies attempting to measure executive dysfunction in ASC individuals have shown reduced performance in task completion, particularly on protocols that affect attentional focus (17, 38). The current study would suggest that tasks of attention setting, sensory perception and integration, and responsive processes require a well-coordinated system of cortical modulation. The present work suggests that to achieve higher order cognitive functions there must exist a seamless communication between the early sensory processing cortical regions and the coordinated network of frontal-executive and posterior-integrative cortices. Additionally, this author suggests that a reduction in synchronized trans-cortical activity, as evidenced by excess lateralization of gamma activity, elicits the consequences of diminished capacity to integrate and

discriminate sensory stimuli, affecting executive control over attentional and responsive processes.

One may say that normal cognitive development is predicated fundamentally on the correct migration, cytoarchitectural arrangement and development of neural progenitor cells in the cortex (23, 24, 25). Any disruption of such, as previously described in the neuropathology of autism, may stymie any further developmental milestones related to higher order cognition and cognitive processes. It is believed that normal cortical and intellectual development is not only predicated on the gradual elaboration and specialization of cortical regions, but additionally on the formation of integrative connections between the specialized regions (17). Cytoarchitectural development dysfunction coupled with a gradient decrease in GABAergic neuron inhibition and prevalence of short excitatory connection fibers could in turn be the basis of impaired interregional connections, temporal binding and coherence between regions (17, 23). Such anatomical aberrations could be responsible for excess oscillatory and hyperactivity recorded by scalp electrodes above specific cortical regions. A combinatorial mechanism of excess activity, low temporal binding and interregional coherence could give segue to more difficult target discrimination as evidenced by increased ERPs and higher error rate in ASC subjects (18, 90).

The collective results of the present study showing ERP irregularities, differences in coherence and gamma activity during active sensory processing, suggest that ASC individuals are equipped with cognitive mechanisms that differ from neurotypical individuals. One would suggest that underlying biological differences correlate into electrophysiological and behavioral changes. It is the opinion of this author that changes in the cytoarchitecture of the basic minicolumn is inherently responsible for the changes in cortical activity and connectivity. This author believes that the associative cellular changes are the basis of atypical cortical sensory processing in ASC individuals.

1.6.2 Summary and Future Implications

Though EEG recordings have poor spatial resolution, the temporal resolution of such measurements far exceeds most other neuroimaging techniques. Thus, ERP recording protocols are a legitimate measure of the time course of cognitive functions. More conclusively, ERP protocol methodologies provide a comprehensive way to investigate the spatial and temporal specifics of atypical neuro-processing associated with cognitive developmental disorders.

Currently hypothesized models regarding intra – and interregional cortical connectivity describe the importance of both combinatory and isolative roles of various neural systems in relation to global processing and integration of exogenously and endogenously elicited cortical activity. Previous findings of this laboratory have shown observable neuroanatomical minicolumn pathologies as well as imbalanced ratios of excitation to inhibition (90). The aforementioned findings coupled with findings in comparable analyses from other researchers further supports the notion of "functional disconnectivity" in ASC.

We propose that the findings in this study additionally corroborate aforesaid hypotheses and that ERP based protocols are apt techniques for further elucidation of excitation versus inhibition irregularities related to sensory response and cognitive processing.

Further analysis of event-related potentials, coherence and gamma frequency oscillations in autism may provide additional insights into the observed neural and cognitive irregularities associated with autism spectrum condition. Electrophysiological measures may hold the key to understanding the processes of how distinct cortical processing regions bind and integrate information within an individual to form a coherent understanding of external sensory information (26).

The DSM-V and additional literature have made behavioral classifications in ASC subjects related to hypersensitivities to sensory stimuli. The results of this study as well as previous studies in the lab further demonstrate that EEG/ERP related methodologies

could be employed to measure atypical responses and cortical activity in regard to multimodal sensory processing.

Our results are indicative that audiovisual oddball tasks are efficient at revealing some encumbrances ASC subjects have with sensory filtration of irrelevant stimuli. It is further believed that such protocols may be used to make strong correlative connections between the behavioral characteristics of ASC and electrophysiological neural activity. With such foundations in mind, the use of cortical measurements of electrophysiological differences may be instrumental in elucidating the underlying mechanisms of ASC.

The use of electrophysiological research may be indicated as part of the process of establishing the endophenotypes of ASC, where the characteristics of endophenotypes represent the underlying mechanism leading to observable behavior. The establishment of endophenotypes would afford clinicians and researchers alike the ability to forecast the development of the atypical social features associated with ASC.

If the idea of founding endophenotypes was to be successfully recognized, the early detection of such would confer the ability of clinicians to establish early, precise medical interventions for high risk individuals and to target their specific deficits during critical periods of development. Evidence from research assessing the advantages of interventional programs have shown that children with autism who enter interventional programs at earlier ages make greater gains in overall dampening of symptoms than those who enter programs when they are older (53).

With such goals in mind, it would appear that multimodal sensory integration analyses of ASC would be the most beneficial way to conceptualize the mechanisms at the base of composite symptomology of ASC and develop targeted medical treatments (49).

Our recent history of enhanced understanding of neuroplasticity may lead segue to interventional strategies that focus on increasing interregional cortical connections, particularly those that would engage both frontal and posterior cortical regions.

1.7 Limitations of Current Study

The ASC subject group consisted of only high functioning individuals, thus the task may have not been difficult enough to extract all possible differences in processing. Additionally, due to time and computing limitations, responses during tasks 3 and 4 were not evaluated. The evaluation of such would possibly yield more conclusive information concerning differences in the individuals' ability to properly allot attentional resources.

Dipole source localization from EEG recordings has endured some criticism; particularly the use of inverse solutions to elucidate the nature of brain localization (92). Srinivasan *et al.* (2006) suggested that because most spontaneous EEG recordings are produced by many spatially distributed sources on various scales, because of this the researchers believe using inverse algorithmic methods is ineffective. The researchers also believe the aforesaid notion is more specifically true for induced potentials.

Lastly, two different algorithms were used to produce results and figures for the gamma frequency data, though the degree of differences between the groups remained the same, some figures reported values in a different units of measurement.

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APPENDIX

A) Diagnostic and Statistics Manual: Criteria for Autism Spectrum Disorder

1) DSM – V Diagnostic Criteria for ASC:

An individual must meet criteria A, B, C and D:

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction.

2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated- verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people.

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases).

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold,

adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

D. Symptoms together limit and impair everyday functioning

2) DSM-IV TR Diagnostic Criteria for ASD

A. Six or more items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
    1. Qualitative impairment in social interaction, as manifested by at least two of the following:

        a. Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

        b. Failure to develop peer relationships appropriate to developmental level

        c. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

        d. Lack of social or emotional reciprocity

    2. Qualitative impairments in communication as manifested by at least one of the following:

        a. Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

        b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

        c. Stereotyped and repetitive use of language or idiosyncratic language

        d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

    3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

        a. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

        b. Apparently inflexible adherence to specific, nonfunctional routines or rituals

c. Stereotyped and repetitive motor manners (e.g., hand or finger flapping or twisting, or complex whole-body movements)

d. Persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Diagnostic Criteria for 299.80 Asperger's Disorder

A. Qualitative impairment in social interaction, as manifested by at least two of the following:

1. Marked impairment in the use of multiple nonverbal behaviors such as eye-to eye gaze, facial expression, body postures, and gestures to regulate social interaction

2. Failure to develop peer relationships appropriate to developmental level

3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)

4. Lack of social or emotional reciprocity

B. Restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least one of the following:

1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity of focus

2. Apparently inflexible adherence to specific, nonfunctional routines or rituals

3. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

4. Persistent preoccupation with parts of objects

C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

299.80 Pervasive Developmental Disorder Not Otherwise Specified

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder. For example, this category includes "atypical autism" - presentations that do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology, or sub threshold symptomatology, or all of these.

CURRICULUM VITAE

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Abbreviated Curriculum Vitae

I) Education

Professional Medical Doctor Degree: University of Louisville School of Medicine - Conditionally accepted for Fall 2013.

Graduate:

University of Louisville School of Medicine, Louisville, KY: August 2010 - Current

Degree: MS - Anatomical Sciences and Neurobiology, (Pursuing)

Post-Baccalaureate:

University of Louisville, Louisville, KY: August 2009 - May 2010

Undergraduate:

University of Louisville, Louisville, KY: January 2003 - May 2009

Degree: BS - Biology, (Cellular/Physiology);

BA - Communication

Florida State University, Tallahassee, FL: August 2000-December 2002

No Degree

II) Relevant Leadership Activities or Employment

Student Mentor: Acted as a graduate student mentor for a DuPont Manual High School junior student.

Graduate Teaching Assistant: Medical Gross Anatomy, August 2012 - December 2012. Acted as weekly rotating zone instructor, directed and assisted medical students in dissections, set up practice exams, assisted in assembling official course exams.

Lab Rotation: Dr. Guillermo Rougier, ASNB Dept., January 2011 - April 2011

Some instruction in the analysis of ancient mammal dentition

International Service Learning Program: Philippines Health Outreach; Dec. 2009

Health Information Outreach, Assisted in Free Dental Clinic

U.S. Army Corps of Engineers, Chemistry Internship: April 2003 - Sept. 2003

Data Validation, Sample Collection, Protocol Development

III) Official Lab: Dr. Manuel. F. Casanova, Psychiatry Dept., April 2011- Current

i) Research Interests:

Thesis Project: Audiovisual Sensory Processing in Autism.

Dr. Estate Sokhadze, (co-mentor)

Assisted Projects:

1) Variable Modalities of Face Recognition Processing in Autism

Investigators: Dr. A. Farag, Dr. Manuel F. Casanova, T. Gault, B. Dombroski

2) Effects of Ambient Prism Lens in Autism

Investigators: Dr. Kaplan, Dr. Edelson, Dr. Manuel F. Casanova, B. Dombroski

IV) Publications:

Abstracts:

Ryan M. B. Kiser, Zachary A. Clemans, Ayman El-Baz, Estate Sokhadze, Manuel Casanova. *2013 International Society for Neurofeedback and Research, ISNR Conference, Dallas, Texas: Abstract: Audiovisual Sensory Perception in Autism Spectrum Disorder - Aberrant Gamma Frequency Oscillations*

Ryan M. B. Kiser, Guela Sokhadze, Zachary A. Clemans, Estate Sokhadze, Manuel Casanova. *2013 Society for Neuroscience, Neuroscience Day University of Louisville*, Louisville, Ky. Abstract: *Audiovisual Stimuli Sensory Integration in Autism Spectrum Disorder Vs. Controls*

Ryan M.B. Kiser, Stephen M. Edelson, Guela Sokhadze, Manuel F. Casanova, Estate Sokhadze 2013 44th Annual Scientific Meeting: Creating Synergy. March 2013, Portland, OR. Abstract: Perception of Auditory Stimuli and Implications of ERP outcomes for Auditory Integration Training in Autism

Kiser, Ryan M.B., Sokhadze, Estate, Casanova, Manuel F. 2012 43rd Annual Scientific Meeting: Evoking Human Potential. March 2012, Baltimore, MD. Abstract: Selective Attention and Audiovisual Integration in Children with Autism

Clinical Manual:

Eugene Oetringer, Dr. Jaap Brand, Prof. Manuel F. Casanova, Brynn A. Dombroski, Jacqueline Drouillet, Prof. Michael Fitzgerald, Femke de Graaff, Ryan M.B. Kiser, Peter van Leen, Marian Molle, Jeroen Mulders, Gerard Out, David van Rooyen, Mariella de Sterke. (2011) The On Mental Health (OMH) Treatment and Prevention List: Therapies, Coaching and Prevention Techniques with Indicators for Delivering Results Today. Version 1.0. December 2011 www.onmentalhealth.org.

V) Awards and Recognition

Graduate:

1) University of Louisville: Society for Neuroscience, Neuroscience Day. 3rd place for excellence in neuroscience research, graduate student category.
2) University of Louisville Student of the Month, January 2013
3) Golden Key Honor Society

Undergraduate: Dean's Scholar, Dean's List