DISRUPTIONS IN THE SPATIAL FILTERING AND TEMPORAL PROCESSING OF LOW-LEVEL UNISENSORY AND MULTISENSORY STIMULI IN AUTISM SPECTRUM DISORDERS

By

Leslie D. Kwakye

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Neuroscience

December 2011

Nashville, Tennessee

Approved by:

Mark T Wallace, PhD

Craig Kennedy, PhD

Daniel Polley, PhD

Micah Murray, PhD

In loving memory of Ronnie Dale Dowell

ACKNOWLEDGEMENTS

The work contained in this document would not have been possible without the generous funding support by the National Institutes of Health, Marino Autism Research Institute, Vanderbilt University Graduate School, Vanderbilt Neuroscience Graduate Program, Vanderbilt Brain Institute (VBI), Vanderbilt Kennedy Center, and the Society for Neuroscience (SfN) Neuroscience Scholars Program.

I am eternally grateful to my kind, understanding, generous, and wonderful husband, best friend, and soul mate, Dr. Gunnar Kwakye, for his never ending support and encouragement. I would not have gotten my PhD without him. My parents, Carleen and Ronnie Dowell, are at the root of my success and I would like to thank them for their love. They encouraged and inspired me to learn and supported me throughout my education and career.

I am very grateful to all those with whom I have had the pleasure of working with during my graduate studies. I would like to thank my buddy Dr. Albert Russell (Danger) Powers III for always being there to discuss new and exciting ideas. His help and guidance with Matlab were invaluable, and I know he'll be an amazing doctor. Dr. Vera Blau-McCandliss has been a great friend and colleague. I will miss our discussions of fun ideas and coffee breaks during times of trials and tribulations. I am exceptionally grateful to Tiffany Woynaroski for her bottomless enthusiasm and help. I am also thankful to Jenifer Foss-Feig for her partnership and assistance in a large portion of the work presented in this document. I will greatly miss all the great scientific discussions that I had with the hardworking and intelligent fellow graduate students (Dr. Andrea Dunn, Juliane Fister, Dipanwita Ghose, and Aaron Nidiffer) in the Wallace laboratory. I am very grateful to the many undergraduate research assistances (Haleh Kadivar,

Brittany Schneider, Rachna Patel, Aniket Rali, and Adeola Harewood) that I have worked with throughout my graduate career.

I am eternally grateful to Dr. Mark Wallace for his untiring support, mentorship, and my professional development. His dedication and enthusiasm for science, perseverance, and critical interpretation of experimental results were a few of the countless qualities that I count myself incomparably fortunate to have gained under his mentorship. Through his guidance I have become a better writer and scientist and a stronger person.

Finally, I would like to express my heart field gratitude to my thesis committee. To Dr. Craig Kennedy, Dr. Micah Murray, and Dr. Daniel Polley, who have inspired, provided constructive feedback, and whose doors have always been opened to me. Thank you all for the insightful discussions, support, and mentorship.

TABLE OF CONTENTS

Page

DEDICATION ii
ACKNOWLEDGEMENTS iii
LISTS OF TABLES x
LIST OF FIGURES xi

Chapter

I. ALTERATIONS IN SENSORY PROCESSING IN AUTISM 1
  General Introduction to Autism 1
  Sensory Observations in Autism 2
  Unisensory Perception in Autism 3
    Vision 4
    Audition 7
    Somatosensation 8
  Multisensory Integration in Autism 9
    Integration of Complex and Social Multisensory Stimuli in Autism .. 10
    Integration Of Simple Multisensory Stimuli In Autism 13
  Anatomical Changes in the Autistic Brain 15
    Gray Matter 15
    White Matter 16
    Minicolumns 17
  Functional Changes in the Connectivity of Neural Networks in the Autistic Brain 18
    EEG: Oscillations 18
    fMRI: Functional Connectivity 20
  Potential for Disruptions in Fundamental Sensory Processing in Autism 21
    Unisensory Filtering as a Potential Sensory Disruption in Autism ... 21

        Multisensory Integration as a Potential Sensory Disruption in Autism 24
            Benefits of Multisensory Integration 24
            Contribution Of Multisensory Illusions To Our Understanding of Multisensory Integration 25
            Principles of Multisensory Integration 26
            Neurological Mechanisms Of Multisensory Integration 28
    Introduction to Current Topics 32
    References 33

II. AN EXTENDED MULTISENSORY TEMPORAL BINDING WINDOW IN AUTISM SPECTRUM DISORDERS: MULTISENSORY TEMPORAL BINDING IN ASD 52
    Abstract 52
    Introduction 53
    Methods 54
        Participants 54
        General Procedure 56
        Flash-Beep Task 57
        Data Analysis 59
    Results 60
    Discussion 64
    References 68

III. ALTERED AUDITORY AND MULTISENSORY TEMPORAL PROCESSING IN AUTISM SPECTRUM DISORDERS: AUDIOVISUAL TEMPORAL PROCESSING IN ASD 72
    Abstract 72
    Introduction 73
    Methods 76
        Participants 76

General Procedure 78

Tasks 78

Visual TOJ Task 78

Multisensory TOJ Task 81

Auditory TOJ Task 82

Data Analysis 83

Group Differences 84

Differences in the Temporal Window of Multisensory Integration 84

Results 85

Performance on the Unisensory TOJ Tasks 85

Performance on the Multisensory TOJ Task 86

Temporal Dependence of the Multisensory TOJ Task 89

Discussion 93

General Findings 93

Alterations in Auditory Temporal Processing in ASD 94

Comparisons with Prior Studies of Multisensory Processing in ASD 95

Mechanistic Implications: Toward the Brain Bases for Altered Multisensory Temporal Binding 96

Disrupted Temporal Multisensory Processing: A Common Disruption in Developmental Disorders? 97

Conclusions and Implications 99

References 102

IV. TEMPORAL MULTISENSORY PROCESSING AND ITS RELATIONSHIP TO AUTISTIC FUNCTIONING 106

Abstract 106

Introduction 107

Methods 109

Participants 109

General Procedure 111

Data Analysis 112

            - Calculation of Response Times 112
            - Group Differences in Overall Performance 113
            - Differences in Improvement in Response Time for Multisensory Trials 113
            - Differences in the Temporal Window of Multisensory Integration 114
    - Results 115
        - Performance on Unisensory Trials 115
        - Temporal Dependence of Performance on Multisensory Trials 116
        - Improvements in Performance on Multisensory Trials 118
        - Differences in the Temporal Window of Multisensory Integration ... 120
    - Discussion 121
    - References 124

V. DISRUPTED FREQUENCY FILTERING IN AUDITION AND VISION IN AUTISM SPECTRUM DISORDERS... 128
    - Abstract 128
    - Introduction.. 129
    - Methods... 131
        - Participants... 131
        - General Procedure 134
        - Tasks 135
            - Visual Critical Bandwidth Task 135
            - Auditory Critical Bandwidth Task 136
        - Estimation of the Critical Bandwidth in Vision and Audition 138
        - Data Analysis... 139
    - Results 139
        - Influence of Notch Bandwidth on Visual Thresholds 139
        - Differences in the Visual Critical Bandwidth 141
        - Influence of Notch Bandwidth on Visual Thresholds 142
        - Differences in the Visual Critical Bandwidth 143
    - Discussion 144
    - References 146

VI. GENERAL DISCUSSION AND FUTURE DIRECTIONS 151
  Summary of Results 151
  Current Results in the Context of Established Theories of Sensory Functioning in Autism 154
  Potential Hierarchical Neurobiological Model of Observed Sensory Disruptions in Autism 156
  Contributions of the Processing of Simple Stimuli to the Perception of Complex Stimuli in Autism 159
  Potential Impact of Observed Disruptions in Sensory Processing to Autistic Symptomology 160
  Future Directions 161
    Potential Interactions between Temporal Processing and Frequency Filtering 162
    Temporal Multisensory Processing and Filtering in Higher-Order Stimuli 163
    Influence of the Processing of Simple Stimuli on the Perception of Complex and Autistic Symptomology 164
    Role of Perceptual Learning in Remediation 165
    Use of Imaging Tasks in Identifying Neural Correlates of Disrupted Temporal Multisensory Processing in Autism 166
    The Use of Animal Models for Studying the Role of Disrupted Neuronal Functioning in Temporal Multisensory Processing and Frequency Filtering 168
  Conclusions 170
  References 171
APPENDIX 180

LIST OF TABLES

Table Page

2.1. Participant Demographics 56

3.1. Participant Demographics 77

3.2. One-sample t-tests for improvements in performance accuracy at each SOA for both children with ASD and TD 91

3.3. One-sample t-tests for improvements in response time at each SOA for both children with ASD and TD 91

4.1. Participant Demographics 109

5.1. Participant Demographics 132

LIST OF FIGURES

Figure Page

1.1. Perceptual thresholds as a function of noise bandwidth in vision and audition 23

2.1. Task Design 59

2.2. Group Results 61

2.3. Percent of trials on which two flashes were reported for each control trial type for a subset of children with ASD and TD 63

3.1. Task Design 80

3.2. Threshold values for visual and auditory temporal order judgment tasks 86

3.3. Performance accuracy and response time 88

3.4. Percent improvement in accuracy relative to visual only performance as a function of multisensory delay.. 90

3.5. Improvement in response times relative to visual only performance as a function of multisensory delay.. 90

4.1. Task Design 110

4.2. Average response times for visual only and auditory only trials 114

4.3. Response times for multisensory trials for TD and HFA groups 116

4.4. Response times for multisensory trials for HFA and LFA groups 116

4.5. Improvement in response times for multisensory trials for TD and HFA groups.......... 117

4.6. Improvement in response times for multisensory trials for HFA and LFA groups........ 118

4.7. Average improvement in response times for multisensory trials with short SOA's 119

4.8. Temporal window of integration 120

5.1. Visual CB task and stimuli 134

5.2. Frequency representation of auditory stimuli 135

5.3. Auditory CB task 136

5.4. Visual thresholds as a function of notch bandwidth 139

5.5. Visual CB values 140

5.6. Auditory thresholds as a function of notch bandwidth... 142

5.7. Auditory CB values 143

CHAPTER I

ALTERATIONS IN SENSORY PROCESSING IN AUTISM

General Introduction to Autism

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders which are diagnosed using the following triad of symptoms: impairments in social interaction, impairments in language, restricted, repetitive, and stereotyped behavior, interests, and activities[2]. A great deal of heterogeneity in the severity of the three symptom classes exists amongst individuals affected by this disorder giving rise to distinct diagnoses such as Autism, Asperger's, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)[2]. When incorporating all disorders on the autism spectrum, the current prevalence estimate indicates that one in every 150 children is affected by ASD[3]. Twin and family studies have shown that ASD may be the most 'genetic' of neuropsychiatric disorders, with concordance rates of 82–92% in monozygotic twins versus 1–10% in dizygotic twins with a sibling recurrence risk of 6%[4]. Studies of rare single nucleotide polymorphisms (SNPs) and genome wide association studies suggest that while a portion of cases of autism may be due to rare SNPs that follow Mendelian genetics, in the vast majority of individuals with autism a complex interplay between several genes and the environment are likely to contribute to their autistic symptomology[4-7]. The complexity of the genetic and environmental influences on autistic symptomology creates the extreme heterogeneity observed in autism and contributes to the difficulty in studying autism as a unified disorder.

Sensory Observations in Autism

In addition to the diagnostic triad of symptoms, sensory and perceptual disruptions are frequently associated with ASD. In fact, the original depiction of autism published by Kanner in 1943 included descriptions of sensory abnormalities such as fascination with particular stimuli as well as aversions to innocuous stimuli[8]. Many studies have since been published which seek to characterize these sensory disturbances in ASD. One insight into the sensory disturbances in autism comes from autobiographical reports. For example, Temple Grandin, a well known high-functioning professor with autism, describes her hearing experiences as "like having a sound amplifier set on maximum loudness"[9]. Retrospective analysis of home videos of infants who would later be diagnosed as autistic have found symptoms of abnormal reactions to sensory stimuli indicating that sensory disruptions are present even before a diagnosis is made[10]. Other reports indicate a difficulty for individuals with ASD to process stimuli from multiple senses concurrently which often results in "sensory overload." Lovaas et al. trained children with autism, mental retardation, and typical development (TD) to respond to a multisensory cue (visual, auditory, and tactile) then tested which of the cues elicited a response. They found that children with TD, and to some extent children with mental retardation, did respond to each stimulus when presented separately. However, children with autism tend to respond to one component of the multisensory stimulus (i.e. visual, auditory, or tactile). The authors concluded that this finding may have resulted from an overselectivity of attention within a multisensory object[11].

One strategy for quantifying sensory disturbances in ASD that has been used extensively since 1977 is the sensory questionnaire. These questionnaires are administered to parents or caregivers and usually include items from all modalities and both hypo- and hyper-responsiveness to stimuli from each modality. Hyper-responsiveness is generally characterized by sensory aversions including avoidance and/or sensitivity to loud noises, lights, particular textures or food, etc. Hypo-responsiveness includes behaviors involving both the lack of orienting to sensory events (i.e. not responding to sounds or the child's name being called) and sensory fascinations or the need for increased sensory stimulation (swinging, starting at lights, mouthing objects, etc)[12]. These studies have shown that abnormal reactions to sensory stimulation as reported by parents are nearly universal in ASD with estimates up to 90% of individuals with ASD showing sensory symptoms[13,14]. These studies have also shown that sensory disruptions are present in multiple modalities and include both hypo- and hyper-responsiveness to stimulation[13-20]. Collectively, this literature represents the entire range of both age and ability in autism indicating that sensory disturbances are an integral component in autism[13-20]. Although this literature is vital in describing and quantifying abnormal reactions to sensory stimulation, it does not provide any information as to the underlying mechanisms of sensory disruption in ASD.

Unisensory Perception in Autism

The initial studies into sensory disturbances in autism revealed the extent and nature of the unusual responses that many children with autism have to events in their environment; however, observational and survey studies are unable to determine whether these unusual reactions are due to differences in the neural processing of sensory stimuli (and the nature of these potential differences) or a higher level emotional or attentional modulation of sensory stimulation. Many studies have sought to address this question by utilizing psychophysical testing and brain imaging to investigate potential differences in perceptual abilities and neural processing. The following section will outline important findings in this domain in each of the main sensory modalities and describe the generalities that have been observed across the modalities.

Vision

Many studies have investigated how the perception and neural processing of visual information differs in individuals with autism. Many diverse aspects of visual processing have been studied ranging in complexity from simple detection of visual gratings modulated in contrast/luminance to processing of faces and complex scenes. The pattern of relative strengths and weaknesses in visual perception in autism suggest unique disruptions in the neural networks that subserve visual processing in the brain. Many studies have shown intact and even superior performance on tasks involving relatively simple visual stimuli. For example, children and adults with autism are able to find simple figures such as a triangle embedded in a complex figure much faster than typically developing controls[21-24]. Similarly, individuals with autism show enhancements in visual search paradigms. In these tasks, participants are instructed to find a particular object in an array of distractors of increasing number (set size). In a feature search, the target differs in one feature such as color or shape and can be quickly located regardless of the number of distractors (i.e. little increase in reaction time as the set size increases). In a conjunction search the target differs on two features such as color and shape and must be identified by integrating the two features for each distractor resulting in markedly increased reaction times as set size increases[25]. Individuals with autism have shorter reaction times than typically developing controls for larger set sizes during conjunction search demonstrating their superiority in visual search[26-28]. This perceptual superiority suggests that visual processing may be conserved or even enhanced in autism; however, the simple nature of the stimuli (i.e. involving basic aspects of visual features such as color and/or shape) may restrict this observation to low-level visual processing.

Another aspect of visual perception that has been studied is the detection and discrimination of sinusoidal visual gratings that can differ in contrast, spatial frequency, and orientation. Jemel and colleagues showed that individuals with autism could detect a sinusoidal visual grating at a lower contrast than TD controls[29]. The superior detection of visual gratings lends support to the hypothesis that the autistic brain may be more adept at processing simple visual information; however, these studies alone cannot determine whether superior detection of simple visual stimuli comes at the expense of more complex processing or whether higher order processing is relatively spared. Bertone and colleagues tested this hypothesis by altering the complexity of the stimulus to be discriminated. In this task, participants were asked to discriminate the orientation of a grating that could be luminance-defined (V1-dependent processing) or texture defined (V2-dependent processing). Individuals with ASD were superior at identifying orientation for luminance-defined gratings but inferior at identifying orientation for texture-defined gratings indicating that visual stimulus complexity has an inverse relationship with perceptual performance in autism[30].

Another extensively studied aspect of visual processing in autism is motion perception. Early studies of the ability of individuals with autism to detect the direction of a random dot display suggest that they needed a higher percentage of coherent dots (moving in the same direction) to perform at the same level as TD controls[31,32]. This finding as well as the superior performance on tasks with simple static visual stimuli led to the hypothesis that autism was characterized by a deficit in the dorsal visual (responsible for location and motion perception) pathway but enhanced processing in the ventral (responsible for fine spatial detail and form) pathway[32]. Recent research, however, suggest that the pattern of enhancements and disruptions is better explained by stimulus complexity rather than divergent visual pathways. For example, many recent studies have reported that individuals with autism perform just as well as controls in detecting the direction of a random dot display but are inferior at detecting the identity and direction of movement of point light displays that depict biological motion (e.g. a walking person)[33-35]. Disruptions in the perception of biological motion in autism have been observed in children as young as three years old[36]. These studies in conjunction with the above study by Bertone et al. have reported that within both the dorsal and ventral pathway, the perception of individuals with autism is spared or even enhanced for simple/low-level stimuli but disrupted for relatively higher order stimuli.

One very complex aspect of visual processing which has been extensively studied is face processing. Behavioral studies have shown that people with autism are less able to discriminate features of faces or the emotion displayed on the face when compared to controls[37-39]. Similarly, activation in the fusiform gyrus on the ventral surface of the brain, which has been repeatedly associated with the processing of faces and facial recognition, is markedly decreased in individuals with autism[40-44]. Furthermore, current studies have provided evidence to suggest an impaired network processing mechanism as the basis for the disrupted face processing in autism[45-47]. However, it is still unclear whether the disrupted face processing in autism is due to altered face processing networks or a tendency of individuals with autism to avoid looking at faces[38]. Furthermore, it is still unknown whether the disruptions observed in the network for processing faces is due to differences in the pattern of looking behavior in autism or if individuals with autism avoid looking at faces because they do not provide the same social information due to disrupted processing.

The theory of weak central coherence has been a major theory in autism that seeks to explain the dichotomy observed in the performance of individuals with autism on psychophysical tasks. This theory proposes that autism is characterized by a processing bias for featural or low-level information at the expense of global processing[48]. Importantly, Nakahachi and colleagues have investigated whether individuals with autism show diminished holistic processing compared to controls. Participants were asked to detect changes in scenes that could either be related to the theme of the scene or unrelated to the theme of the scene. For example, a related change would be a child holding a bowl instead of a plate in a scene of a family engaged in washing dishes. An unrelated change in the same scene would be a different pair of shoes in the corner of the room. ASD participants showed lower accuracy for changes related to the theme of the scene but not for changes unrelated to the theme when compared to controls[49]. In the same experiment, participants discriminated between Thatcherized faces (faces in which features such as the eyes and mouth are inverted) and normal faces presented upright or inverted. Typical adults can discriminate Thatcherized faces from normal faces much faster when they are presented upright than when they are presented inverted. This is theorized to occur because people tend to process faces holistically when upright but not when inverted[50]. Participants with ASD showed longer reaction times than controls for upright faces but not for inverted faces[51]. Another study found an inverse relationship between disrupted higher order processing (Global Dot Motion Task) and a measure of central coherence (Children's Embedded Figures Test) in ASD also lending support to the weak central coherence model[52]. These experiments together indicate that individuals with autism may have disruptions in processing complex stimuli holistically.

Audition

Investigations into the perception and processing of auditory stimuli are less numerous than studies of visual processing; however, these studies follow the same pattern of demonstrating intact or enhanced perception of simple stimuli but disrupted perception of more complex stimuli. For example, Bonnel et al. showed that high-functioning individuals with autism were superior at discriminating pitch as well as categorizing "high" vs. "low" tones when compared to controls[53]. O'Riordan et al. later replicated the finding of enhanced pitch discrimination in autism[54]. This is directly comparable to enhanced discrimination of visual gratings and strongly suggests a general change in the way that sensory information in processed in different modalities.

In further accordance with studies of visual processing, individuals with autism show disruptions in the perception of complex auditory stimuli such as speech including a reduced ability to discriminate different speech sounds, phonemes, etc. For example, discrimination of a particular vowel sound may be disrupted while in the context of a word or phoneme but not disrupted in isolation[55]. Disruptions in language are a core symptom in autism, making it unclear whether poor speech discrimination is a feature of disrupted auditory processing or specific to language stimuli but not other relatively complex auditory stimuli. However, many researchers have attempted to replicate the findings of Bertone et al. in the auditory modality by showing that the perception of complex but not social/speech auditory stimuli is selectively disrupted compared to simple auditory stimuli. One such study compared the ability of autistic and TD individuals to discriminate pure tones as well as temporally and spectrally complex sounds[56]. The autism group showed enhanced discrimination of pure tones but similar discrimination of complex sounds; however, neural imaging using fMRI diverged from the behavioral observations and revealed a greater activation in primary auditory cortex but less activation in non-primary auditory cortex[56]. Though behavioral differences were not found in this study, the functional differences in activation suggests that the processing of auditory stimuli may be altered in autism and may differentially affect the perception of simple versus complex stimuli.

Somatosensation

Surprisingly few studies have been published to date investigating differences in the processing of tactile information in individuals with ASD. Interestingly, the studies that have been published are in accordance with reports of enhanced processing of low level stimuli but disrupted processing of higher order stimuli. For example, Cascio et al. .have found enhanced detection abilities in the tactile modality for some but not all measures. For example, no differences between groups were found for warm/cool detection or ratings of pleasantness for texture. The ASD group did have lower thresholds for thermal pain as well as lower thresholds for vibration detection on the forearm but not the palm[57].

The relationship between stimulus complexity and perceptual performance in autism was examined directly by Minshew and Hobson in the tactile domain. In this study the authors differentiated simple vs. complex tactile processing by comparing scores on both simple and complex composite scales between individuals with ASD and without ASD. The simple sensory composite included the following items: localization of cutaneous sensation, sharp vs. dull pressure, and muscle and joint sensation; whereas, the complex sensory composite included the following items: finger-tip writing, tactile finger recognition, wrist shape drawing, and tactile form recognition. The number of errors made in each composite determined performance. Similar to vision, a dichotomy in performance between simple vs. complex processing in ASD was observed. Error rates for the simple sensory composite were similar between groups, whereas, error rates were much higher in individuals with ASD for the complex sensory composite[58]. This study suggests that the inverse relationship between stimulus complexity and perceptual abilities in ASD may be an amodal phenomenon, affecting all modalities.

Multisensory Integration in Autism

Multisensory processing in autism has not been studied as extensively as unisensory processing. Accordingly, much less is known about whether deficits in the integration of information across modalities exist in autism and what the nature and degree of these disruptions may be; however, the presence of deficient processing in all modalities is suggestive of a larger multisensory defect. This section will review the few articles, which have studied multisensory integration in autism and attempt to link them to the known disruptions in unisensory perception.

Integration of Complex and Social Multisensory Stimuli in Autism

The vast majority of studies of multisensory integration in autism have focused on complex stimuli such as speech or other forms of communication. Williams et al. .presented visual, auditory, and audiovisual syllables such as “ba,” “da,” and “tha” to children with ASD. The authors found that children with ASD were less accurate at identifying unimodally-presented syllables. The children with ASD also did not benefit from the congruent multisensory (same information presented in both modalities) presentation of “ba” as compared to the incongruent presentation of visual “da” with auditory “ba;” whereas, the controls did benefit from congruent multisensory presentations of “ba.” This suggests that the children with ASD were not able to utilize the visual information to improve their performance. However, the deficit in multisensory integration seen in the ASD group could be due to their decreased ability to interpret the visual stimuli. When visual only performance was statistically controlled for, group differences disappeared. Also when a group of children with ASD were trained to lip-read, they did show a benefit from the congruent presentation of “ba” which contrasted with their performance before training[59].

Smith et al. did find deficits in multisensory integration of speech stimuli in addition to the unisensory deficits. In this task adolescents with autism were presented with auditory speech stimuli in noise and asked to repeat the words that they heard. These stimuli were presented in an adaptive staircase procedure in which correct responses resulted in a decrease in speech volume relative to noise whereas incorrect responses resulted in an increase in speech volume relative to noise. This staircase was run twice: once with auditory only stimuli and once with congruent audiovisual stimuli. Both the ASD and TD group showed similar performance on the auditory only task and improvements with the addition of the congruent visual stimuli; however, the TD adolescents showed significantly more improvement from the visual stimuli than the ASD group. Similar to the Williams et al. study, lipreading was found to be deficient in ASD and significantly affected the ability of the visual stimuli to improve performance. Unlike the Williams et al. study, this study found that when visual and auditory performance was statistically accounted for, a significant effect still remained suggesting disrupted multisensory integration of speech stimuli in autism[60].

Magnee et al. studied the processing of multisensory speech stimuli by recording EEGs while adults with autism and typical controls observed a woman producing either congruent or incongruent speech syllables (/ada/ or /aba/). To investigate early pre-phonological processing, the multisensory ERP waveform was compared to the sum of the unisensory waveforms, and differences in the latency and amplitude between the multisensory and summed waveforms were compared across groups. Both groups showed similar reductions in the amplitude of the N1 and P1 components in response to the multisensory stimuli; however, the autistic adults showed a smaller decrease in the latency of the N1 and P1 components in response to multisensory stimuli though this difference did not reach significance in the small study sample. The authors concluded that early pre-phonological processing is conserved in autism though clear differences were observed in the multisensory waveform. To investigate later, more complex, phonological processing, the authors compared the multisensory waveforms in response to congruent versus incongruent stimuli. The congruent and incongruent waveforms of typical adults were significantly different from each other starting at 590 ms after incongruency (750 ms after auditory onset). Interestingly, the multisensory waveforms of autistic adults were indistinguishable, suggesting a deficit in later phonological processing of multisensory speech stimuli[61].

A study by Taylor et al. suggests that multisensory processing of speech stimuli may improve to a typical level during later development. The authors tested the ability to identify unisensory syllables and the susceptibility to the McGurk effect in autistic and typical children aged 7-16 years. They found that visual accuracy improved with age for both groups though the improvement in autistic children was much steeper. Both groups were highly accurate for identifying auditory syllables throughout the age range. Typical children showed similar rates of reporting the McGurk effect at all age levels; however, older children with autism reported the McGurk effect much more often than younger children with autism. The oldest children with autism in the study did not show deficits in unisensory or multisensory perception of speech stimuli when compared to their typical peers. This study shows that the disruptions in multisensory processing observed in autism may not persist into adulthood and may be a potential target for sensory therapies which could improve the processing of multisensory speech stimuli at an earlier stage of life[62].

One study examined the perception of temporal synchrony in audiovisual stimuli in autism. In this study, children with autism participated in a preferential looking paradigm in which linguistic or non-linguistic stimuli were presented synchronously on one screen and at a delay of 3 seconds on a second screen. Children with TD and children with other developmental disabilities showed preferential looking for both linguistic and non-linguistic asynchronous stimuli; however, children with autism only showed preferential looking for asynchronous non-linguistic stimuli. This study demonstrates that temporal multisensory processing may be disrupted in autism and that it may also follow the pattern of increased disruptions for complex/social or verbal stimuli than for simple/non-social or non-verbal stimuli[63].

Integration Of Simple Multisensory Stimuli In Autism

A few studies have examined the integration of simple multisensory stimuli in autism, one of which was published recently by Van der Smagt et al. In this study high-functioning adults with autism and controls completed a task, which incorporated a well-known multisensory illusion known as the flash-beep illusion. This illusion occurs when one flash is presented with two or more beeps, shifting the perception of one flash to two flashes. The authors found no differences between groups on the strength of this illusion, suggesting that multisensory integration of low-level stimuli is intact in high-functioning autism[64].

The multisensory studies reviewed thus far suggest the same dichotomy between simple vs. complex/social or verbal stimuli seen in individuals with autism for unisensory stimuli. Mongillo et al. recently tested this hypothesis by running children with ASD on a battery of multisensory psychophysical tasks that included both tasks incorporating human faces and tasks incorporating inanimate objects. Differences were observed between ASD and TD performance of tasks involving human faces (i.e. male/female face classification, Mcgurk, and AV vowel match/mismatch); however, no differences were observed for tasks involving objects (ball composition and size match/mismatch). This study, however, cannot differentiate stimulus complexity from the social nature of facial stimuli[65].

ERP studies of multisensory integration of simple stimuli in autism complicate the hypothesis that individuals with autism are able to appropriately integrate simple but not complex multisensory stimuli. Magnee et al. used a cross-modal P50 gating paradigm to assess the integration of simple multisensory stimuli in adults with autism. They found that both an auditory and visual conditioning stimulus was able to suppress the amplitude of the P50 component in response to a test auditory stimulus[66]. This study lends support to the hypothesis that the integration of simple multisensory stimuli is preserved in autism; however, an ERP study recently published by Russo et al. found that the integration of simple stimuli might be impaired in high functioning children with autism. In this study, EEG's were recorded while children with autism and typical development were presented with auditory and somatosensory stimuli. Waveforms in response to the multisensory stimuli were compared to the summed waveforms for the unisensory stimuli. Significant differences between the multisensory and summed waveforms fit the expected temporal and topographic pattern (significant differences beginning around 100 ms across several electrode locations) in typical but not autistic children. The autistic children tended to show less pronounced and delayed (by approximately 200 ms) differences between the multisensory and summed waveforms. The results of this study could indicate that children with autism are less able to integrate even simple multisensory stimuli; however, since behavioral responses were not collected, the alterations in multisensory processing could represent a different neural strategy for integrating the stimuli (e.g. a shift from early processing in secondary sensory areas to later processing in association cortex)[67].

Although previous studies have provided evidence to support the idea that the integration of complex multisensory stimuli seems more impaired than the integration of simple stimuli, this hypothesis cannot be properly evaluated because of the limited number of articles studying multisensory processing in autism. For example, the ERP study by Russo et al. described above shows that the integration of simple multisensory stimuli may be disrupted in autism and does not support the hypothesis proposed by Mongillo et al. The extreme heterogeneity in autism could explain the apparent decrease in the ability of children with autism to integrate simple multisensory stimuli. A study by Martineau et al. suggests that a large range in the ability of individuals with autism to integrate simple multisensory stimuli may exist. In their 1991 study they separated their autistic participants into three groups based on differences in the ERP waveform in response to a tone presented alone as compared to a tone followed by a flash. The three subgroups differed in the initial response to the tone alone as well as the degree to which the waveform was modulated by the flash with only one group having similar responses to the TD group. Interestingly, the three groups also differed on measures of autistic behavior used at the time of publication[67].

Importantly, both unisensory and multisensory atypicalities in autism have been extensively studied. Despite the numerous reports of impaired sensory disruptions in individuals with autism, there is still paucity of studies aimed at understanding the basic aspects of sensory processing and how they are altered in autism. The following sections will highlight research into anatomical and functional disruptions in autism, which are likely to result in dysfunction of the fundamental aspects of sensory processing.

Anatomical Changes in the Autistic Brain

Many studies have sought to identify key changes in the anatomy of the autistic brain using post mortem brain tissue and MRI and to determine whether these changes serve a causative function. Disruptions in both gray matter and white matter volume and organization have been found in the brains of individuals with ASD. This section will review these studies with emphasis on those that sought to link anatomical changes to the disruptions in sensory processing described above.

Gray Matter

The first anatomical observation in autism was an increase in head size early in life, which was later discovered to be due to an increase in the number of cells within the brain. This period of early overgrowth (before two years of age) is followed by a slowing of growth later in development[68]. These gross anatomical disruptions led researchers to investigate whether the volume and organization of the neurons comprising the gray matter is changed in autism. Emerging studies have investigated and found differences in gray matter volume in brain structures thought most likely to result in the pattern of symptoms observed in autism such as frontal cortex, temporal lobe (cortex and medial temporal lobe structures such as the amygdala), and the cerebellum[69,70].

White Matter

The volume, organization, and integrity of white matter in the autistic brain have been extensively studied. Reports of alterations in white matter volume have been shown mainly as decreases in key structures such as the corpus callosum and inferior longitudinal fasciculus[70,71]. The corpus callosum has been one of the most studied white matter structures in autism with researchers finding decrease in the volume of either the entire corpus callosum or in particular subregions[72,73]. Furthermore, the anatomical studies have suggested impaired functional connectivity and transmission of information between the two hemispheres in individuals with autism. Although changes in white matter volume are intriguing, they cannot truly inform researchers as to the exact nature of differences in the pattern of connectivity in the autistic brain. Recent years have seen an explosion of studies published which use diffusion tensor imaging (DTI) to investigate the integrity and organization of white matter tracts between particular brain areas in autism. Several studies have found a general decrease in functional anisotropy (FA) which measures the propensity for water to flow in one direction (e.g. along an axon) versus in many directions (e.g. gray matter)[74]. Decreases in FA can be attributed to a disruption in the organization of many single axons to form a singular cohesive tract or to disruptions in the axonal membranes affecting their ability to prevent water molecules from exiting the membrane (e.g. loss or disruption of myelin wrapping)[75]. Decreases in FA are usually attributed to disruptions in the connectivity of the brain areas that project through the fiber tract. One of the major areas to show decreased FA in autism is the corpus callosum, validating volumetric studies showing that the two hemispheres are under-connected[76-78]. Many researchers have also found decreased FA in the frontal lobe white matter indicating that individuals with autism may have reduced connectivity with the higher order reasoning parts of their brains[79,80]. Lower FA has also been found in tracts associated with areas such as the amygdala and FFA suggesting that they also may be less connected from the rest of the brain[81]. Interestingly, the white matter connecting many of the structures subserving both unisensory and multisensory processing such as the white matter in the temporal lobe (including the superior temporal sulcus (STS) and the temporal-parietal junction (TPJ)) have been found to have lower FA as well[82]. Although no studies have currently investigated whether the decreased FA in tracts connecting sensory areas is correlated to the magnitude of sensory disruption in autism, it seems likely that the pattern of superior or unaffected perception of local detail and disrupted perception of complex stimuli may be due to decreased connectivity between distant regions.

Minicolumns

Minicolumns are architectonic structures found in cortex that are composed of vertically oriented pyramidal neurons at the core and GABAergic interneurons in the periphery thus uniting vertical and horizontal components of cortex. The minicolumn is the smallest network for information processing in the brain, and neurons within a minicolumn usually respond to similar sensory input (i.e. all neurons within one minicolumn will have the same receptive field). The inhibitory interneuron surround is responsible for the “fine-tuning” and sharpening of sensory information via lateral inhibition (inhibition of nearby neurons representing an adjacent area of space, frequency, or other sensory feature)[83,84]. Using post-mortem tissue, Casanova and colleagues found that minicolumns in individuals with autism tend to be narrower, more numerous, and denser[85,86]. The disruptions in minicolumn structure have been incorporated into the minicolumnopathy and decreased ratio of excitation/inhibition theories that will be discussed in detail later in this chapter[87,88].

Functional Changes in the Connectivity of Neural Networks in the Autistic Brain

The anatomical disruptions in the structure and organization of both gray and white matter highlighted above are likely to result in vast consequences on a functional level. Studies utilizing electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) have elucidated several key changes in the functioning of neural networks in the brains of individuals with ASD. The most influential and studied is the functional connectivity of neural networks in the autistic brain. Whereas structural connectivity refers to the physical connections between neurons (i.e. axons and synaptic strength), functional connectivity refers to the temporal correlation of neuronal activity between distinct brain structures that may or may not be physically directly connected[89]. This section will highlight the current knowledge of disrupted functional connectivity and explore the consequences of such disruptions on sensory processing in ASD.

EEG: Oscillations

Many researchers have begun to use EEG to study functional connectivity in autism both during rest and during the performance of sensory and cognitive tasks. By measuring the amplitude (power) and temporal correlation (coherence) of neuronal oscillations of varying frequencies, researchers have begun to examine differences in the strength and effectiveness of connections between proximal and distal brain regions. Studies of coherence during the resting state show that distant brain regions tend to be less temporally correlated in autism than in typical development[90-93]. Electrodes over the frontal cortex seem to show a stronger decorrelation with electrodes over other parts of cortex in autism[92]. Decreases in EEG coherence have been observed across several frequency ranges including gamma (> 30 Hz; associated with integrative processes), alpha (8-10 Hz; associated with inhibitive and/or long range associative processes), theta (3-6 Hz; associated with short term memory), and delta (1.5 – 3.5 Hz)[91,94,95].

Researchers have also measured changes in amplitude (power) of gamma oscillations as a way to measure potential disruptions in connectivity in autism. Gamma oscillations are theorized to represent integrative processes that combine information from many disparate areas of the brain; therefore, a decrease in gamma power could reflect disrupted integrative processes and a lack appropriate connectivity[89,95]. Several recent studies have reported decreases in both evoked (time-locked to stimulus presentation and thought to represent sensory encoding) and induced (not time-locked to stimulus presentation and thought to represent higher-order and/or cognitive processing related to stimulus and task) gamma power[90,96,97]. Brown et al. found a decrease in gamma power in response to Kanizsa shapes (shapes with illusory contours) in autistic children even though they were able to detect the illusory shapes as accurately and quickly as their typically developing peers[98]. A later study of Kanizsa figures in autism by Stroganova et al. found that a global change in gamma power could not fully explain differences in the neural processing of illusory contours. They found that the pattern of phase locked beta and gamma oscillations could differentiate between illusory and control conditions in both groups. Interestingly, children with autism displayed differences in the timing and topography of the phase locked gamma and beta oscillations which suggested that children with autism use a different network to process illusory figures which may favor lower-level processing[99]. Grice et al. found that gamma power over frontal cortex did not differ significantly for upright faces as compared to inverted faces in individuals with autism whereas typical individuals showed a dramatic increase in gamma activity in response to upright faces[100]. The studies above demonstrate that individuals with autism show disruptions in the integrative processes that underlie sensory and cognitive functioning. Anatomical studies of white matter as well as EEG studies of neural oscillations have led researchers to propose that autism is characterized and caused by functional disconnectivity between distant brain regions[89]. fMRI studies of functional connectivity between brain regions in autism have also contributed to this theory.

fMRI: Functional Connectivity

Several studies have used fMRI in autism to correlate activity between brain regions during the performance of sensory and cognitive tasks as well as at rest. Horwitz et al. found reduced connectivity between several regions in autism during rest[101]. Disruptions in functional connectivity in autism have also been found in the networks subserving tasks that children with autism are known to have difficulty with including sentence comprehension[102], face processing[103,104], visuomotor tasks[105], emotion recognition[106], executive planning tasks[107], source recognition[108], and visual search[109]. One issue with all the above studies is that they measure changes in functional connectivity within a predetermined network. As observed in the Stroganova study described above, individuals with autism may be utilizing a different network during the completion of the studied tasks. Thus, autism may be characterized not by a decrease in the connectivity within the neural network subserving a particular cognitive/sensory task but by the usage of different networks for cognitive and sensory processing. Welchew et al. measured functional connectivity between 90 regions of interests (ROIs) during an emotion recognition task and found that children with autism did show decreased functional connectivity between areas that are known to be connected within this network. Interestingly, children with autism showed an increase in connectivity between areas thought to be outside the network subserving emotion recognition even though these connections were "long-ranged" [106]. This study highlights the complexity of the differences in neural processing in autism and shows that a global decrease in functional connectivity between distant brain areas may be insufficient in explaining the perceptual deficits and other symptomology seen in autism. Adding a further degree of complexity, some studies have shown an increase in thalamocortical and/or subcortico-cortical connectivity accompanied by a decrease in cortico-cortical connectivity in individuals with autism[110]. Studies of functional connectivity in autism are proving to be an exciting and informative new area of research in the field; however, many studies demonstrate the complexity of this new area of study and the need for further investigation of the neural networks and the connectivity between the nodes of the networks underlying sensory perception in autism.

Potential for Disruptions in Fundamental Sensory Processing in Autism

Although unisensory and, to a lesser extent, multisensory perception has been studied extensively in autism, surprisingly little is known about the fundamental ways in which the neural processing of sensory information differs in autism. Disruptions in the organization of neurons and their axons as well as disordered communication between cortical and subcortical structures are likely to result in extensive and fundamental disruptions in sensory perception. The remainder of this introduction will focus on the basic aspects of unisensory and multisensory processing which may potentially be disrupted in autism.

Unisensory Filtering as a Potential Sensory Disruption in Autism

A theory that has important implications for sensory processing in ASD is the minicolumnopathy theory proposed by Cassanova. This theory is based on the anatomical observations of alterations in the architecture of the minicolumn in the neocortex in postmortem tissue of individuals with autism. The cortical column is a basic building block of sensory information processing; therefore, disruptions in the organization of neurons within the minicolumn and connections between minicolumns are likely to result in serious consequences for sensory processing[85,86,88]. Importantly, Cassanova et al. have proposed that these anatomical alterations will result in decreased lateral inhibition in autism because the inhibitory surrounding neuropil is the largest contributor to decreases in the width of minicolumns in autism[87,88]. The authors further propose that decreased lateral inhibition could account for the dichotomy seen between performance of tasks using simple vs. complex stimuli and that it has important implications for the "filtering capacity of the neocortex" [88].

A second proposed neural mechanism for ASD which is closely related to the minicolumnopathy theory is founded on a decreased signal-to-noise ratio in neural encoding[111]. Under typical conditions, neural responses are sharply tuned to particular features of sensory stimulation. This precise tuning has been clearly shown to depend on a delicate balance between excitatory and inhibitory transmission within the center-surround receptive field structure that typically characterizes sensory neurons. The decreased ratio of excitation/inhibition theory proposes that autism is characterized by disruptions in this balance. Specifically, Rubenstein and Merzenich propose that, given the pattern of sensory observations in autism and the increased rate of epilepsy in autism a decrease in inhibitory processing in autistic cortex results in less precision in the tuning of sensory neurons to specific sensory features[111].

Center-surround receptive fields are a fundamental building block in the perception of both simple and complex sensory information. This receptive field structure is found at the earliest stages of sensory processing. Inhibition has an increasingly important role in shaping more complicated receptive field structures found at later stages of sensory processing; therefore, an alteration in precise inhibitory processing would have an increasingly disruptive role in the perception of complex sensory stimuli[112]. This exact pattern has been found in studies of sensory processing in autism, making this theory an attractive explanation for the etiological cause of disrupted sensory processing in autism. However, the observed concordance between the pattern of sensory abnormalities in autism and the likely consequences of disrupted inhibition is not decisive evidence to support disruptions in the tuning of sensory neurons playing a causative role in autism.

A direct perceptual consequence of altered inhibitory and excitatory processing within minicolumns is a disruption in a person's ability to filter extraneous sensory information to improve task performance[113]. One method for approximating the filtering capabilities in a sensory system is by measuring the critical bandwidth, originally demonstrated by Fletcher in the auditory modality. He showed that a constrained range of frequencies only masks the detection of a pure tone. Specifically, he demonstrated that the detection of a sinusoidal signal was increasingly disrupted by increasing the bandwidth (BW) of narrowband noise until a particular BW (the critical BW) beyond

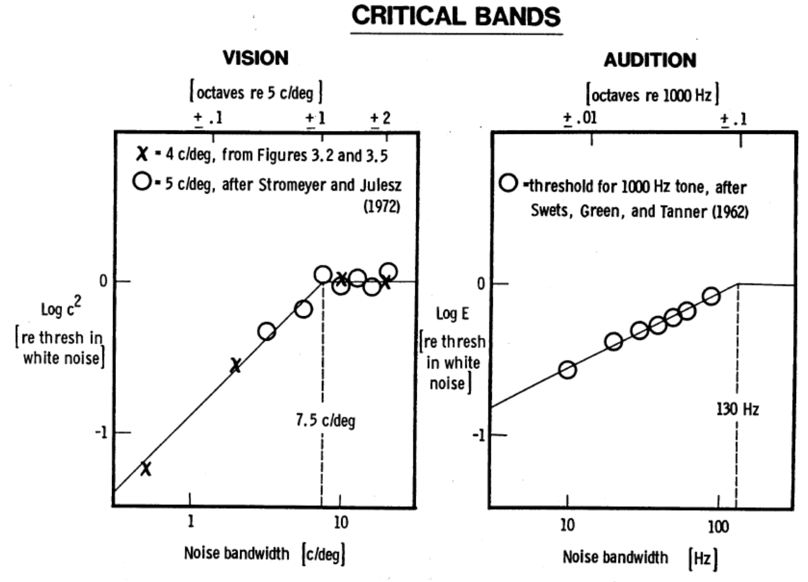


Figure 1.1: Perceptual thresholds as a function of noise bandwidth in vision and audition. [1]

which further increases in noise BW did not produce decrements in performance[114]. Conversely, the critical band can be ascertained by notching white noise (removing a range of frequencies centered at the target frequency) and measuring resulting changes in the accuracy of detecting a target tone[115]. A similar observation was reported for visual stimuli by Pelli and Stromeyer and Julesz who demonstrated that increasing the spatial frequency BW of visual noise resulted in increased threshold for detecting sinusoidal gratings until a critical BW, beyond which increases in the BW of the noise did not result in increased thresholds[1,116]. (Figure 1.1) Studies of the critical BW could elucidate differences in filtering characteristics in autism and contribute to our understanding of the basic processing of sensory information in autism.

Multisensory Integration as a Potential Sensory Disruption in Autism

Although multisensory integration in autism has been investigated in a limited number of studies, none of these studies have examined the fundamental aspects of multisensory processing. Many of these studies have focused on whether individuals with autism are able to effectively utilize information from more than one sense to improve or alter the perception of a multisensory stimulus. The remainder of this chapter will introduce the current knowledge of multisensory processing in the typical brain and highlight connections between neurological mechanisms of multisensory integration and known disruptions in neural anatomy and functioning in autism.

Benefits of Multisensory Integration

We live in a world that is rich in information from many sensory modalities. Each event in our environment can usually be perceived through more than one sense with different senses adding unique perceptual information to our understanding of the happenings in the world around us. Our ability to accurately combine information from multiple senses has evolved to strongly improve our functioning in many ways ranging from increasing our basic survival (avoiding dangers and locating vital objects) to improving our ability to communicate with each other[117]. In fact, congruent stimulation from multiple modalities has been consistently shown to improve performance in both laboratory and “real world” settings. One benefit of multisensory integration is an improvement in the detection of a multisensory stimulus. Multisensory stimuli are detected both more accurately and quickly[118-123]. Perhaps the greatest benefit of being able to utilize information from multiple senses is an improvement in the discriminability of non-salient or ambiguous unisensory cues. For example, understanding speech in a noisy environment is greatly improved by lip reading (cocktail party effect)[124-127]. Additionally, external events are much easier to localize if we can perceive them in more than one modality[128,129]. Discrimination of the direction of movement of simple stimuli is also much improved by congruent multisensory information[130-132]. Although, localization ability has never been studied in autism, speech comprehension and motion discrimination are both known to be disrupted in autism are important for social functioning. Given the immense importance of multisensory integration in our daily lives, disruptions in multisensory processing could have far reaching consequences to the daily functioning of individuals with autism.

Contribution Of Multisensory Illusions To Our Understanding of Multisensory Integration

Many insights into how our brains combine and integrate information from our various senses come from multisensory illusions. One of the most well know of these illusions is the ventriloquist effect. In this illusion the perceived location of a sound (a speaker’s voice) is shifted toward the location of a visual event (a dummy’s moving lips)[133-135]. The ability of a visual stimulus to influence the localization of an auditory stimulus has been extended into laboratory settings using simple light flashes and tones.

When participants are asked to judge the location of a coincident flash and tone that are separated in space, the location of the multisensory stimulus is biased toward the location of the flash[136]. Because the human visual system is more adept at spatial discriminations than the auditory system, researchers have theorized that the brain weights information from the more reliable modality when the unisensory components of a multisensory stimulus are discordant[137]. Whereas the visual system is reliable in the spatial domain, the auditory system is much more accurate in the temporal domain. Accordingly, multisensory tasks that rely on temporally precise information are more influenced by the auditory modality[138-140]. For example, Morein-Zamir and colleagues observed that the addition of two non-informative auditory cues to a visual temporal order judgment (TOJ) task improves visual performance if the second auditory cue is presented following the second visual stimulus by a slight delay (e.g. 100 ms). This task has been coined the "temporal ventriloquist" effect because some researchers have theorized that the tones are "pulling" the visual stimuli apart in time[139]. Multisensory illusions are not only characterized by one modality biasing the perception of another modality. For example, in the McGurk effect, discordant visual and auditory speech stimuli are fused into a novel percept (e.g. a visual "ga" and an auditory "ba" is perceived as either "da" or "tha.")[141].

Principles of Multisensory Integration

The benefits of the integration of multisensory information are strongly dependent on the brain's ability to accurately and precisely bind appropriate unisensory components. This section will describe the principles that govern the binding of unisensory information into a unified multisensory percept.

Multisensory stimuli, which are composed of temporally aligned unisensory components, are likely to be associated with a single external event. The first indications of the temporal properties of multisensory integration arose from studies of multisensory neurons in the superior colliculus (SC). Many of these neurons show superadditive enhancements in response to multisensory stimuli. However, the unisensory components of the multisensory stimulus must be presented in close temporal proximity with one another to produce such enhancements. Interestingly, the unisensory components need not be absolutely synchronous. Instead, a relationship between temporal proximity and enhancements observed exists such that stimuli presented close in time lead to larger enhancements than stimuli present farther apart in time[142,143]. This same relationship has been observed in numerous psychophysical and imaging studies[144-153]. Several studies have also defined a "temporal window" of multisensory integration within which multisensory stimuli are likely to be perceptually bound[146,153-156]. One such study, which was published by Shams et al. defined a temporal window for the flash-beep illusion introduced previously. In this study, one flash was paired with two beeps with stimulus onset asynchronies ranging from 25 to 250 ms[153]. Whereas the first beep was always presented coincident with the flash, the second beep could either be presented before or after the flash. The authors were able to use this task to define a temporal window of approximately 100 ms over which participants were likely to report two flashes. Hairston et al. observed that the temporal window of integration can be delineated by systematically varying the SOA between the second visual and the second auditory stimulus for the task designed by Morein-Zamir and colleagues described above[146].

Similar to the temporal principle, the spatial principle was first observed in single neurons in the SC where it was found that spatially coincident multisensory stimuli tend to elicit superadditive neuronal responses whereas spatially disparate stimuli result in subadditive or inhibited responses[143,157]. Psychophysical studies tend to follow the spatial principle as well with higher rates of integration and binding of spatially proximate stimuli as opposed to spatially disparate stimuli[158-161]. The final principle of multisensory integration (inverse effectiveness) was also first described in the single neuron model of the cat SC where it was discovered that weaker unisensory stimuli when presented together resulted in a much higher relative increase in firing rate. In fact, a clear relationship between stimulus effectiveness (i.e. ability to drive neuronal responses when presented alone) and increased relative firing rate was observed[162-164]. Inverse effectiveness has also been clearly demonstrated in studies of human perception. For example, highly salient light flashes and tone pips do not generally show increases in accuracy when presented together (due to high accuracy of detecting the unisensory components) but improvements in reaction time[165]. If instead the light flash and tone pip are difficult to detect alone, the increase in accuracy in detecting them together will be dramatically increased[166].

Neurological Mechanisms Of Multisensory Integration

The superior colliculus is perhaps the most studied multisensory structure in the brain. The SC receives both ascending and descending sensory input from the visual, auditory, and somatosensory systems. This input converges on neurons in the SC giving them the capacity to both respond to and integrate information from multiple modalities. Input from ascending subcortical structures appear to function in a direct excitatory manner, thus giving multisensory neurons in the SC the ability to respond to inputs form multiple modalities[167-170]. Interestingly, descending cortical input appears to play a modulatory role in the integration of multisensory information. When cortical areas of major input to the SC (e.g. AES in the cat) are deactivated using cooling coils, SC neurons maintain their ability to respond to multiple modalities; however, they lose the capability to effectively integrate the ascending sensory input (i.e. neurons respond in an additive manner and do not show superadditivity)[171,172].

Superadditive multisensory responses have been well documented and characterized in both the SC and cat cortical areas such as the anterior ectosylvian sulcus (AES); however, multisensory integration in single neurons is not only characterized by superadditive responses. Modulatory and inhibitory responses are also common. For example, a neuron may respond to a visual stimulus but not an auditory stimulus when presented in isolation; however, the neuron may increase or decrease its firing rate when the two stimuli are presented together[173-175]. Whereas simple excitatory interactions are sufficient to account for superadditive multisensory responses; more complicated interactions between excitation and inhibition are necessary for producing modulatory responses[167]. Antagonism of GABA receptors has been shown to block inhibitory multisensory interactions in cat SIV cortex[176]. Additionally, recent studies of spatiotemporal receptive fields (STRF) in SC and cortical multisensory neurons demonstrate that the receptive fields of multisensory neurons are much more complicated than originally thought, and inhibition is likely to be essential in shaping these receptive fields[175,177]. A disruption in the balance between excitation and inhibition as has been proposed in autism would have vast consequences to the precision and nature of multisensory integration. This lack of precision in the integration of simple stimuli or in the individual aspects of a complex multisensory stimulus such as speech are likely to result in severe deficits in the integration of complex multisensory stimuli. Additionally, disruptions in inhibition would strongly impact the nature of modulatory interactions in multisensory neurons.

Human imaging and animal physiology studies have identified several key areas of multisensory integration. Several of these areas overlap with areas known to be disrupted in autism. One such area of overlap is the superior temporal sulcus (STS) which is an association area that receives input from visual and auditory cortices[178]. The STS is thought to process complex perceptual information such as speech, biological motion, and social cues[179-181]. Given the multisensory nature of such complex perceptual stimuli, it is not surprising that the STS is also very strongly associated with multisensory integration[178,182-185]. Many fMRI studies have shown activation of the STS in response to the presentation and/or integration of multisensory speech stimuli[182,186]. Activation of the STS is associated with the perception of the McGurk effect during fMRI studies[187]. In fact, disruption of the normal functioning of the STS using transcranial magnetic stimulation (TMS) has been shown to decrease the perception of the McGurk effect[187] demonstrating is important role in the integration of speech stimuli. fMRI studies have also shown that the processing of multisensory stimuli within the STS follow the principles of multisensory integration signifying its importance as a locus of multisensory integration in human perception[186]. Importantly, the STS is able to dynamically alter its functional connectivity with unisensory areas depending on the reliability of the component unisensory information[182]. This flexibility in connectivity serves to optimize the integration of information from multiple senses and expected to be severely disrupted in autism. Electrophysiological studies in primates confirm the importance of precise functional interactions between unisensory cortex and the STS in the integration of complex social multisensory stimuli[178]. Disturbed functional connectivity in autism is not the only implication for disrupted integration of multisensory inputs in the STS. Both functional (decreased fMRI activation during rest) and anatomical (cortical thinning) studies show disruptions in the STS in autism[179,188-190]. fMRI studies of social cognition (e.g. face and voice perception) have shown decreased activation of STS in autism which are correlated with disruptions in social cognition[109,191].

Higher order association areas are not the only cortical sites, which have been shown to integrate multisensory information. Many studies have indicated that connectivity between primary and/or secondary sensory areas may also play a role in integrating multisensory stimuli. Retrograde tracer injections into primary and secondary unisensory cortices (visual, auditory, and somatosensory) have identified feedback connections from association as well as other primary and secondary unisensory cortices[192-196].

The importance of both structural and functional connectivity between brain areas in the integration of multisensory information observed in studies of the SC, STS, and sensory specific cortices is validated in EEG and MEG studies of oscillatory activity during the completion of multisensory tasks. Increases in gamma and beta band activity have been associated with multisensory integration in a number of studies[197-201]. For example, trials in which an illusory flash was perceived during the flash beep illusion were characterized by significantly increased gamma power as compared to trials during which an illusory flash was not perceived[202].

Given the importance of both functional and structural connectivity in the precise integration of multisensory information, the disruptions in connectivity observed in both anatomical and functional studies of autism are likely to result in dysfunctional multisensory processing. For example, Brock et al. theorize that the dissociation between performance on simple vs. complex perceptual tasks might be due to a deficit in temporal synchronization between local networks (functional connectivity) rather than a general “cognitive style” as proposed by the weak central coherence model[203]. This disruption in temporal binding between cortical and subcortical regions could also manifest as a disruption in multisensory integration, since multisensory “binding” is also thought to rely on the precise synchronous activity within and across various brain regions. Altered temporal binding in ASD could manifest as a disruption in multisensory integration and, in particular, as a distortion in the temporal dynamics of multisensory binding (e.g. integrating multisensory stimuli over a larger period of time).

Introduction to Current Topics

Autism spectrum disorders (ASD) form a continuum of developmental disorders which are characterized by deficits in communication and social interactions, as well as by repetitive behaviors and restricted interests. Sensory disturbances are also frequently reported in clinical and autobiographical accounts. A number of studies have highlighted that high functioning individuals with ASD have enhanced perceptual abilities for fairly simple stimuli but that complex stimuli tend to disrupt performance on psychophysical tasks. In an effort to account for the observed dissociations between performance on simple and complex perceptual tasks in individuals with ASD, Brock et al. (2002) theorized that ASD might be characterized by a deficit in temporal synchronization between local neural networks. Binding of multisensory events into unified percepts depends on temporal synchronization among neural networks; therefore, disruption in temporal binding could manifest as a disruption in multisensory integration and/or a distortion in the temporal characteristics of multisensory binding. The observed dissociation between performance on simple and complex perceptual tasks in addition to anatomical evidence that the architecture of minicolumns may be disrupted in autism suggest that the ability to filter specific frequency information may be an additional aspect of basic sensory processing which is disrupted in ASD. In the current document, we sought to characterize some of the basic characteristics of unisensory and multisensory perception in ASD including temporal processing and frequency filtering, with the hypothesis being that there would be disruptions in these processes. The following chapters will present evidence for the existence of these disruptions and discuss their importance in autistic symptomology.

References

1. Pelli, D. Cambridge University (1981).

2. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

3. (CDC), C.f.D.C.a.P. Prevalence of autism spectrum disorders – Autism and developmental disabilities monitory network. *Morbidity and Mortality Weekly Report Surveillance Summary* **56**, 12-28 (2007).

4. Toro, R., Konyukh, M., Delorme, R., Leblond, C., Chaste, P., Fauchereau, F., Coleman, M., Leboyer, M., Gillberg, C. & Bourgeron, T. Key role for gene dosage and synaptic homeostasis in autism spectrum disorders. *Trends in Genetics* **26**, 363-372 (2010).

5. State, M.W. The Genetics of Child Psychiatric Disorders: Focus on Autism and Tourette Syndrome. *Neuron* **68**, 254-269 (2010).

6. Abrahams, B.S. & Geschwind, D.H. Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* **9**, 341-355 (2008).

7. Grafodatskaya, D., Chung, B., Szatmari, P. & Weksberg, R. Autism Spectrum Disorders and Epigenetics. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 794-809 (2010).

8. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217-250 (1943).

9. Grandin, T. My Experiences with visual thinking, sensory problems, and communication difficulites. (2000).

10. Baranek, G. Autism During Infancy: A Retrospective Video Analysis of Sensory-Motor and Social Behaviors at 9–12 Months of Age. *Journal of Autism and Developmental Disorders* **29**, 213-224 (1999).

11. Lovaas, O., Schreibman, L, Koegel, R, Rehm, R. Selective responding by autistic children to multiple sensory input. *Journal of Abnormal Psychology* **77**, 211-222 (1971).

12. Baranek, G., David, F., Poe, M., Stone, W. & Watson, L. Sensory Experiences Questionnaire: discriminating sensory features in young children with autism, developmental delays, and typical development. *Journal of Child Psychology and Psychiatry* **47**, 591-601 (2006).

13. Omitz, E.M., Guthrie, D., & Farley, A. J. . The early development of autistic children. *Journal of Autism and Childhood Schizophrenia* **7**, 207-209 (1977).

14. Omitz, E.M., Guthrie, D., & Farley, A. J. . The early symptoms of childhood autism. in *Cognitive defects in the development of mental illness* (ed. Serban, G.) 24-42 (Brunner/Mazel, New York, 1978).

15. Leekam, S., Nieto, C, Libby, SJ, Wing, L, Gould, J. Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord.* **37**, 894-910 (2007).

16. Dunn, W., Myles, BS, Orr, S. Sensory processing issues associated with Asperger syndrome: a preliminary investigation. *Am J Occup Ther.* **56**, 97-102 (2002).

17. Kern, J.K., Trivedi, M.H., Garver, C.R., Grannemann, B.D., Andrews, A.A., Savla, J.S., Johnson, D.G., Mehta, J.A., Schroeder, J.L. The pattern of sensory processing abnormalities in autism. *Autism* **10**, 480-494 (2006).

18. Watling, R., Deitz, J, White, O. Comparison of Sensory Profile scores of young children with and without autism spectrum disorders. *Am J Occup Ther.* **55**, 416-423 (2001).

19. Rogers, S., Hepburn, S, Wehner, E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *J Autism Dev Disord.* **33**, 631-642 (2003).

20. Kientz, M., Dunn, W. A comparison of the performance of children with and without autism on the sensory profile. *Am J Occup Ther.* **51**, 530-537 (1997).

21. White, S. & Saldaña, D. Performance of Children with Autism on the Embedded Figures Test: A Closer Look at a Popular Task. *Journal of Autism and Developmental Disorders*, 1-8 (2011).

22. Lee, P.S., Foss-Feig, J., Henderson, J.G., Kenworthy, L.E., Gilotty, L., Gaillard, W.D. & Vaidya, C.J. Atypical neural substrates of Embedded Figures Task performance in children with Autism Spectrum Disorder. *Neuroimage* **38**, 184-193 (2007).

23. de Jonge, M., Kemner, C. & van Engeland, H. Superior Disembedding Performance of High-Functioning Individuals with Autism Spectrum Disorders and Their Parents: The Need for Subtle Measures. *Journal of Autism and Developmental Disorders* **36**, 677-683 (2006).

24. Joliffe, T. & Baron-Cohen, S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *J Child Psychol Psychiatry* **38**, 527-34 (1997).

25. Quinlan, P. & Humphreys, G. Visual search for targets defined by combinations of color, shape, and size: An examination of the task constraints on feature and conjunction searches. *Attention, Perception, & Psychophysics* **41**, 455-472 (1987).

26. Joseph, R.M., Keehn, B., Connolly, C., Wolfe, J.M. & Horowitz, T.S. Why is visual search superior in autism spectrum disorder? *Developmental Science* **12**, 1083-1096 (2009).

27. Baldassi, S., Pei, F., Megna, N., Recupero, G., Viespoli, M., Igliozzi, R., Tancredi, R., Muratori, F. & Cioni, G. Search superiority in autism within, but not outside the crowding regime. *Vision Research* **49**, 2151-2156 (2009).

28. Almeida, R.A., Dickinson, J.E., Maybery, M.T., Badcock, J.C. & Badcock, D.R. Visual search performance in the autism spectrum II: The radial frequency search task with additional segmentation cues. *Neuropsychologia* **48**, 4117-4124 (2010).

29. Jemel, B., Mimeault, D., Saint-Amour, D., Hosein, A. & Mottron, L. VEP contrast sensitivity responses reveal reduced functional segregation of mid and high filters of visual channels in Autism. *Journal of Vision* **10**(2010).

30. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

31. Milne, E., Swettenham, J., Hansen, P., Campbell, R., Jeffries, H. & Plaisted, K. High motion coherence thresholds in children with autism. *Journal of Child Psychology and Psychiatry* **43**, 255-263 (2002).

32. Spencer, J., O'Brien, J., Riggs, K., Braddick, O., Atkinson, J. & Wattam-Bell, J. Motion processing in autism: evidence for a dorsal stream deficiency. *NeuroReport* **11**, 2765-2767 (2000).

33. Blake, R., Turner, L.M., Smoski, M.J., Pozdol, S.L. & Stone, W.L. Visual Recognition of Biological Motion is Impaired in Children With Autism. *Psychological Science* **14**, 151-157 (2003).

34. Rutherford, M. & Troje, N. IQ Predicts Biological Motion Perception in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, 1-9 (2011).

35. Annaz, D., Remington, A., Milne, E., Coleman, M., Campbell, R., Thomas, M.S.C. & Swettenham, J. Development of motion processing in children with autism. *Developmental Science* **13**, 826-838 (2010).

36. Annaz, D., Campbell, R., Coleman, M., Milne, E. & Swettenham, J. Young Children with Autism Spectrum Disorder Do Not Preferentially Attend to Biological Motion. *Journal of Autism and Developmental Disorders*, 1-8 (2011).

37. Boucher, J. & Lewis, V. Unfamiliar Face Recognition in Relatively Able Autistic Children. *Journal of Child Psychology and Psychiatry* **33**, 843-859 (1992).

38. Jemel, B., Mottron, L. & Dawson, M. Impaired Face Processing in Autism: Fact or Artifact? *Journal of Autism and Developmental Disorders* **36**, 91-106 (2006).

39. Klin, A., Sparrow, S.S., de Bildt, A., Cicchetti, D.V., Cohen, D.J. & Volkmar, F.R. A Normed Study of Face Recognition in Autism and Related Disorders. *Journal of Autism and Developmental Disorders* **29**, 499-508 (1999).

40. McCarthy, G., Puce, A., Gore, J.C. & Allison, T. Face-Specific Processing in the Human Fusiform Gyrus. *Journal of Cognitive Neuroscience* **9**, 605-610 (1997).

41. Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J. & Gore, J.C. Abnormal Ventral Temporal Cortical Activity During Face Discrimination Among Individuals With Autism and Asperger Syndrome. *Arch Gen Psychiatry* **57**, 331-340 (2000).

42. Pierce, K., Muller, R.A., Ambrose, J., Allen, G. & Courchesne, E. Face processing occurs outside the fusiform `face area' in autism: evidence from functional MRI. *Brain* **124**, 2059-2073 (2001).

43. Wang, A.T., Dapretto, M., Hariri, A.R., Sigman, M. & Bookheimer, S.Y. Neural Correlates of Facial Affect Processing in Children and Adolescents With Autism Spectrum Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **43**, 481-490 (2004).

44. Tsao, D.Y. & Livingstone, M.S. Mechanisms of Face Perception. *Annual Review of Neuroscience* **31**, 411-437 (2008).

45. Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., Alexander, A.L. & Davidson, R.J. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci* **8**, 519-526 (2005).

46. Hubl, D., Feineis-Mathews, S., Lanfermann, H., Federspiel, A., Strik, W., Poustka, F. & Dierks, T. Functional imbalance of visual pathways indicates alternative face processing strategies in autism. *Neurology* **61**, 1232-7 (2003).

47. Dawson, G., Webb, S., Wisjan, E., Schellenberg, G., Estes, A., Munson, J. & Faja, S. Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology* **17**, 679-697 (2005).

48. Happé, F. & Frith, U. The Weak Coherence Account: Detail-focused Cognitive Style in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* **36**, 5-25 (2006).

49. Nakahachi, T., Yamashita, K., Iwase, M., Ishigami, W., Tanaka, C., Toyonaga, K., Maeda, S., Hirotsune, H., Tei, Y., Yokoi, K., Okajima, S., Shimizu, A. & Takeda, M. Disturbed holistic processing in autism spectrum disorders verified by two cognitive tasks requiring perception of complex visual stimuli. *Psychiatry research* **159**, 330-338 (2008).

50. Bartlett, J.C. & Searcy, J. Inversion and Configuration of Faces. *Cognitive Psychology* **25**, 281-316 (1993).

51. Nakahachi, T., Yamashita, K, Iwase, M, Ishigami, W, Tanaka, C, Toyonaga, K, Maeda, S, Hirotsune, H, Tei, Y, Yokoi, K, Okajima, S, Shimizu, A, Takeda, M. Disturbed holistic processing in autism spectrum disorders verified by two cognitive tasks requiring perception of complex visual stimuli. *Psychiatry Res.* **159**, 330-338 (2008).

52. Pellicano, E., Gibson, L, Maybery, M, Durkin, K, Badcock, DR. Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence? . *Neuropsychologia.* **43**, 1044-1053 (2005).

53. Bonnel, A., Mottron, L, Peretz, I, Trudel, M, Gallun, E, Bonnel, AM. Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *J Cogn Neurosci.* **15**, 226-235 (2003).

54. O'Riordan, M., Passetti, F. Discrimination in Autism Within Different Sensory Modalities. *J Autism Dev Disord* **36**, 665-675 (2006).

55. Lepisto, T., Kujala, T, Vanhala, R, Alku, P, Huotilainen, M, Naatanen, R. The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Res.* **1066**, 147-157 (2005).

56. Samson, F., Hyde, K.L., Bertone, A., SouliËres, I., Mendrek, A., Ahad, P., Mottron, L. & Zeffiro, T.A. Atypical processing of auditory temporal complexity in autistics. *Neuropsychologia* **49**, 546-555 (2011).

57. Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. & Essick, G. Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. *Journal of Autism and Developmental Disorders* **38**, 127-137 (2008).

58. Minshew, N., Hobson, JA. Sensory Sensitivities and Performance on Sensory Perceptual Tasks in High-functioning Individuals with Autism. *J Autism Dev Disord* (2008).

59. Williams, J., Massaro, DW, Peel, NJ, Bosseler, A, Suddendorf, T. Visual-auditory integration during speech imitation in autism. *Research in Developmental Disabilities* **25**, 559-575 (2004).

60. Smith, E.G. & Bennetto, L. Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry* **48**, 813-821 (2007).

61. Magnee, M.J.C.M., Gelder, B.d., Engeland, H.v. & Kemner, C. Audiovisual speech integration in pervasive developmental disorder: evidence from event-related potentials. *Journal of Child Psychology and Psychiatry* **49**, 995-1000 (2008).

62. Taylor, N., Isaac, C. & Milne, E. A Comparison of the Development of Audiovisual Integration in Children with Autism Spectrum Disorders and Typically Developing Children. *Journal of Autism and Developmental Disorders* **40**, 1403-1411 (2010).

63. Bebko, J., Weiss, JA, Demark, JL, Gomez, P. Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *J Child Psychology and Psychiatry* **47**, 88-98 (2006).

64. van der Smagt, M., van Engeland, H. & Kemner, C. Brief Report: Can You See What is Not There? Low-level Auditory–visual Integration in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders* **37**, 2014-2019 (2007).

65. Mongillo, E., Irwin, J., Whalen, D., Klaiman, C., Carter, A. & Schultz, R. Audiovisual Processing in Children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* **38**, 1349-1358 (2008).

66. Magnee, M.J.C.M., Oranje, B., van Engeland, H., Kahn, R.S. & Kemner, C. Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia* **47**, 1728-1732 (2009).

67. Russo, N., Foxe, J.J., Brandwein, A.B., Altschuler, T., Gomes, H. & Molholm, S. Multisensory processing in children with autism: high-density electrical mapping of auditory–somatosensory integration. *Autism Research* **3**, 253-267 (2010).

68. Courchesne, E. Brain development in autism: early overgrowth followed by premature arrest of growth. *Ment Retard Dev Disabil Res Rev.* **10**, 106-11 (2004).

69. Amaral, D.G., Schumann, C.M. & Nordahl, C.W. Neuroanatomy of autism. *Trends in Neurosciences* **31**, 137-145 (2008).

70. Stanfield, A.C., McIntosh, A.M., Spencer, M.D., Philip, R., Gaur, S. & Lawrie, S.M. Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry* **23**, 289-299 (2008).

71. Jou, R.J., Mateljevic, N., Minshew, N.J., Keshavan, M.S. & Hardan, A.Y. Reduced central white matter volume in autism: Implications for long-range connectivity. *Psychiatry and Clinical Neurosciences* **65**, 98-101 (2011).

72. Hardan, A.Y., Pabalan, M., Gupta, N., Bansal, R., Melhem, N.M., Fedorov, S., Keshavan, M.S. & Minshew, N.J. Corpus callosum volume in children with autism. **174**, 57-61 (2009).

73. Vidal, C.N., Nicolson, R., DeVito, T.J., Hayashi, K.M., Geaga, J.A., Drost, D.J., Williamson, P.C., Rajakumar, N., Sui, Y., Dutton, R.A., Toga, A.W. & Thompson, P.M. Mapping Corpus Callosum Deficits in Autism: An Index of Aberrant Cortical Connectivity. *Biological psychiatry* **60**, 218-225 (2006).

74. Weinstein, M., Ben-Sira, L., Levy, Y., Zachor, D.A., Itzhak, E.B., Artzi, M., Tarrasch, R., Eksteine, P.M., Hendler, T. & Bashat, D.B. Abnormal white matter integrity in young children with autism. *Human Brain Mapping* **32**, 534-543 (2011).

75. Feldman, H.M., Yeatman, J.D., Lee, E.S., Barde, L.H.F. & Gaman-Bean, S. Diffusion Tensor Imaging: A Review for Pediatric Researchers and Clinicians. *Journal of*

Developmental & Behavioral Pediatrics **31**, 346-356 10.1097/DBP.0b013e3181dcaa8b (2010).

76. Shukla, D.K., Keehn, B. & Müller, R.-A. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *Journal of Child Psychology and Psychiatry* **52**, 286-295 (2011).

77. Thomas, C., Humphreys, K., Jung, K.-J., Minshew, N. & Behrmann, M. The anatomy of the callosal and visual-association pathways in high-functioning autism: A DTI tractography study. *Cortex; a journal devoted to the study of the nervous system and behavior* **47**, 863-873 (2011).

78. Alexander, A.L., Lee, J.E., Lazar, M., Boudos, R., DuBray, M.B., Oakes, T.R., Miller, J.N., Lu, J., Jeong, E.-K., McMahon, W.M., Bigler, E.D. & Lainhart, J.E. Diffusion tensor imaging of the corpus callosum in Autism. *Neuroimage* **34**, 61-73 (2007).

79. Sundaram, S.K., Kumar, A., Makki, M.I., Behen, M.E., Chugani, H.T. & Chugani, D.C. Diffusion Tensor Imaging of Frontal Lobe in Autism Spectrum Disorder. *Cerebral Cortex* **18**, 2659-2665 (2008).

80. Langen, M., Leemans, A., Johnston, P., Ecker, C., Daly, E., Murphy, C.M., dell'Acqua, F., Durston, S. & Murphy, D.G.M. Fronto-striatal circuitry and inhibitory control in autism: Findings from diffusion tensor imaging tractography. *Cortex* **In Press, Corrected Proof**.

81. Stigler, K.A., McDonald, B.C., Anand, A., Saykin, A.J. & McDougle, C.J. Structural and functional magnetic resonance imaging of autism spectrum disorders. *Brain Research* **1380**, 146-161 (2011).

82. Lee, J.E., Bigler, E.D., Alexander, A.L., Lazar, M., DuBray, M.B., Chung, M.K., Johnson, M., Morgan, J., Miller, J.N., McMahon, W.M., Lu, J., Jeong, E.-K. & Lainhart, J.E. Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. *Neuroscience Letters* **424**, 127-132 (2007).

83. Buxhoeveden, D.P. & Casanova, M.F. The minicolumn hypothesis in neuroscience. *Brain* **125**, 935-951 (2002).

84. Buxhoeveden, D.P. & Casanova, M.F. The Minicolumn and Evolution of the Brain. *Brain, Behavior and Evolution* **60**, 125-151 (2002).

85. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E. & Roy, E. Minicolumnar pathology in autism. *Neurology* **58**, 428-432 (2002).

86. Casanova, M., van Kooten, I., Switala, A., van Engeland, H., Heinsen, H., Steinbusch, H., Hof, P., Trippe, J., Stone, J. & Schmitz, C. Minicolumnar abnormalities in autism. *Acta Neuropathologica* **112**, 287-303 (2006).

87. Raghanti, M.A., Spocter, M.A., Butti, C., Hof, P.R. & Sherwood, C.C. A comparative perspective on minicolumns and inhibitory GABAergic interneurons in the neocortex. *Frontiers in Neuroanatomy* **4**(2010).

88. Casanova, M.F., Buxhoeveden, D. & Gomez, J. Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim. *The Neuroscientist* **9**, 496-507 (2003).

89. Wass, S. Distortions and disconnections: Disrupted brain connectivity in autism. *Brain and Cognition* **75**, 18-28 (2011).

90. Rippon, G., Brock, J., Brown, C. & Boucher, J. Disordered connectivity in the autistic brain: Challenges for the `new psychophysiology'. *International Journal of Psychophysiology* **63**, 164-172 (2007).

91. Coben, R., Clarke, A.R., Hudspeth, W. & Barry, R.J. EEG power and coherence in autistic spectrum disorder. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* **119**, 1002-1009 (2008).

92. Perez Velazquez, J.L., Barcelo, F., Hung, Y., Leshchenko, Y., Nenadovic, V., Belkas, J., Raghavan, V., Brian, J. & Garcia Dominguez, L. Decreased brain coordinated activity in autism spectrum disorders during executive tasks: Reduced long-range synchronization in the fronto-parietal networks. *International Journal of Psychophysiology* **73**, 341-349 (2009).

93. Bernier, R., Dawson, G., Webb, S. & Murias, M. EEG mu rhythm and imitation impairments in individuals with autism spectrum disorder. *Brain and Cognition* **64**, 228-237 (2007).

94. Murias, M., Webb, S.J., Greenson, J. & Dawson, G. Resting State Cortical Connectivity Reflected in EEG Coherence in Individuals With Autism. *Biological psychiatry* **62**, 270-273 (2007).

95. Uhlhaas, P.J., Haenschel, C., Nikolic, D. & Singer, W. The Role of Oscillations and Synchrony in Cortical Networks and Their Putative Relevance for the Pathophysiology of Schizophrenia. *Schizophrenia Bulletin* **34**, 927-943 (2008).

96. Elsabbagh, M., Volein, A., Csibra, G., Holmboe, K., Garwood, H., Tucker, L., Krljes, S., Baron-Cohen, S., Bolton, P., Charman, T., Baird, G. & Johnson, M.H. Neural Correlates of Eye Gaze Processing in the Infant Broader Autism Phenotype. *Biological psychiatry* **65**, 31-38 (2009).

97. Wilson, T.W., Rojas, D.C., Reite, M.L., Teale, P.D. & Rogers, S.J. Children and Adolescents with Autism Exhibit Reduced MEG Steady-State Gamma Responses. *Biological psychiatry* **62**, 192-197 (2007).

98. Brown, C., Gruber, T, Boucher, J, Rippon, G, Brock, J. Gamma abnormalities during perception of illusory figures in autism. *Cortex* **41**, 364-376 (2005).

99. Stroganova, T.A., Orekhova, E.V., Prokofyev, A.O., Tsetlin, M.M., Gratchev, V.V., Morozov, A.A. & Obukhov, Y.V. High-frequency oscillatory response to illusory contour in typically developing boys and boys with autism spectrum disorders. *Cortex* **In Press, Corrected Proof**.

100. Grice, S.J., Spratling, M.W., Karmiloff-Smith, A., Halit, H., Csibra, G., de Haan, M. & Johnson, M.H. Disordered visual processing and oscillatory brain activity in autism and Williams Syndrome. *NeuroReport* **12**, 2697-2700 (2001).

101. Horwitz, B., Rumsey, J.M., Grady, C.L. & Rapoport, S.I. The Cerebral Metabolic Landscape in Autism: Intercorrelations of Regional Glucose Utilization. *Arch Neurol* **45**, 749-755 (1988).

102. Just, M.A., Cherkassky, V.L., Keller, T.A. & Minshew, N.J. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain* **127**, 1811-1821 (2004).

103. Kleinhans, N.M., Richards, T., Sterling, L., Stegbauer, K.C., Mahurin, R., Johnson, L.C., Greenson, J., Dawson, G. & Aylward, E. Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain* **131**, 1000-1012 (2008).

104. Koshino, H., Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J. & Just, M.A. fMRI Investigation of Working Memory for Faces in Autism: Visual Coding and Underconnectivity with Frontal Areas. *Cerebral Cortex* **18**, 289-300 (2008).

105. Villalobos, M.E., Mizuno, A., Dahl, B.C., Kemmotsu, N. & M¸ller, R.-A. Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. *Neuroimage* **25**, 916-925 (2005).

106. Welchew, D.E., Ashwin, C., Berkouk, K., Salvador, R., Suckling, J., Baron-Cohen, S. & Bullmore, E. Functional disconnectivity of the medial temporal lobe in Asperger,Äôs syndrome. *Biological psychiatry* **57**, 991-998 (2005).

107. Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K. & Minshew, N.J. Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry. *Cerebral Cortex* **17**, 951-961 (2007).

108. Noonan, S.K., Haist, F. & M¸ller, R.-A. Aberrant functional connectivity in autism: Evidence from low-frequency BOLD signal fluctuations. *Brain Research* **1262**, 48-63 (2009).

109. Shih, P., Keehn, B., Oram, J.K., Leyden, K.M., Keown, C.L. & M¸ller, R.-A. Functional Differentiation of Posterior Superior Temporal Sulcus in Autism: A Functional Connectivity Magnetic Resonance Imaging Study. *Biological psychiatry* **In Press, Corrected Proof**(2011).

110. Mizuno, A., Villalobos, M.E., Davies, M.M., Dahl, B.C. & M¸ller, R.-A. Partially enhanced thalamocortical functional connectivity in autism. *Brain Research* **1104**, 160-174 (2006).

111. Rubenstein, J.L.R. & Merzenich, M.M. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior* **2**, 255-267 (2003).

112. Alitto, H.J. & Dan, Y. Function of inhibition in visual cortical processing. *Current Opinion in Neurobiology* **20**, 340-346 (2010).

113. Blake, R., Holopigian, K. & Wilson, H.R. Spatial-frequency discrimination in cats. *J. Opt. Soc. Am. A* **3**, 1443-1449 (1986).

114. Fletcher, H. Auditory Patterns. *Reviews of Modern Physics* **12**, 47-66 (1940).

115. Patterson, R. Auditory filter shapes derived with noise stimul. *J. Aooust.S Oc.A m.* **59**, 640-654 (1976).

116. Stromeyer, C. & Julesz, B. Spatial-Frequency Masking in Vision: Critical Bands and Spread of Masking. *JOSA* **62**, 1221-1232 (1972).

117. Stein, B.E., Meredith, M.A., Huneycutt, W.S. & McDade, L. Behavioral Indices of Multisensory Integration: Orientation to Visual Cues is Affected by Auditory Stimuli. *Journal of Cognitive Neuroscience* **1**, 12-24 (1989).

118. Sperdin, H.F., Cappe, C.I., Foxe, J.J. & Murray, M.M. Early, low-level auditory-somatosensory multisensory interactions impact reaction time speed. *Frontiers in Integrative Neuroscience* **3**(2009).

119. Noesselt, T., Bergmann, D., Hake, M., Heinze, H.-J. & Fendrich, R. Sound increases the saliency of visual events. *Brain Research* **1220**, 157-163 (2008).

120. Odgaard, E., Arieh, Y. & Marks, L. Cross-modal enhancement of perceived brightness: Sensory interaction versus response bias. *Perception & Psychophysics* **65**, 123-132 (2003).

121. Stein, B.E., London, N., Wilkinson, L.K. & Price, D.D. Enhancement of Perceived Visual Intensity by Auditory Stimuli: A Psychophysical Analysis. *Journal of Cognitive Neuroscience* **8**, 497-506 (1996).

122. Forster, B., Cavina-Pratesi, C., Aglioti, S. & Berlucchi, G. Redundant target effect and intersensory facilitation from visual-tactile interactions in simple reaction time. *Experimental Brain Research* **143**, 480-487 (2002).

123. Lovelace, C.T., Stein, B.E. & Wallace, M.T. An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Cognitive Brain Research* **17**, 447-453 (2003).

124. Ross, L.A., Saint-Amour, D., Leavitt, V.M., Javitt, D.C. & Foxe, J.J. Do You See What I Am Saying? Exploring Visual Enhancement of Speech Comprehension in Noisy Environments. *Cerebral Cortex* **17**, 1147-1153 (2007).

125. Callan, D.E., Jones, J.A., Munhall, K., Callan, A.M., Kroos, C. & Vatikiotis-Bateson, E. Neural processes underlying perceptual enhancement by visual speech gestures. *NeuroReport* **14**, 2213-2218 (2003).

126. Ma, W.J., Zhou, X., Ross, L.A., Foxe, J.J. & Parra, L.C. Lip-Reading Aids Word Recognition Most in Moderate Noise: A Bayesian Explanation Using High-Dimensional Feature Space. *PLoS ONE* **4**, e4638 (2009).

127. Bishop, C.W. & Miller, L.M. A Multisensory Cortical Network for Understanding Speech in Noise. *Journal of Cognitive Neuroscience* **21**, 1790-1804 (2009).

128. Rowland, B., Stanford, T. & Stein, B. A Bayesian model unifies multisensory spatial localization with the physiological properties of the superior colliculus. *Experimental Brain Research* **180**, 153-161 (2007).

129. Hairston, W.D., Laurienti, P.J., Mishra, G., Burdette, J.H. & Wallace, M.T. Multisensory enhancement of localization under conditions of induced myopia. *Experimental Brain Research* **152**, 404-408 (2003).

130. Alais, D. & Burr, D. No direction-specific bimodal facilitation for audiovisual motion detection. *Cognitive Brain Research* **19**, 185-194 (2004).

131. Baumann, O. & Greenlee, M.W. Neural Correlates of Coherent Audiovisual Motion Perception. *Cerebral Cortex* **17**, 1433-1443 (2007).

132. Wuerger, S., Hofbauer, M. & Meyer, G. The integration of auditory and visual motion signals at threshold. *Attention, Perception, & Psychophysics* **65**, 1188-1196 (2003).

133. Alais, D. & Burr, D. The Ventriloquist Effect Results from Near-Optimal Bimodal Integration. *Current biology : CB* **14**, 257-262 (2004).

134. Choe, C., Welch, R., Gilford, R. & Juola, J. The “ventriloquist effect”: Visual dominance or response bias? *Attention, Perception, & Psychophysics* **18**, 55-60 (1975).

135. Bonath, B., Noesselt, T., Martinez, A., Mishra, J., Schwiecker, K., Heinze, H.-J. & Hillyard, S.A. Neural Basis of the Ventriloquist Illusion. *Current biology : CB* **17**, 1697-1703 (2007).

136. Wallace, M.T., Roberson, G.E., Hairston, W.D., Stein, B.E., Vaughan, J.W. & Schirillo, J.A. Unifying multisensory signals across time and space. *Experimental Brain Research* **158**, 252-258 (2004).

137. Alais, D. & Burr, D. The Ventriloquist Effect Results from Near-Optimal Bimodal Integration. **14**, 257-262 (2004).

138. Shams, L., Kamitani, Y. & Shimojo, S. Visual illusion induced by sound. *Cognitive Brain Research* **14**, 147-152 (2002).

139. Morein-Zamir, S., Soto-Faraco, S, Kingstonek, A. Auditory capture of vision: examining temporal ventriloquism. *Brain Res. Cogn Brain Res.* **17**, 154-163 (2003).

140. Hairston, W., Burdette, JH, Flowers, DL, Wood, FB, Wallace, MT. Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Exp Brain Res.* **166**, 474-480 (2005).

141. McGurk, H. & Macdonald, J. Hearing lips and seeing voices. *Nature* **264**, 746-748 (1976).

142. Meredith, M., Nemitz, JW, Stein, BE. Determinants of Multisensory Integration in Superior Colliculus Neurons. I. Temporal Factors. *J Neuroscience* **7**, 3215-3229 (1987).

143. Stein, B.E., Huneycutt, W.S. & Meredith, M.A. Neurons and Behavior: the same rules of multisensory integration apply. *Brain Research* **448**, 355-358 (1988).

144. Conrey, B., Pisoni, DB. Auditory-visual speech perception and synchrony detection for speech and nonspeech signals. *J Acous Soc am.* **119**, 4065-4073 (2006).

145. Frens, M., Van Opstal, AJ, Van der Willigen, RF. Spatial and temporal factors determine auditory-visual interactions in human saccadic eye movements. *Percept Psychophys.* **57**, 802-816 (1995).

146. Hairston, W.D., Hodges, D.A., Burdette, J.H. & Wallace, M.T. Auditory enhancement of visual temporal order judgment. *NeuroReport* **17**, 791-795 10.1097/01.wnr.0000220141.29413.b4 (2006).

147. Hanson, J., Heron, J. & Whitaker, D. Recalibration of perceived time across sensory modalities. *Experimental Brain Research* **185**, 347-352 (2008).

148. Koppen, C. & Spence, C. Audiovisual asynchrony modulates the Colavita visual dominance effect. *Brain Research* **1186**, 224-232 (2007).

149. Munhall, K., Gribble, P, Sacco, L, Ward, M. Temporal constraints on the McGurk effect. . *Percept Psychophys.* **58**, 351-362 (1996).

150. Noesselt, T., Rieger, JW, Schoenfeld, MA, Kanowski, M, Hinrichs, H, Heinze, HJ, Driver, J. Audiovisual temporal correspondence modulates human multisensory superior temporal sulcus plus primary sensory cortices. *J Neurosci.* **27**, 11431-11441 (2007).

151. Powers, A.R., III, Hillock, A.R. & Wallace, M.T. Perceptual Training Narrows the Temporal Window of Multisensory Binding. *J. Neurosci.* **29**, 12265-12274 (2009).

152. Senkowski, D., Talsma, D, Grigutsch, M, Herrmann, CS, Woldorff, MG. Good times for multisensory integration: Effects of the precision of temporal synchrony as revealed by gamma-band oscillations. *Neuropsychologia* **45**, 561-571 (2007).

153. Shams, L., Kamitani, Y. & Shimojo, S. Illusions: What you see is what you hear. *Nature* **408**, 788 (2000).

154. Hillock, A.R., Powers, A.R. & Wallace, M.T. Binding of sights and sounds: Age-related changes in multisensory temporal processing. *Neuropsychologia* **49**, 461-467 (2011).

155. Colonius, H. & Diederich, A. Multisensory Interaction in Saccadic Reaction Time: A Time-Window-of-Integration Model. *Journal of Cognitive Neuroscience* **16**, 1000-1009 (2004).

156. Diederich, A. & Colonius, H. Crossmodal interaction in saccadic reaction time: separating multisensory from warning effects in the time window of integration model. *Experimental Brain Research* **186**, 1-22 (2008).

157. Meredith, M.A. & Stein, B.E. Spatial determinants of multisensory integration in cat superior colliculus neurons. *Journal of Neurophysiology* **75**, 1843-1857 (1996).

158. Teder-Sälejärvi, W.A., Russo, F.D., McDonald, J.J. & Hillyard, S.A. Effects of Spatial Congruity on Audio-Visual Multimodal Integration. *Journal of Cognitive Neuroscience* **17**, 1396-1409 (2005).

159. Plank, T., Rosengarth, K., Song, W., Ellermeier, W. & Greenlee, M.W. Neural correlates of audio-visual object recognition: Effects of implicit spatial congruency. *Human Brain Mapping*, n/a-n/a (2011).

160. Innes-Brown, H. & Crewther, D. The Impact of Spatial Incongruence on an Auditory-Visual Illusion. *PLoS ONE* **4**, e6450 (2009).

161. Macaluso, E. & Driver, J. Multisensory spatial interactions: a window onto functional integration in the human brain. *Trends in Neurosciences* **28**, 264-271 (2005).

162. Wallace, M.T., Meredith, M.A. & Stein, B.E. Multisensory Integration in the Superior Colliculus of the Alert Cat. *Journal of Neurophysiology* **80**, 1006-1010 (1998).

163. Wallace, M.T., Wilkinson, L.K. & Stein, B.E. Representation and integration of multiple sensory inputs in primate superior colliculus. *Journal of Neurophysiology* **76**, 1246-1266 (1996).

164. Stanford, T., Quessy, S. & Stein, B. Evaluating the Operations Underlying Multisensory Integration in the Cat Superior Colliculus. *The Journal of Neuroscience* **25**, 6499-6508 (2005).

165. Molholm, S., Ritter, W., Murray, M.M., Javitt, D.C., Schroeder, C.E. & Foxe, J.J. Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Cognitive Brain Research* **14**, 115-128 (2002).

166. Diederich, A. & Colonius, H. Bimodal and trimodal multisensory enhancement: Effects of stimulus onset and intensity on reaction time. *Attention, Perception, & Psychophysics* **66**, 1388-1404 (2004).

167. Meredith, M.A. On the neuronal basis for multisensory convergence: a brief overview. *Cognitive Brain Research* **14**, 31-40 (2002).

168. Meredith, M.A. & Stein, B.E. Visual, auditory, and somatosensory convergence on cells in superior colliculus results in multisensory integration. *Journal of Neurophysiology* **56**, 640-662 (1986).

169. Meredith, M., Wallace, M. & Stein, B. Visual, auditory and somatosensory convergence in output neurons of the cat superior colliculus: multisensory properties of the tecto-reticulo-spinal projection. *Experimental Brain Research* **88**, 181-186 (1992).

170. Wallace, M.T., Meredith, M.A. & Stein, B.E. Converging influences from visual, auditory, and somatosensory cortices onto output neurons of the superior colliculus. *Journal of Neurophysiology* **69**, 1797-1809 (1993).

171. Alvarado, J., Stanford, T., Vaughan, J. & Stein, B. Cortex Mediates Multisensory but not Unisensory Integration in Superior Colliculus. *The Journal of Neuroscience* **28**, 1787-1788 (2007).

172. Jiang, W., Wallace, M.T., Jiang, H., Vaughan, J.W. & Stein, B.E. Two Cortical Areas Mediate Multisensory Integration in Superior Colliculus Neurons. *Journal of Neurophysiology* **85**, 506-522 (2001).

173. Perrault, T.J., Vaughan, J.W., Stein, B.E. & Wallace, M.T. Superior Colliculus Neurons Use Distinct Operational Modes in the Integration of Multisensory Stimuli. *Journal of Neurophysiology* **93**, 2575-2586 (2005).

174. Carriere, B.N., Royal, D.W., Perrault, T.J., Morrison, S.P., Vaughan, J.W., Stein, B.E. & Wallace, M.T. Visual Deprivation Alters the Development of Cortical Multisensory Integration. *Journal of Neurophysiology* **98**, 2858-2867 (2007).

175. Carriere, B.N., Royal, D.W. & Wallace, M.T. Spatial Heterogeneity of Cortical Receptive Fields and Its Impact on Multisensory Interactions. *Journal of Neurophysiology* **99**, 2357-2368 (2008).

176. Dehner, L.R., Keniston, L.P., Clemo, H.R. & Meredith, M.A. Cross-modal Circuitry Between Auditory and Somatosensory Areas of the Cat Anterior Ectosylvian Sulcal Cortex: A ‚ÄòNew‚Äô Inhibitory Form of Multisensory Convergence. *Cerebral Cortex* **14**, 387-403 (2004).

177. Royal, D., Carriere, B. & Wallace, M. Spatiotemporal architecture of cortical receptive fields and its impact on multisensory interactions. *Experimental Brain Research* **198**, 127-136 (2009).

178. Ghazanfar, A.A., Chandrasekaran, C. & Logothetis, N.K. Interactions between the Superior Temporal Sulcus and Auditory Cortex Mediate Dynamic Face/Voice Integration in Rhesus Monkeys. *The Journal of Neuroscience* **28**, 4457-4469 (2008).

179. Zilbovicius, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y. & Boddaert, N. Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences* **29**, 359-366 (2006).

180. Pelphrey, K.A., Morris, J.P. & McCarthy, G. Grasping the Intentions of Others: The Perceived Intentionality of an Action Influences Activity in the Superior Temporal Sulcus during Social Perception. *Journal of Cognitive Neuroscience* **16**, 1706-1716 (2004).

181. Redcay, E. The superior temporal sulcus performs a common function for social and speech perception: Implications for the emergence of autism. *Neuroscience & Biobehavioral Reviews* **32**, 123-142 (2008).

182. Nath, A.R. & Beauchamp, M.S. Dynamic Changes in Superior Temporal Sulcus Connectivity during Perception of Noisy Audiovisual Speech. *The Journal of Neuroscience* **31**, 1704-1714 (2011).

183. Calvert, G.A. Crossmodal Processing in the Human Brain: Insights from Functional Neuroimaging Studies. *Cerebral Cortex* **11**, 1110-1123 (2001).

184. Dahl, C., Logothetis, N. & Kayser, C. Modulation of Visual Responses in the Superior Temporal Sulcus by Audio-Visual Congruency. *Frontiers in Integrative Neuroscience* **4**, 1-8 (2010).

185. Barraclough*, N.E., Xiao*, D., Baker, C.I., Oram, M.W. & Perrett, D.I. Integration of Visual and Auditory Information by Superior Temporal Sulcus Neurons Responsive to the Sight of Actions. *Journal of Cognitive Neuroscience* **17**, 377-391 (2005).

186. Stevenson, R.A. & James, T.W. Audiovisual integration in human superior temporal sulcus: Inverse effectiveness and the neural processing of speech and object recognition. *Neuroimage* **44**, 1210-1223 (2009).

187. Beauchamp, M.S., Nath, A.R. & Pasalar, S. fMRI-Guided Transcranial Magnetic Stimulation Reveals That the Superior Temporal Sulcus Is a Cortical Locus of the McGurk Effect. *The Journal of Neuroscience* **30**, 2414-2417 (2010).

188. Zilbovicius, M., Boddaert, N., Belin, P., Poline, J.-B., Remy, P., Mangin, J.-F., Thivard, L., Barthelemy, C. & Samson, Y. Temporal Lobe Dysfunction in Childhood Autism: A PET Study. *Am J Psychiatry* **157**, 1988-1993 (2000).

189. Barnea-Goraly, N., Kwon, H., Menon, V., Eliez, S., Lotspeich, L. & Reiss, A.L. White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biological psychiatry* **55**, 323-326 (2004).

190. Boddaert, N., Chabane, N., Gervais, H., Good, C.D., Bourgeois, M., Plumet, M.H., BarthÈlÈmy, C., Mouren, M.C., Artiges, E., Samson, Y., Brunelle, F., Frackowiak, R.S.J. & Zilbovicius, M. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage* **23**, 364-369 (2004).

191. Castelli, F., Frith, C., Happe, F. & Frith, U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain* **125**, 1839-1849 (2002).

192. Rockland, K.S. & Ojima, H. Multisensory convergence in calcarine visual areas in macaque monkey. *International Journal of Psychophysiology* **50**, 19-26 (2003).

193. Clavagnier, S., Falchier, A. & Kennedy, H. Long-distance feedback projections to area V1: implications for multisensory integration, spatial awareness, and visual consciousness. *Cogn Affect Behav Neurosci.* **4**, 117-26 (2004).

194. Cappe, C. & Barone, P. Heteromodal connections supporting multisensory integration at low levels of cortical processing in the monkey. *European Journal of Neuroscience* **22**, 2886-2902 (2005).

195. Budinger, E., Heil, P., Hess, A. & Scheich, H. Multisensory processing via early cortical stages: Connections of the primary auditory cortical field with other sensory systems. *Neuroscience* **143**, 1065-1083 (2006).

196. Hall, A. & Lomber, S. Auditory cortex projections target the peripheral field representation of primary visual cortex. *Experimental Brain Research* **190**, 413-430 (2008).

197. Keil, J., Muller, N., Ihssen, N. & Weisz, N. On the Variability of the McGurk Effect: Audiovisual Integration Depends on Prestimulus Brain States. *Cerebral Cortex* (2011).

198. Chen, Y.-H., Edgar, J.C., Holroyd, T., Dammers, J., Thönneßen, H., Roberts, T.P.L. & Mathiak, K. Neuromagnetic oscillations to emotional faces and prosody. *European Journal of Neuroscience* **31**, 1818-1827 (2010).

199. Senkowski, D., Schneider, T., Tandler, F. & Engel, A. Gamma-band activity reflects multisensory matching in working memory. *Experimental Brain Research* **198**, 363-372 (2009).

200. Yuval-Greenberg, S. & Deouell, L.Y. What You See Is Not (Always) What You Hear: Induced Gamma Band Responses Reflect Cross-Modal Interactions in Familiar Object Recognition. *The Journal of Neuroscience* **27**, 1090-1096 (2007).

201. Senkowski, D., Molholm, S., Gomez-Ramirez, M. & Foxe, J.J. Oscillatory Beta Activity Predicts Response Speed during a Multisensory Audiovisual Reaction Time Task: A High-Density Electrical Mapping Study. *Cerebral Cortex* **16**, 1556-1565 (2006).

202. Mishra, J., Martinez, A. & Hillyard, S.A. Cortical processes underlying sound-induced flash fusion. *Brain Research* **1242**, 102-115 (2008).

203. Brock, J., Brown, CC, Boucher, J, Rippon, G. The temporal binding deficit hypothesis of autism. *Development and Psychopathology* **14**, 209-224 (2002).

CHAPTER II

AN EXTENDED MULTISENSORY TEMPORAL BINDING WINDOW IN AUTISM SPECTRUM DISORDERS: MULTISENSORY TEMPORAL BINDING IN ASD[†]

Abstract

Autism spectrum disorders (ASD) form a continuum of neurodevelopmental disorders, characterized by deficits in communication and reciprocal social interaction, as well as by repetitive behaviors and restricted interests. Sensory disturbances are also frequently reported in clinical and autobiographical accounts. However, surprisingly few empirical studies have characterized the fundamental features of sensory and multisensory processing in ASD. The current study tested for potential differences in multisensory temporal function in ASD by making use of a temporally-dependent low-level multisensory illusion. In this illusion, the presentation of a single flash of light accompanied by multiple sounds often results in the perception of multiple flashes. By systematically varying the temporal structure of the audiovisual stimuli, a "temporal window" within which the auditory and visual stimuli are likely to be bound into a single perceptual entity can be defined. The results revealed that children with ASD report the flash-beep illusion over an extended range of stimulus onset asynchronies (SOAs) relative to children with typical development, indicating that children with ASD have altered multisensory temporal function. These findings provide valuable new insights

---

[†] The contents of this chapter were first published as:
Jennifer H. Foss-Feig*, Leslie D. Kwakye*, Carissa J. Cascio, Courtney P. Burnette, Haleh Kadivar, Wendy L. Stone, and Mark T. Wallace **An Extended Multisensory Temporal Binding Window in Autism Spectrum Disorders: Multisensory temporal binding in ASD** Exp Brain Res 203(2):381-9 , DOI: 10.1007/s00221-010-2240-4. (*) *Indicates joint first authorship*

into our understanding of sensory processing in ASD and may hold promise for the development of more sensitive diagnostic measures and improved remediation strategies.

Introduction

Autism spectrum disorders (ASD) comprise a continuum of neurodevelopmental disorders typically characterized by a triad of symptoms that includes deficits in social reciprocity and communication skills, and repetitive behaviors and restricted interests [1]. In addition, reports of altered sensory processing abound in autobiographical, caregiver and clinical reports, and detail a host of sensory aversions, sensitivities, and fascinations in individuals with ASD [2-13]. Indeed, reports of sensory disturbances date back to Kanner's original description of autism [14].

Several recent empirical studies have further highlighted changes in sensory processes in individuals with ASD. Interestingly, some of these studies have shown *superior* visual, auditory, and somatosensory perceptual discrimination in individuals with ASD relative to control subjects [15-17]. Other studies suggest that these enhanced perceptual abilities are limited to fairly simple stimuli and that disrupted performance characterizes responses to more complex stimuli [18,19]. In addition to differences in sensory processing within individual sensory systems, there is some evidence that alterations in the integration of information across the different senses (i.e., multisensory integration; see [20]) may exist in individuals with ASD, though strong empirical support for this is lacking.

In an effort to account for the observed dissociation between performance on simple and complex perceptual tasks in individuals with ASD, it has been theorized that the critical deficit may lie in the temporal synchronization among local neural networks [21].

In support of this view, several studies have shown differences in various aspects of sensory temporal function in individuals with ASD, including duration and rate processing [22-24]. Temporal synchronization is also likely to be critically important in the binding of multisensory stimuli into unified perceptual constructs (Senkowski 2008), and alterations in multisensory temporal function could give rise to significant deficits in perceptual abilities.

A recent study sought to directly examine multisensory processing in ASD using the sound-induced double-flash ("flash-beep") illusion, in which the pairing of multiple auditory cues (i.e., beeps) with a single visual cue (i.e., flash) frequently results in the perception of additional flashes [25]. Using the flash-beep task, no differences were found in the strength of illusion between individuals with ASD and controls, suggesting intact multisensory binding mechanisms [26]. However, the flash-beep illusion is critically dependent on the temporal structure of the visual and auditory cues [27], a dependence not explored in the Van der Smagt study. Given previous findings of impaired temporal processing in ASD, we hypothesized that changes in the temporal structure of the visual and auditory cues in the flash-beep task might reveal differences in the temporal "binding window" for multisensory stimuli in individuals with ASD.

Methods

Participants

Forty-six children (29 with ASD and 17 with typical development (TD)) comprised the study sample. Eligibility criteria for children in both groups were as follows: a) age 8-17 years; b) normal or corrected-to-normal hearing and vision; c) Full Scale IQ (FSIQ) above 70; and d) no evidence or past diagnosis of a specific reading disorder. Adequate cognitive functioning for inclusion in the study (i.e., FSIQ above 70) was confirmed using the Wechsler Abbreviated Scale of Intelligence (WASI; [28]) unless a child had completed cognitive testing in the past year and the parents could provide the scores. Reading abilities were screened using the Letter-Word Identification and Word Attack subtests of the Woodcock-Johnson Tests of Achievement – Third Edition (WJA-III:[29]), since differences in multisensory processing have been demonstrated in individuals with reading disorders [30]. All children in both groups were required to have reading standard scores above 70 on both subtests. Additional eligibility criteria for the ASD group required that children: a) have a confirmed diagnosis of Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified; and b) have no history of seizure disorders or identified genetic disorders (e.g., Fragile X, tuberous sclerosis). ASD diagnosis was confirmed with the Autism Diagnostic Observation Schedule (ADOS [31], Module 3 by a research-reliable examiner. Parents of children with ASD completed the Autism Diagnostic Interview – Revised (ADI-R; [32]) with a trained, research-reliable interviewer to confirm history of ASD. All children included in the ASD group met criteria for autism or autism spectrum on the ADOS and ADI-R and also had prior clinical diagnoses of ASD confirmed by a licensed clinical psychologist as part of this study. Five children with ASD who passed the telephone screening did not meet eligibility criteria during the diagnostic session (three based on diagnosis, two based on cognitive functioning levels) and therefore did not participate in the psychophysics session. Two additional children with ASD who attempted the experimental procedures were excluded from analyses due to difficulties with attention, comprehension, and/or compliance. Additional eligibility criteria for children with TD were as follows: a) no history of or current psychiatric, neurological, or learning disorders (e.g., ADHD, depression, epilepsy) or symptoms of ASD; and b) no first-degree relatives with ASD. Parent report of ASD symptoms was obtained using the Lifetime version of the Social

Communication Questionnaire (SCQ; [33]); all children with TD had SCQ scores below at-risk cutoff for ASD. Finally, because it was the primary measure of interest, children who failed to report the flash-beep illusion were excluded from analyses. One child with ASD was excluded based upon this criterion. The resulting sample consisted of 21 children with ASD and 17 children with TD. No group differences in age, gender, Full Scale IQ, Verbal IQ, Performance IQ, or word reading abilities were found (Table 2.1). Significant group differences were found for parent report of ASD symptoms on the SCQ ($t(35) = 8.41$, $p < 0.001$).

Parents of all participants gave informed consent and all children in both groups gave assent prior to participation in any component of this study. All children received compensation for their participation at each visit. All recruitment and experimental procedures were approved by the Vanderbilt University Institutional Review Board.

General Procedure

Participants sat in a light- and sound-attenuated room and wore headphones through which auditory stimuli were presented. They indicated their responses to the visual task stimuli, presented on a computer monitor, through button presses on a

Table 2.1. Participant Demographics.

Measure	ASD	TD
Gender $^{n.s.}$	17M; 4F	14M; 3F
Age $^{n.s.}$	12.60 ± 2.6	12.09 ± 2.2
Verbal IQ $^{n.s.}$	105.10 ± 17.6	109.41 ± 12.5
Performance IQ $^{n.s.}$	109.80 ± 18.3	103.41 ± 7.32
Full Scale IQ $^{n.s.}$	108.45 ± 18.7	107.29 ± 9.3
Social Communication Questionnaire**	19.84 ± 8.1	2.71 ± 2.3

n.s. – non-significant; ** - p<.001

response box. Visual stimuli were presented as white flashes against a black background on a high-refresh rate PC monitor (NEC Multisync FE992, 22 inch screen; 150 Hz refresh rate; 640x480 pixel resolution). Auditory stimuli were presented via noise-canceling extra-aural headphones (Philips SBC HN110) to both ears (peak sound level - 96 dB SPL). Stimulus presentation was controlled using E-Prime (Psychology Software Tools Inc., Pittsburgh, PA, USA). Responses (i.e., accuracy and response time) were recorded via a Serial Response box (Psychology Software Tools Inc., Pittsburgh, PA, USA).

Participants were monitored by the experimenter, using closed-circuit CCD video cameras, to ensure that they were engaged in the tasks. Eye gaze was not monitored, but participants were instructed to fixate on a central cross that preceded all stimulus presentations. On the rare occasions when a participant was not on-task, a variety of strategies were implemented to increase engagement (e.g., reminders to stay on task, additional breaks, parent in the testing room, etc). Participants were allowed to take breaks as necessary to increase compliance and maintain effort, motivation, and on-task behavior. All participants completed the experimental task within a single session.

Flash-Beep Task

This task explored the sound-induced illusory flash phenomenon (here termed the flash-beep illusion), wherein the addition of multiple auditory stimuli (beeps) presented in conjunction with a single visual stimulus (flash) often results in the illusory perception of additional flashes [25]. Importantly, the relative timing of the flash and beeps is crucial to the perception of the illusion in typical adults (i.e., beeps presented in close temporal proximity to the flash are more likely to produce illusory flashes [27]). In all trials, participants were asked to report the number of flashes perceived. At the start of each trial a white fixation cross appeared at the center of the black screen. Visual stimuli consisted of the brief (20 ms) appearance of a white circle (4.2 cm in diameter subtending 4.37° of visual space) 4 cm (4.17°) below the center of the fixation cross. The circle was presented either once or twice, with a 50 ms interstimulus interval on double-flash trials. Flashes could be accompanied by no, one, or two beeps (7 ms duration, ramped on and off for 3 ms each; 1850 Hz frequency) depending on condition. Conditions containing one flash and two beeps were used to explore the temporal dependence of the flash-beep illusion in children with ASD and TD. In these conditions, the two beeps were presented at varying stimulus onset asynchronies (SOAs) relative to the single flash in order to determine the temporal window within which multisensory integration (i.e., report of the illusory percept) occurred. Whereas the onset of one of the beeps always coincided with the onset of the single flash, the second beep was either delayed by 25-500 ms relative to the offset of the flash (i.e., positive SOAs) or occurred 25-500 ms prior to the flash (i.e., negative SOAs). The SOA increments in both directions were as follows: 25, 50, 100, 150, 200, 300, 400, 500 ms (Figure 2.1). Ten trials for each condition were presented in random order (giving rise to 160 total illusory trials), pseudo-randomly interleaved with several other trial types that were included in the task to limit cognitive bias. These other trial types included those containing two flashes and two beeps, where the SOAs between the beeps and the flashes were similar in structure to the illusory trials (120 total trials), as well as ten trials each of the following other conditions: one flash, no beeps; one flash, one beep; two flashes, no beeps; and two flashes, one beep. Altogether, participants were presented with 320 total trials, 50% of which represented one-flash/two-beep conditions used to explore the temporal dependence of the flash-beep illusion. Because of the length of time required to complete the task (e.g., 12-20 minutes, depending on the participant's pace), the task was divided into two blocks with a break in the middle. Participants were allowed to take a break as needed and could restart the task with a button press. Participants indicated their response (i.e., how many flashes they perceived) by pressing buttons labeled “1” and “2”. Prior to completing the task, participants completed six practice trials in which they counted flashes presented without auditory stimuli. They were subsequently reminded that their task was to count the flashes and they were explicitly instructed to ignore the beeps.

Data Analysis

The mean number of flashes perceived at each one-flash/two-beep SOA condition was calculated separately for each individual. Differences in the proportion of trials on which an illusory flash was reported (i.e., the participant indicated seeing two flashes when only one was presented) were examined between groups using independent samples t-tests at each SOA condition. Performance differences on the one-flash/one-beep control condition were examined in a similar manner to test for any response biases. In an effort to provide a unitary measure of the processing differences

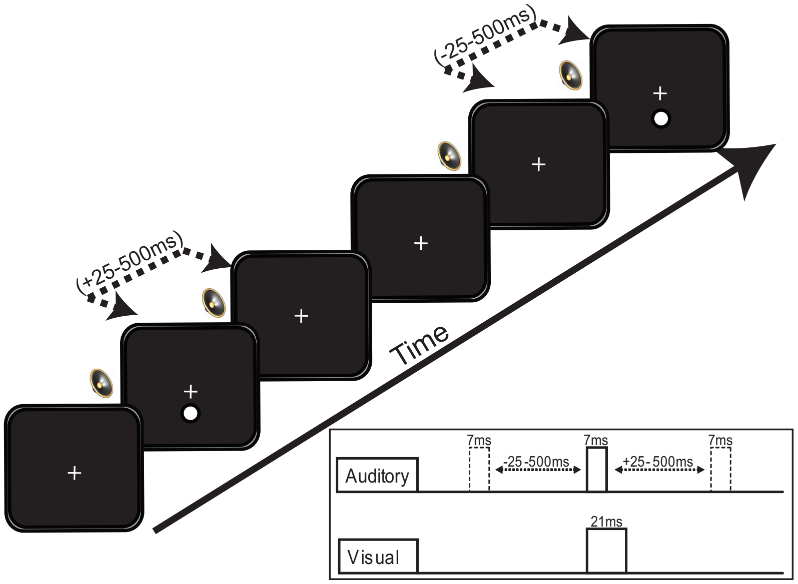


Figure 2.1. Task design. In illusory conditions, two beeps were presented with a single flash. One beep was always presented coincidently with the single flash. For positive SOA conditions, a second beep was presented with variable delay (25-500 ms) following the onset of the coincident flash-beep presentation. For negative SOA conditions, an initial beep was presented preceding the onset of the coincident flash-beep presentation by variable temporal increments (25-500 ms).

between the two groups, a temporal “window” was defined as the contiguous span of consecutive one-flash/two-beep SOAs at which the mean number of flashes reported was significantly greater than the mean number of flashes reported on the one-flash/one-beep condition. To examine the temporal window of this multisensory illusion in children with ASD and TD, paired-sample t-tests comparing the proportion of trials on which two flashes were reported for each one-flash/two-beep SOA condition to the one-flash/one-beep control condition were conducted separately for the ASD and TD groups. Corrections for multiple comparisons were not conducted because the method of analysis described above was planned *a priori*. Family-wise error was limited in the determination of the temporal window by requiring continuous significant differences from the one-flash/one-beep condition.

Results

The proportion of trials on which participants perceived two flashes was determined at each of the SOA conditions that manipulated the temporal structure of the single flash and two beeps. Higher proportions of reports of perceiving two flashes indicate a greater strength of illusion. Between-group comparisons in the proportion of trials on which two flashes were reported were conducted for each of the one-flash/two-beep SOA conditions as well as for the one-flash/one-beep condition, which served as a control condition against which to measure response bias. On the one-flash/one-beep condition, children in both groups did not always report a single flash, indicating that there was some degree of response bias. In both groups, the proportion of trials on which two flashes was reported was significantly different from zero (ASD group (M=0.15; SD=.20): t (20) = 3.468, p = .002; TD group (M=0.08; SD=.13): t (16) = 2.599, p

= .02). Most importantly, these values, and thus the assumed response bias, did not differ between groups (t (36) = 1.196, p = .24).

For the one-flash/two-beep condition, between-group comparisons of the probability of reporting the illusion (i.e., proportion of trials on which the illusory second flash was reported) were conducted at each SOA condition. Significant group differences were observed, with children with ASD more frequently reporting two flashes than children with TD at the following SOAs: -500ms, -300ms, -200ms, -25ms, +25ms, +200ms, +300ms, and +400ms (all p's < .05). Additionally, a difference approaching significance was seen at an SOA of -400ms, (p = .056). This result indicates that children with ASD

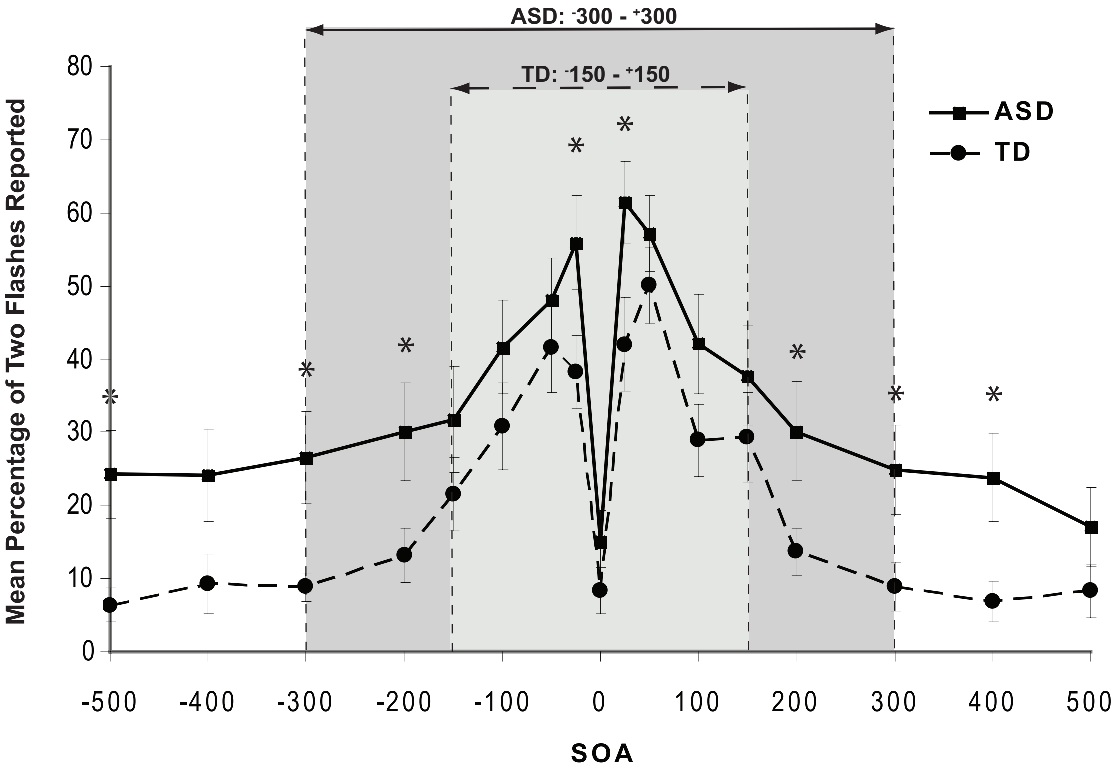


Figure 2.2. Group results. The strength of flash-beep illusion is greater in ASD than in TD across several SOA conditions (asterisks represent $p < 0.05$). Furthermore, the temporal window for multisensory integration is extended in ASD. Significant increases in the proportion of trials on which an illusory second flash was reported over the proportion reported on the one-flash/one-beep control condition (represented here as an SOA of 0 ms) extend from -150ms to +150ms in children with TD, but from -300ms to +300ms in children with ASD. This difference represents a two-fold increase in the temporal binding window for audiovisual stimuli in ASD.

show a greater propensity to report the flash-beep illusion when compared with children with TD (Figure 2.2).

An additional analysis was structured in order to define differences in the temporal window of multisensory integration between ASD and TD children. In children with TD, significant increases in the proportion of trials on which two flashes were reported (above the one-flash/one-beep baseline) were seen at the following one-flash/two-beep SOAs: -150ms, -100ms, -50ms, -25ms, +25ms, +50ms, +100ms, and +150ms (all p's < 0.005). In comparison, in children with ASD, significant increases in the proportion of trials on which two flashes were reported were seen at the following SOAs: -500ms, -300ms, -200ms, -150ms, -100ms, -50ms, -25ms, +25ms, +50ms, +100ms, +150ms, +200ms, and +300ms (all p's < 0.05). These findings suggest an approximate doubling in the size of the temporal binding window in children with ASD, in that the contiguous span of SOAs at which the illusion is observed is approximately 300 ms in TD (i.e., from –150ms to +150ms) and approximately 600 ms in ASD (i.e., from –300ms to +300ms) (Figure 2). Further validating the significance of these findings is the observation that the windows defined for each group show continuous significance at all SOAs within the window. Similarly, the between-group comparisons show continual significance at the SOAs outside of the TD temporal window but inside the ASD temporal window (i.e., -200, +200, -300, and +300 ms).

To further address the potential influences of response bias on the perceptual reports, additional analyses focused on the other control conditions beyond the one-flash/one-beep condition described above (i.e., two-flashes/zero-beeps, two-flashes/one-beep, two-flashes/two-beeps, one-flash/zero-beeps) in a subset of children (Figure 2.3).

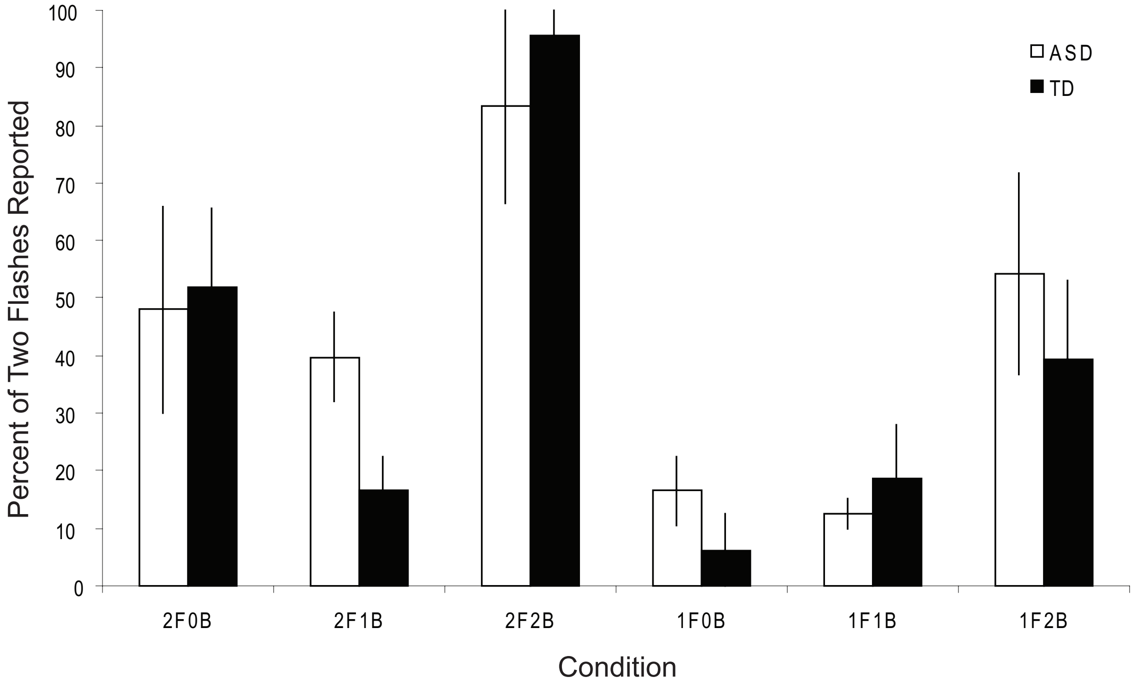


Figure 2.3. Percent of trials on which two flashes were reported for each control trial type for a subset of children with ASD and TD. Children with ASD did not differ significantly from children with TD in their report of two flashes for any trial type tested. This finding suggests that the observed increase in the report of two flashes across several illusory conditions in children with ASD is not attributable to an increased bias for reporting two flashes relative to children with TD.

Although none of these analyses revealed a significant difference between the two groups, in the two-flash/one-beep condition, children with ASD (40% of trials) were more likely to accurately report two flashes than were children with TD (17% of trials), a difference that approached significance (t (6) = 2.375, p = .06). On other control conditions, performance was nearly identical between the two groups. For example, on the two-flash/zero-beep condition, children with TD reported two flashes on 52% of trials, while children with ASD reported two flashes on 48% of trials (t (6) = -1.77, p = .87).

While the low accuracy for the two-flash/zero-beep condition across both children with ASD and TD suggests that visual temporal acuity may be low in children relative to adults, the lack of differences between groups suggests that differences in visual temporal acuity do not play a role in the highlighted perceptual differences. The results of the control conditions suggest that the extended temporal window of multisensory integration in ASD discussed above is mainly the result of alterations in sensory processing and is not purely driven by differences in cognitive bias.

Discussion

The results of the current study suggest that children with ASD have an extended temporal window within which they bind together multisensory stimuli, as evidenced by their heightened propensity to report the flash-beep illusion over an extended range of stimulus onset asynchronies (i.e., SOAs) between the component visual and auditory stimuli. Although our results are in accord with a previous study showing intact integration of low-level visual and auditory stimuli in individuals with ASD (i.e., in that integration of multisensory information does occur) (Van der Smagt et al., 2007), we have refined our understanding by showing for the first time alterations in the temporal constraints within which audiovisual stimuli are bound in children with ASD.

The finding of intact integrative processes is in contrast to prior studies that have reported a decreased ability for individuals with ASD to integrate information across multiple modalities [34,35]. However, these studies focused on audiovisual speech stimuli, which are rich in social and contextual information and typically also are associated with affective demands. The processing of these communication signals may itself be altered in ASD, making it difficult to parse apart alterations in basic sensory function. Consistent with this interpretation is work that has reported that children with ASD performed comparably to children with TD on multisensory tasks involving non-speech stimuli but disparately on multisensory tasks involving speech stimuli [36]. The current study confirms that individuals with ASD are able to integrate simple, non-linguistic audiovisual information. However, our results also highlight a striking difference in the integration of low-level multisensory stimuli, specifically in the temporal constraints within which auditory stimuli can influence visual perceptions in generating a compelling illusion.

There are several possible neurophysiological mechanisms for the enlarged temporal binding window seen in children with ASD, which fit within the conceptual framework of previously proposed neurally-based models. Brock et al. (2002) have posited that a core neurological cause of autism may be rooted in disruptions in temporal processing. According to this theory, perceptual binding is a result of strongly correlated activity among a network of interconnected brain regions, and alterations in these patterns of correlation in ASD result in concomitant reductions in binding. The current study suggests that rather than these networks being completely decoupled in ASD, the time constants between brain regions may instead be altered in such a way so as to continue to support binding, but over an atypically large set of temporal intervals. A second proposed neural mechanism for ASD is founded on a decreased signal-to-noise ratio in neural encoding [37]. In this view, a briefly presented unisensory (e.g., auditory) stimulus typically results in a discrete neural response time-locked to the presentation of the stimulus. In contrast, the same stimulus presented to an individual with autism may result in a response whose neural signature is less clearly time-locked to the stimulus event. Extending this theory into the multisensory domain, it can be envisioned that increased temporal variability in the unisensory responses could necessitate a compensatory enlargement in the time interval over which multisensory stimuli can influence one another. Future studies will focus on devising methods for distinguishing between these and other potential neural mechanisms for the extended temporal binding window in ASD.

Autism spectrum disorders are extremely heterogeneous, and our task and study design limited us to evaluating children with relatively intact intellectual abilities (i.e., IQ score above 70). Thus, our findings may not generalize to lower functioning individuals with ASD and a concomitant intellectual disability. Although the task employs low-level stimuli and simple behavioral responses (hence offering promise for extending it to more impaired participants), continued adaptation and streamlining of this experimental design for use with a broader sample of children with ASD will be the focus of future research.

The extended temporal window for multisensory integration described in the current study is likely to have far-reaching consequences for children with ASD. At a very basic level, an alteration in the characteristics of the incoming sensory stream will have profound implications for all brain regions and processes "upstream" of the impacted (multi)sensory domain, since the integrity of the sensory signaling will have been altered or compromised. Differences in the processing and integration of sensory stimuli for individuals with ASD could underlie the atypical responses to sensory stimuli so frequently reported in the autism clinical literature. For instance, if integration is occurring over an extended temporal window, it could cause difficulty with responding to input from a specific modality if there is concurrent input from other modalities. Difficulties identifying the source modality of information, as have been reported in ASD, could also be explained by altered multisensory temporal function. In addition, numerous activities of daily life are dependent on the ability of the nervous system to precisely match stimuli from multiple modalities. For example, the dynamic auditory and visual stimuli involved in any social interchange (e.g., subtle changes in facial expression, tone of voice, body language) must all be integrated sequentially and seamlessly with precise temporal accuracy for the interaction to be successful. Misalignment or inappropriate integration of this basic sensory information would likely negatively impact this interaction by changing the information content and, with such altered experiences repeated over time, would be expected to impair complex social abilities such as empathy and reciprocity as well as endow social interaction with confusing and irrelevant associations. These results could also be relevant to others' findings of reduced integration in more complex (e.g., speech) stimuli, though future research is necessary to elucidate the role an expanded temporal window for binding low-level sensory stimuli plays in impaired integration of higher-order cross-modal input.

In conclusion, this study represents an important first step in our understanding of the temporal processing of multisensory stimuli in ASD. Further research is needed to fully characterize the extent of these multisensory processing changes in ASD, to elucidate their neural substrates, and to relate these findings to the core deficits in ASD. It is anticipated that this line of investigation will ultimately contribute to a broader understanding of this disorder and lead to improved diagnostic instruments and more targeted interventions.

Acknowledgments

This work was supported by a Marino Autism Research Institute Discovery Grant (PI: MTW); National Institute of Child Health and Development T32 HD07226 predoctoral fellowship for JHF; Meharry-Vanderbilt Alliance Training Grant for LDK; Vanderbilt Kennedy Center

References

1. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

2. Williams, D. *Somebody Somewhere*, (Doubleday, London, 1994).

3. Kientz, M., Dunn, W. A comparison of the performance of children with and without autism on the sensory profile. *Am J Occup Ther.* **51**, 530-537 (1997).

4. O'Neill, M., Jones, RSP Sensory-perceptual abnormalities in autism: a case for more research? . *J Autism Dev Disord* **27**, 283-293 (1997).

5. Sigman, M., Capps, L Children with autism: A developmental perspective. 369-398 (Harvard University Press, Cambridge, MA, 1997).

6. Dawson, G., Watling, R. Interventions to facilitate auditory, visual, and motor integration in autism: a review of the evidence. *J Autism Dev Disord* **30**, 415-421 (2000).

7. Grandin, T. My Experiences with visual thinking, sensory problems, and communication difficulites. (2000).

8. Talay-Ongan, A., Wood, K Unusual sensory sensitivities in autism: a possible crossroads. *International Journal of Disabilities, Development and Education* **47**, 201-212 (2000).

9. Watling, R., Deitz, J, White, O. Comparison of Sensory Profile scores of young children with and without autism spectrum disorders. . *Am J Occup Ther.* **55**, 416-423 (2001).

10. Wing, L. & Potter, D. The epidemiology of autistic spectrum disorders: is the prevalence rising? *Ment Retard Dev Disabil Res Rev* **8**, 151-61 (2002).

11. Rogers, S., Hepburn, S, Wehner, E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *J Autism Dev Disord.* **33**, 631-642 (2003).

12. Baranek, G., David, F., Poe, M., Stone, W. & Watson, L. Sensory Experiences Questionnaire: discriminating sensory features in young children with autism,

developmental delays, and typical development. *Journal of Child Psychology and Psychiatry* **47**, 591-601 (2006).

13. Leekam, S.R., Nieto, C., Libby, S.J., Wing, L. & Gould, J. Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord* **37**, 894-910 (2007).

14. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217-250 (1943).

15. Mottron, L., Dawson, M, Soulieres, I, Hubert, B, Burack, J Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord* **36**, 27-43 (2006).

16. O'Riodan, M., Passetti, F. Discrimination in Autism Within Different Sensory Modalities. *J Autism Dev Disord* **36**, 665-675 (2006).

17. Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. & Essick, G. Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. *Journal of Autism and Developmental Disorders* **38**, 127-137 (2008).

18. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

19. Minshew, N., Hobson, JA. Sensory Sensitivities and Performance on Sensory Perceptual Tasks in High-functioning Individuals with Autism. . *J Autism Dev Disord* (2008).

20. Iarocci, G., McDonald, J Sensory integration and the perceptual experience of persons with autism. *J Autism Dev Disord* **36**, 77-90 (2006).

21. Brock, J., Brown, CC, Boucher, J, Rippon, G. The temporal binding deficit hypothesis of autism. *Development and Psychopathology* **14**, 209-224 (2002).

22. Tecchio, F., Benassi, F, Zappasodi, F, Gialloreti, LE, Palermo, M, Seri, S, Rossini, PM Auditory sensory processing in autism: a magnetoencephalographic study. . *Biol Psychiatry* **54**, 647-654 (2003).

23. Szelag, E., Kowalska, J, Galkowski, T, Poppel, E Temporal processing deficits in high-functioning children with autism. *Br J Psychol* **95**, 269-282 (2004).

24. Gomot, M., Bernard, FA, Davis, MH, Belmonte, MK, Ashwin, C, Bullmore, ET, Baron-Cohen, S. Change detection in children with autism: an auditory event-related fMRI study. *Neuroimage* **29**, 475-484 (2006).

25. Shams, L., Kamitan,i Y, Shimojo, S Illusions: What you see is what you hear. *Nature* **408**, 788 (2000).

26. Van der Smagt, M., Van Engeland, H, Kemner, C. Brief report: can you see what is not there? Low-level auditory-visual integration in autism spectrum disorder. . *J Autism Dev Disord* **37**, 2014-2019 (2007).

27. Shams, L., Kamitani, Y, Shimojo, S. Visual illusion induced by sound. . *Brain Res Cogn Brain Res.* **14**, 147-152 (2002).

28. Wechsler, D. *WASI: Wechsler Abbreviated Scale of Intelligence.* , (Harcourt Assessment, Inc., San Antonio, TX, 1999).

29. Woodcock, R., McGrew, KS, Mather, N *Woodcock-Johnson Tests of Achievement – Third Edition.*, (Riverside Publishing, Rolling Meadows, IL, 2001).

30. Hairston, W., Burdette, JH, Flowers, DL, Wood, FB, Wallace, MT. Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Exp Brain Res.* **166**, 474-480 (2005).

31. Lord C, R.S., Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M Autism Diagnostic Observation Schedule - Generic: A standard measure of social and communication deficits associated with the spectrum of autism. . *J Autism Dev Disord* **30**, 205-223 (2000).

32. Lord C, R.M., Le Couteur A Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* **24**(1994).

33. Rutter M, B.A., Lord C *SCQ: Social Communication Questionnaire.* , (Western Psychological Services, Los Angeles, CA, 2003).

34. Williams, J., Massaro, DW, Peel, NJ, Bosseler, A, Suddendorf, T. Visual-auditory integration during speech imitation in autism. . *Research in Developmental Disabilities* **25**, 559-575 (2004).

35. Smith, E., Bennetto,L Audiovisual speech integration and lipreading in autism. . *Journal of Child Psychology and Psychiatry* **48**, 813-821 (2007).

36. Mongillo, E., Irwin, JR, Whalen, DH, Klaiman, C, Carter, AS, Schultz, RT. Audiovisual Processing in Children with and without Autism Spectrum Disorders. . *J Autism Dev Disord* (2008).

37. Rubenstein, J., Merzenich, MM Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav* **2**, 255-267 (2003).

CHAPTER III

ALTERED AUDITORY AND MULTISENSORY TEMPORAL PROCESSING IN AUTISM SPECTRUM DISORDERS: AUDIOVISUAL TEMPORAL PROCESSING IN ASD [†]

Abstract

Autism spectrum disorders (ASD) are characterized by deficits in social reciprocity and communication, as well as repetitive behaviors and restricted interests. Unusual responses to sensory input and disruptions in the processing of both unisensory and multisensory stimuli have also frequently been reported. However, the specific aspects of sensory processing that are disrupted in ASD have yet to be fully elucidated. Recent published work has shown that children with ASD can integrate low-level audiovisual stimuli, but do so over an extended range of time when compared with typically-developing (TD) children. However, the possible contributions of altered unisensory temporal processes to the demonstrated changes in multisensory function are yet unknown. In the current study, unisensory temporal acuity was measured by determining individual thresholds on visual and auditory temporal order judgment (TOJ) tasks, and multisensory temporal function was assessed through a cross-modal version of the TOJ task. Whereas no differences in thresholds for the visual TOJ task were seen between children with ASD and TD, thresholds were higher in ASD on the auditory TOJ task, providing preliminary evidence for impairment in auditory temporal processing. On the multisensory TOJ task, children with ASD showed performance improvements over a wider range of temporal intervals than TD children, reinforcing prior work showing an extended temporal window of multisensory integration in ASD. These findings contribute

---

[†] Kwakye LD, Foss-Feig JH, Cascio CJ, Stone WL and Wallace MT (2011) Altered auditory and multisensory temporal processing in autism spectrum disorders. Front. Integr. Neurosci. 4:129. doi: 10.3389/fnint.2010.00129

to a better understanding of basic sensory processing differences, which may be critical for understanding more complex social and cognitive deficits in ASD, and ultimately may contribute to more effective diagnostic and interventional strategies.

Introduction

Autism spectrum disorders (ASD) are characterized by deficits in social reciprocity, communication, and behavioral flexibility that emerge in the first few years of life [1]. Sensory disturbances were reported in Kanner's original description of autism [2], and have been reported consistently in the clinical literature [3-6]. Though not currently part of the diagnostic criteria for ASD, the presence of unusual sensory behaviors has been proposed for inclusion in updated diagnostic criteria for the DSM-V, highlighting emerging consensus that sensory abnormalities are central features of ASD. Reports of abnormal sensory function that span the visual, auditory, gustatory, and tactile domains reinforce the "multisensory" nature of sensory processing alterations in ASD (for review, see [7], and emerging evidence suggests that abnormalities also extend to the selective integration of information across the different sensory modalities (i.e., multisensory integration – see [8]).

Although evidence for deficits in sensory (and multisensory) processing is abundant in the ASD literature, there are also a number of reports detailing enhanced perceptual capabilities in response to specific sensory stimuli. For example, discrimination of discrete details within complex visual spatial displays has widely been found to be a relative strength in ASD [9-12] and at least one study has reported enhanced visual acuity in autism [13]. Similarly, in the auditory domain, Bonnel and colleagues have shown that individuals with autism have superior pitch discrimination and categorization abilities in comparison to controls [14]. In an effort to reconcile these findings showing both impaired and enhanced sensory function in ASD, it has been suggested that perceptual abilities may depend on the nature and complexity of the sensory stimuli, with impairments characterizing responses to more complex stimuli and enhancements seen more often with simple stimuli [15,16]. For instance, in the same study, adolescents and adults with autism were found to show superior orientation discrimination of luminance-defined gratings but inferior discrimination of texture-defined gratings that are believed to be processed further along the visual pathway [17]. Given that multisensory function depends on stimulus integration, it may be an inherently complex process even when the component stimuli are exceedingly low level. Such a view is supported by the tendency for multisensory processing to occur both within and beyond primary sensory cortices [18]. Hence, a better understanding of multisensory processing in ASD, as well as the processing of component unisensory stimuli used to test multisensory function, may provide important clues into the neural bases of sensory differences in ASD.

In addition to these broad sensory findings, there has been some indication that the temporal aspects of sensory information processing also may be impacted in ASD. Szelag and colleagues found that children with autism had difficulty reproducing the lengths of both auditory and visual unisensory stimuli of standardized durations [19]. Other studies have found atypical neural responses to changes in the pitch of repeated, sequential auditory stimuli in children and adults with ASD [20,21]. Extending to multisensory function, children with ASD showed impairments in the detection of violations of temporal synchrony of audiovisual linguistic stimuli in comparison to typically developing children and to those with non-autistic developmental delays [22]. Together, these studies suggest alterations in the processing of basic timing information contained within both simple and complex (i.e., linguistic) sensory stimuli, both within and across sensory systems. However, although these studies establish the presence of temporal processing abnormalities in ASD, the extent of these deficits is unknown. Further characterization of these differences using low-level stimuli devoid of social or linguistic context is necessary to clarify the nature and scope of alterations in temporal processing specific to basic sensory functioning.

Our results from a previous study revealed an expanded temporal window for multisensory integration in children with ASD [23]. This result not only replicated a previous finding that individuals with ASD are capable of integrating basic auditory and visual information [24], but also extended this work to show that significant changes in basic multisensory function appear to lie in the temporal realm. However, given the nature of the task employed in our previous study (a common multisensory illusion in which there is no direct measure of unisensory temporal acuity), it was not possible to determine the potential contribution of changes in unisensory temporal function to the demonstrated change in multisensory performance.

The goal of the current study was to expand upon this previous finding of an extended temporal binding window for simple audiovisual input in autism spectrum disorders. To this end, we examined both unisensory and multisensory temporal processing abilities in a single sample of children and adolescents with ASD. First, temporal acuity in the auditory and visual systems was examined using temporal order judgment (TOJ) tasks to establish baseline auditory and visual temporal resolution abilities. Then, task-irrelevant auditory signals were added to the visual TOJ task in order to assess multisensory binding processes and their temporal constraints. Previous work has shown that the addition of task-irrelevant auditory stimuli can improve performance on the visual TOJ task, but only if presented within a particular window of time that reflects the duration of the multisensory temporal binding process [25-27]. Due to the inherently multisensory nature of language and social stimuli, an enlargement in the temporal window of multisensory binding is likely to have far-reaching consequences for children with ASD. Clarification of the nature and extent of temporal processing differences in ASD represents an important step in understanding the level at which sensory processing is altered in this disorder, which could in turn be important for developing targeted interventions.

Methods

Participants

Thirty-five children with ASD and 27 with typical development (TD) comprise the study sample, which overlaps in part with the sample reported in [23]. Eligibility criteria for children in both groups were as follows: a) age 8-17 years; b) normal or corrected-to-normal hearing and vision; c) Full Scale IQ (FSIQ) score above 70; and d) no evidence or past diagnosis of a specific reading disorder. Adequate cognitive functioning for inclusion in the study (i.e., FSIQ score above 70) was confirmed using the Wechsler Abbreviated Scale of Intelligence (WASI; [28]) unless a child had completed cognitive testing in the past year and the parents could provide the scores. Reading abilities were screened using the Letter-Word Identification and Word Attack subtests of the Woodcock-Johnson Tests of Achievement – Third Edition (WJA-III: [29]), since differences in multisensory processing have been demonstrated in individuals with reading disorders. All children in both groups were required to have reading standard scores above 70 on both WJA-III subtests. Additional eligibility criteria for the ASD group required that children: a) have a confirmed diagnosis of Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified; and b) have no history of seizure disorders or identified genetic disorders (e.g., Fragile X, tuberous sclerosis). Children with ASD were not excluded based on use of psychotropic medication.

Children's prior ASD diagnoses were confirmed in the present study using gold-standard procedures: the Autism Diagnostic Observation Schedule (ADOS; [30]) was administered by a research-reliable examiner, parent(s) completed the Autism Diagnostic Interview – Revised (ADI-R; [31]) with a research-reliable interviewer, and DSM-IV-based clinical diagnoses were made by a licensed clinical psychologist on the basis of this information. All children included in the ASD group met criteria for autism or autism spectrum on both the ADOS and ADI-R at a session scheduled prior to psychophysical testing. Additional eligibility criteria for children with TD were as follows: a) no history of or current psychiatric, neurological, or learning disorders (e.g., ADHD, depression, epilepsy, dyslexia) or symptoms of ASD; and b) no first-degree relatives with ASD. Parent report of ASD symptoms was obtained using the Lifetime version of the Social Communication Questionnaire (SCQ; [32]); all children with TD had SCQ scores below the at-risk cutoff for ASD. No differences in age, gender, or Full Scale IQ score were found between groups (Table 3.1). As expected, a significant group difference was found for parent report of ASD symptoms on the SCQ, t (56) = 11.75, p < .001.

Table 3.1: Participant Demographics.

Measure	ASD	TD
Gender	30 M; 5F	22 M; 5 F
Age	12.21 ± 2.7	11.73 ± 2.4
Full Scale IQ	102.91 ± 18.7	109.54 ± 10.8
Social Communication Questionnaire **	20.11 ± 6.8	3.00 ± 2.7

Parents of all participants gave informed consent and all children in both groups gave assent prior to participation in any component of this study. All children received compensation for their participation at each visit. All procedures were approved by the Vanderbilt University Institutional Review Board.

General Procedure

Participants sat in a light- and sound-attenuated room and wore headphones through which auditory stimuli were presented. Visual stimuli were presented as open white circles against a black background on a high-refresh rate PC monitor (NEC Multisync FE992, 22 inch screen; 150 Hz refresh rate; 640x480 pixel resolution). Auditory stimuli were presented via noise-canceling supra-aural headphones (Philips SBC HN110) to both ears (90 dB peak SPL). Stimulus presentation was controlled using E-Prime (Psychology Software Tools Inc., Pittsburgh, PA, USA). Responses (i.e., accuracy and response time) were recorded via a Serial Response box (Psychology Software Tools Inc., Pittsburgh, PA, USA).

Participants were monitored continuously via closed-circuit video cameras to ensure that they were engaged in the tasks. On the rare occasions that a participant was not on-task, a variety of strategies were implemented to increase engagement (e.g., reminders to stay on task, additional breaks, parent in the testing room, etc). Participants were allowed to take breaks as necessary to increase compliance and maintain effort, motivation, and on-task behavior. All participants completed each of the tasks described below within a single session; while some participants had difficulty completing one or more tasks or produced data that could not always be reliably interpreted (see below for further details, broken down by task), data from the maximum number of participants possible were included for analyses of individual tasks.

Tasks

Visual TOJ Task

The visual TOJ task was used to test temporal acuity of the visual system and was the first task completed. In this task, participants were asked to determine which of two circles (above and below a fixation cross) presented in close temporal proximity (i.e., stimulus onset asynchronies [SOAs] ranging between 7 and 252 ms) appeared on the computer screen first. Following instructions, a white fixation cross appeared on a black screen. After a delay of 1000 ms, the first of two circles appeared, either 7 cm above or below the fixation cross, and remained on the screen. Following a variable SOA, a second circle appeared at the location opposite the first circle (e.g., above the fixation if the first circle appeared below). (Figure 3.1) Participants indicated via button presses on the response box their judgment as to which of the two circles appeared first (i.e., "top first" or "bottom first"). Following a response, both circles disappeared simultaneously and a new trial began. Participants completed 10 practice trials (visual SOA 91-119 ms in 7 ms increments presented randomly), which included feedback regarding response accuracy, before completing the full task. The practice session was repeated until participants could correctly identify which circle occurred first on a majority of trials.

After practicing the task, a staircase procedure was used to determine the threshold SOA necessary for each participant to perform the visual TOJ task between 70 and 75% accuracy. An adaptive staircase procedure, in which three independent staircases were run concurrently, was used. One staircase started at an SOA of 84 ms, the second started at an SOA of 7 ms, and the third started at an SOA of 56 ms. The initial step size (i.e., amount by which the SOA was adjusted) was 28 ms, which was decreased to 14 ms after five reversals in response accuracy and decreased again to 7 ms after an additional four reversals. The SOA increased one step (i.e., became longer) after each incorrect response, and decreased one step (i.e., became shorter) after two consecutive correct responses. Each staircase terminated after sixteen reversals in response accuracy and an average was calculated from the last five reversals to produce the threshold SOA. The mean threshold value was calculated from the three staircase outputs and then rounded to the nearest value compatible with the vertical scan rate of the monitor (i.e., multiple of 7 ms). Following the staircase procedure, participants performed a shorter confirmation procedure with SOA values set relative to their individual threshold. In this process three SOAs were used relative to the calculated threshold: 0 ms (i.e., threshold), 7 ms above, 7 ms below. Each of these SOAs was repeated 20 times in a random order; at each SOA, the first visual stimulus appeared above fixation on half of the trials. If results of the confirmation procedure did not indicate that 70-75% accuracy rates had been produced for any of the three SOAs (i.e., performance was not near threshold), the confirmation procedure was repeated with higher or lower SOA values, depending on whether accuracy rates were too low or too high in the initial confirmation procedure.

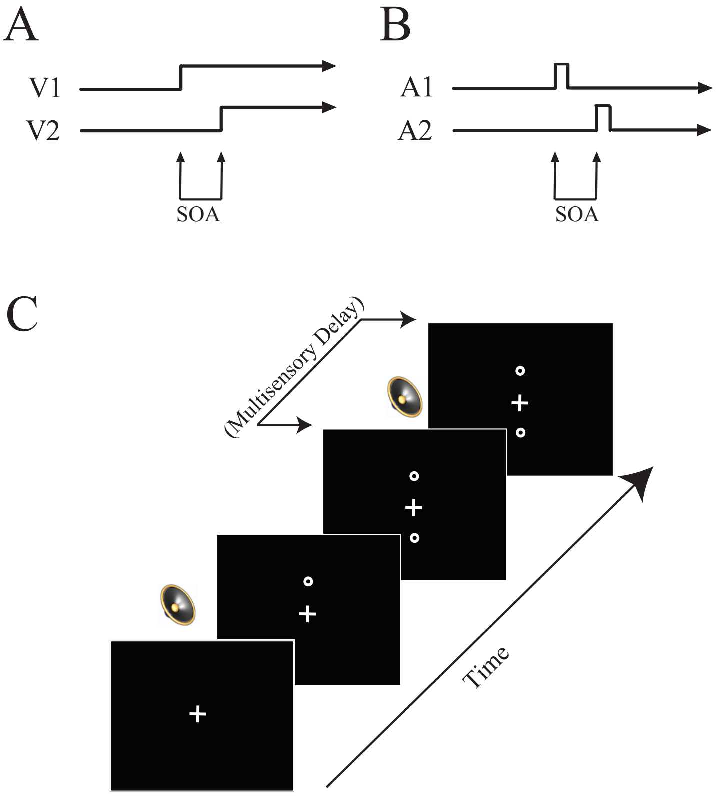


Figure 3.1: Task design. A. Visual TOJ task. B. Auditory TOJ task. C. Multisensory TOJ task. In multisensory conditions, two circles are presented sequentially above and below the central fixation point. One beep is always presented simultaneously with the first circle, whereas the second beep is presented with a varied delay (0-500 ms) from the onset of the second circle. See text for additional detail.

Multisensory TOJ Task

This task always followed the visual TOJ task. Here, task-irrelevant auditory stimuli were added to the visual TOJ task. Previous work has shown that such auditory stimuli are capable of improving performance on the visual TOJ task (i.e., enabling individuals to discriminate between the two visual stimuli when they are presented at shorter intervals), but only if the auditory cues are presented within a defined temporal structure relative to the visual stimuli [25-27]. Although the mechanisms responsible for these multisensory-mediated performance enhancements remain unknown, some have theorized that they are due to a temporal shift in the perception of the visual stimulus toward the auditory stimulus (i.e., temporal ventriloquism (Spence and Squire, 2003)). In contrast, others have theorized that the auditory stimulus speeds the processing of the visual stimulus, thus allowing the participant to discriminate smaller time intervals between the visual stimuli (Hairston et al., 2006; Keetels and Vroomen, 2010).

For this task, visual stimuli were presented as described above for the visual TOJ task except that, on each trial, the SOA between the two visual stimuli (visual SOA) was fixed according to each individual's threshold value. Two identical sounds were also presented on 89% of trials through supra-aural headphones, with the first sound always occurring synchronously with the first visual stimulus onset. The second sound was delayed by 0-500 ms relative to the onset of the second visual stimulus (multisensory delay increments were as follows: 0, 50, 100, 150, 200, 300, 400, 500 ms) (Figure 3.1). A randomly interleaved no-sound (i.e., visual only) condition provided baseline performance and represented the remaining 11% of trials. This baseline was also used to ensure reliability of the behavioral threshold by identifying participants who's baseline accuracies were significantly different from the established threshold and excluding these data form further analysis (ASD: n = 14; TD: n = 11).

Each condition was presented 16 times in random order; at each multisensory delay as well as in the visual only condition, the first visual stimulus appeared above fixation on half of the trials. Participants were told from the outset that while they often would be hearing sounds through the headphones, the task was the same as in the visual TOJ (i.e., determine whether the top or bottom circle appears first) and that they should ignore the sounds. Given that sounds were presented binaurally through headphones with no interaural timing or amplitude level differences, they did not provide any task-relevant spatial information that would have provided clues as to whether the "top" or "bottom" circle occurred first. However, though not relevant for making the spatial discriminations required in this task, the auditory cues did provide temporal information.

Auditory TOJ Task

The auditory TOJ task was designed to test auditory temporal acuity and was completed last. In this task, participants heard two identical clicks, one presented to each ear in close temporal proximity, and were asked to make a judgment as to which ear the first click was presented. Following instructions, a white fixation cross appeared on a black screen for 1000 ms. Immediately following the 1000 ms fixation, the first of two auditory stimuli was presented through headphones to either the right or left ear. Following a variable stimulus onset asynchrony (SOA), a second identical auditory stimulus was presented through the headphones to the opposite ear. The fixation cross then turned red, signaling participants to respond. (Figure 3.1) Participants indicated in which ear they had heard the first auditory stimulus by pressing a button on the response box (i.e., "left first" or "right first"). Following a response, a new trial began. As in the visual TOJ task, prior to completing the full task, participants completed a 10-trial practice including feedback regarding response accuracy.

After the practice session, participants completed an adaptive staircase procedure similar to that used in the visual TOJ task with three independent, interleaved staircases (each starting at an SOA of 100 ms) to determine the SOA necessary to discriminate the order of clicks at approximately 75% accuracy. The SOA between auditory stimuli changed from a step size of 10 ms for the first five reversals to a step size of 5 ms for the next four reversals, then to 1 ms steps until sixteen reversals were reached. An average threshold SOA was calculated from the final ten reversals of each staircase, then entered into a confirmation procedure as in the visual TOJ task. In the confirmation procedure, three SOAs were used relative to this threshold: 0 ms (i.e., threshold), 10 ms above, 10 ms below. If results of the confirmation procedure did not indicate that 70-75% accuracy rates had been attained for any of the three SOAs, the confirmation procedure was repeated with higher or lower SOA values.

Data Analysis

Response accuracy and timing data were recorded for each trial within each task. For unisensory tasks, participant data were included if: a) the participant comprehended instructions and was on-task; and, b) a threshold value at which the participant performed the task at 75% accuracy could reliably be determined. For unisensory TOJ tasks, threshold values for each participant were obtained from the staircase confirmation procedures described above.

For the multisensory task, participant data were included if: a) the participant comprehended instructions and was on-task; b) the participant performed the visual-only control trials (see below) at between 60-89% accuracy; and c) the participant showed at least some multisensory gains with the addition of task-irrelevant auditory stimuli. For the multisensory TOJ task, accuracy gains at each multisensory delay were defined by subtracting the accuracy rate for the visual-only baseline trials from the accuracy rate at each of the multisensory delay conditions. Similarly, improvements in response time were determined for each multisensory delay by subtracting the average response time for visual-only trials from the average response time for each of the different delays conditions.

Group Differences

Data from each experiment were first analyzed using independent samples t-tests to examine any between-group differences on the dependent variables of interest. Specifically, for the auditory and visual TOJ tasks, t-tests were used to explore potential group differences in threshold SOA values. For the multisensory task, in order to explore potential groups differences in improvements in multisensory temporal processing, separate ANOVAs for accuracy and response time gains were conducted with SOA as the within-subjects variable and group as the between-subjects variable in each. Independent-sample t-tests were also conducted with the accuracy and response time gain values at each delay to determine whether the magnitude of multisensory integration-related performance gains differed between groups at any of the delay conditions.

Differences in the Temporal Window of Multisensory Integration

The temporal binding window for integration was defined as the span of consecutive multisensory delay conditions within which there were significant gains in accuracy or (analyzed separately) significant improvements in response time at all included delay conditions. To determine the delay conditions at which significant accuracy and response time improvements were observed within each group, one-sample t-tests were conducted for each multisensory delay condition, comparing percent accuracy gain or decrease (improvement) in response time to an alternative value of 0, representing no gain in accuracy or response time relative to the visual-only baseline condition. These analyses were run separately for the ASD and TD groups in order to examine group-specific temporal binding windows. P-values were not corrected for multiple comparisons because the t-tests were planned a-priori. Family wise error was limited by requiring continuous significance across the entire temporal window of integration.

Results

Performance on the Unisensory TOJ Tasks

To determine whether visual and auditory temporal processing differ in children with ASD as compared to children with TD, we determined the threshold SOA values at which participants could report which of two stimuli occurred first at approximately 75% accuracy. On the visual TOJ task, data from one child with ASD were excluded because it was impossible to determine a threshold value from the confirmation procedure; remaining groups (ASD: n=34; TD: n=27) did not differ on gender, age, or IQ score (*ps* > 0.19). Performance on the visual TOJ task did not differ significantly between groups. On average, children with ASD required 52.7 ms to determine which circle onset first, whereas children with TD required 60.7 ms, a difference that did not reach statistical significance, t (58) = -1.01, p = 0.32, (Figure 3.2). For the auditory TOJ task, 15 children with ASD were excluded from analyses due to non-compliance, inattention, or inability to comprehend the task (n = 4), or inability to verify the auditory threshold from the confirmation procedure (i.e. accuracy lower than 75% (n = 11)). Children with ASD who were excluded from analyses for this task did not differ from those were included on age, gender, or Full Scale IQ (*ps* > 0.12). Five children with TD completed an alternate version of the auditory TOJ task, thus their data are not included here, though they are included in visual and multisensory TOJ analyses. Remaining groups (ASD: n=20; TD: n=22) did not differ on gender, age, or IQ score (*ps* > 0.18). In contrast to results for the visual TOJ task, performance on the auditory TOJ task did differ significantly between groups. Children with ASD required 48% more time between auditory stimuli to reliably determine which click occurred first. Thus, whereas children with ASD required 107.8 ms to perform at threshold, children with TD required only 73.0 ms, t (40) = 3.98, p = .0002, (Figure 2).

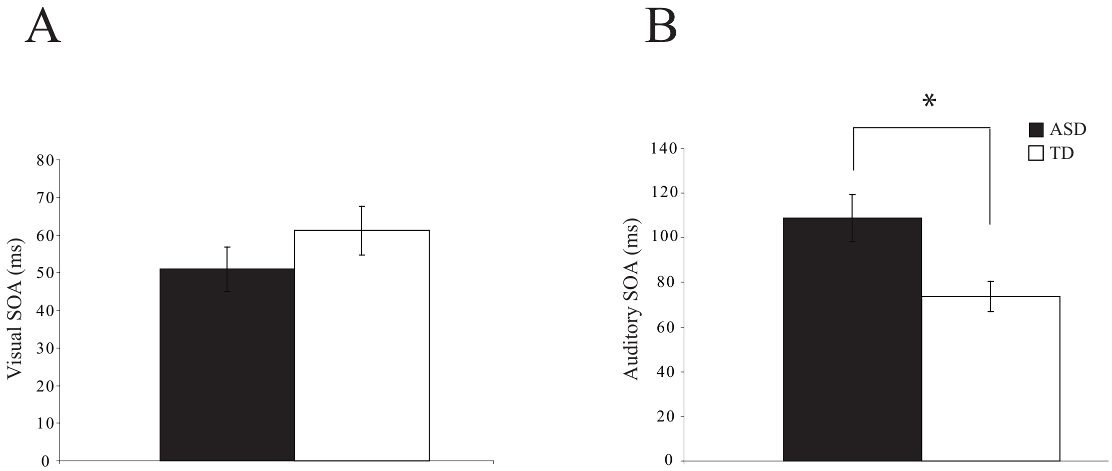


Figure 3.2: Threshold values for visual and auditory temporal order judgment tasks. Children with autism spectrum disorders (ASD) show similar thresholds to typically developing children for the visual TOJ task (A). However, children with ASD show significantly larger thresholds for the auditory TOJ task (B). (* p< .05) Note that each of these threshold values was confirmed via a validation procedure (see text for additional detail). Error bars represent standard error of the mean (SEM).

Performance on the Multisensory TOJ Task

In addition to assessing visual temporal acuity, the visual TOJ staircase procedure also allowed us to specify the visual SOA within the multisensory TOJ task for each participant such that performance was approximately equivalent (75%) across all individuals. In this way we could then determine the effect of task-irrelevant auditory stimuli on performance during this visual task, as well as assess the temporal aspects of the performance enhancements that represent the hallmark of multisensory integration in this task. Twenty-five participants (ASD: n = 14; TD: n = 11) who completed experimental procedures were excluded from the multisensory analysis because their accuracies on visual-only trials within the multisensory task were well outside of the individually established threshold criterion (i.e., < 60% (23 participants) or > 89% (two participants)). The latter two participants were excluded because their high accuracy presented a ceiling issue; there was no room for improvement in these participants. The remaining 23 participants likely did not meet their initial thresholds because of fatigue from working at threshold for approximately 30-45 minutes. Because this study was primarily interested in measuring differences in temporal multisensory processing, seven additional participants (ASD: n = 5; TD: n = 2) were excluded because they did not show improvements in accuracy with the addition of auditory stimuli. Interestingly, these seven participants showed strong performance decrements with the addition of the auditory stimuli. Unfortunately, there were too few participants who showed these performance decrements to analyze whether they comprise a unique subsample of children. Importantly, there were no significant differences in exclusions from the multisensory task based on group, χ^2 (3, N = 62) = 3.53, p = .32. Further, remaining groups (ASD: n = 16; TD: n = 14) did not differ on gender, age, or IQ score (*ps* > 0.59).

Due to the large number of participants excluded from analyses for the multisensory task, we first used between-groups, independent-sample t-tests to compare the unisensory thresholds for the remaining ASD and TD subsets in order to confirm that the differences in unisensory temporal acuity (i.e., equivalent visual TOJ thresholds, but higher auditory TOJ thresholds in ASD relative to TD) observed for the larger samples analyzed in the unisensory tasks held for the subsample who successfully completed the multisensory task. As for the larger samples, we found that auditory thresholds remained significantly higher in children with ASD (t(26)=2.11, p=0.02) whereas visual thresholds did not differ between groups (t(26)=1.24, p=0.23). This finding suggests that, despite the large number of participants excluded across both groups, the remaining subset described in the analyses below is representative of the full sample in displaying similar patterns of unisensory temporal functioning.

To test for multisensory integration-related performance gains related to the addition of task-irrelevant auditory stimuli to the visual TOJ task, we conducted between-group comparisons for both the accuracy and the response times for trials in which there was no delay between the onsets of the second visual and auditory stimuli (i.e., multisensory delay = 0) and trials in which only visual stimuli were presented (i.e., visual-only trials) (Figure 3.3). Accuracy and response times for visual-only trials did not differ significantly between children with ASD and children with TD, (accuracy: t (28) = .60, p = .55; response time: t (28) = .22, p = .83), confirming that both groups performed equivalently on the baseline visual task in the context of the multisensory TOJ task. However, one-sample t-tests for the 0 ms multisensory delay condition revealed that children with ASD significantly improved with the addition of the simultaneous auditory stimuli in both performance accuracy, t (15) = 2.47, p = .02 and response time, t (15) =

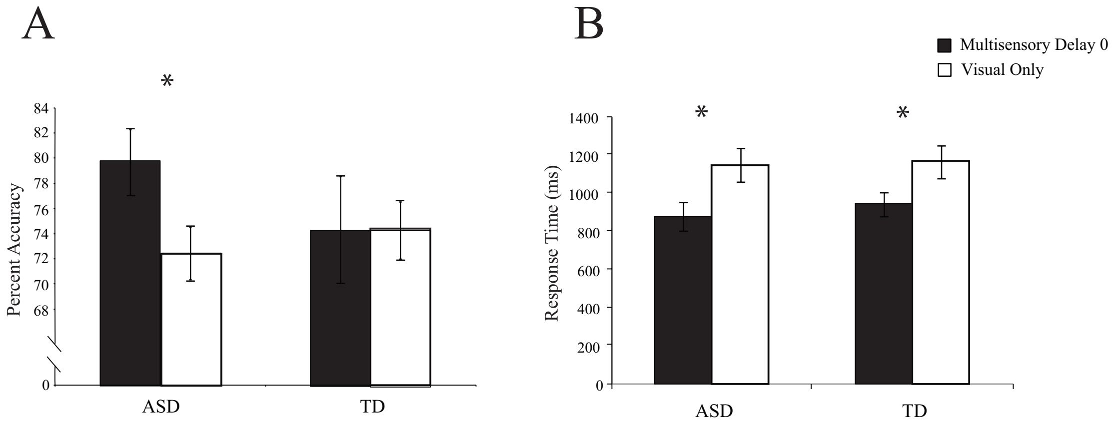


Figure 3.3: Performance accuracy (A) and response time (B) for simultaneous multisensory trials (i.e., multisensory delay = 0) compared to visual only trials. Error bars represent standard error of the mean (SEM).

5.48, p < .001, whereas children with TD improved significantly in response time, t (13) = 3.07, p = .005, but not in performance accuracy, t (13) = -.31, p = .38.

Temporal Dependence of the Multisensory TOJ Task

In accordance with previous studies [25-27], we found that delaying the second auditory stimulus relative to the second visual stimulus led to significant improvements in both accuracy and response time over a specific range of multisensory delays for both the ASD and TD participants.

Separate ANOVAs with SOA as the within-subjects factor and group as the between-subjects factor were conducted for improvements in both accuracy and response time. The main effect of SOA was significant for both the accuracy, F (7,210) = 3.38, p<0.002, and response time, F (7,210) = 20.9, p<.001, data, confirming the relationship between temporal proximity and probably of integration. The main effect of group was significant for the accuracy, F (1,30) = 4.45, p<0.04, but not response time, F (1,30) = 1.14, p<0.29, data, indicating that children with ASD show greater performance gains with the addition of auditory stimuli than do children with TD. The interaction between SOA and group was not significant for either accuracy, F (7,210) = 1.53, p<0.16, or response time, F (7,210) = 0.50, p<0.83, indicating that the global relationship between temporal proximity of auditory and visual stimuli and improvement in performance does not differ between groups.

The temporal window was defined for each group as the contiguous span of multisensory delays within which significant improvements over the visual-only baseline were observed. Windows were defined separately for each group using both the accuracy and response time data. Interestingly, the range of delays (i.e., the multisensory temporal window) that led to these performance improvements differed substantially between groups (accuracy: Figure 3.4; response time: Figure 3.5).

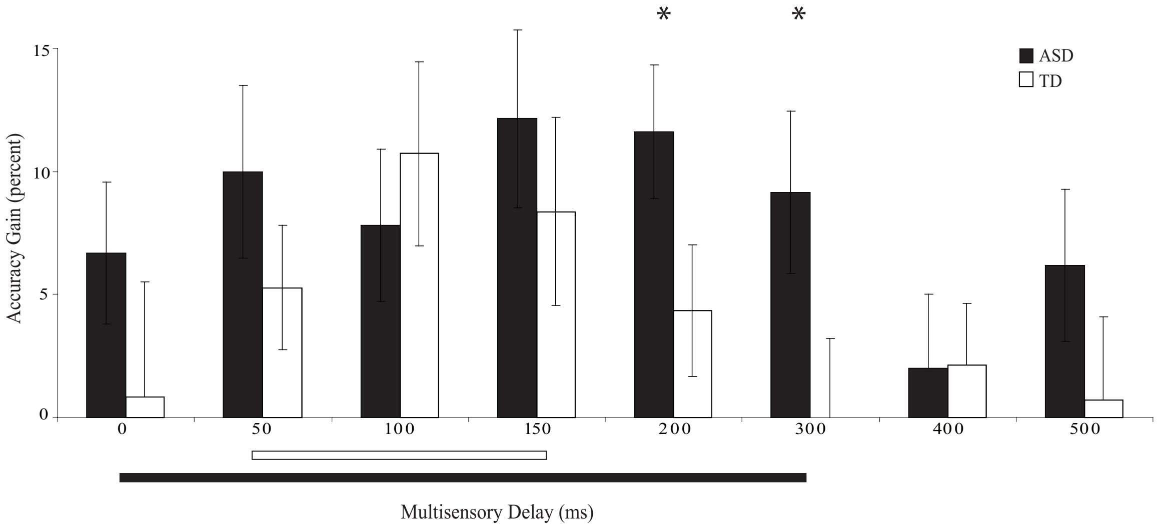


Figure 3.4: Percent improvement in accuracy relative to visual only performance as a function of multisensory delay. Whereas typically developing children show improvements for short delays (i.e., 50-150 ms), children with ASD show improvements for both moderate and short delays (i.e. 0-300 ms). The solid line indicates continuous significant (p<.05) differences from zero (i.e., the multisensory temporal window). Error bars represent standard error of the mean (SEM).

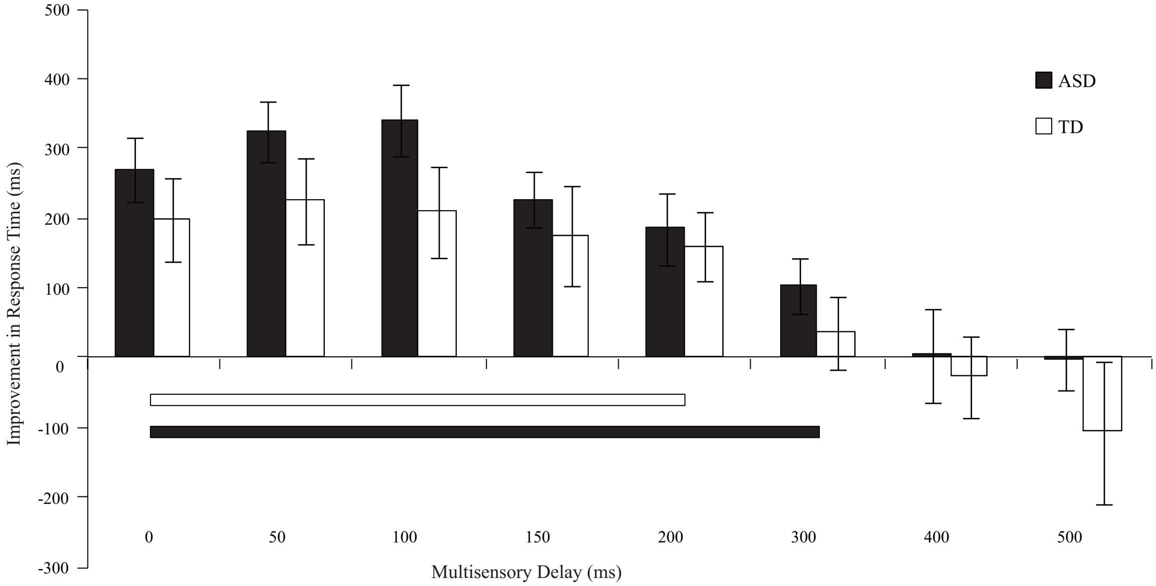


Figure 3.5: Improvement in response times relative to visual only performance as a function of multisensory delay. Whereas typically developing children show improvements for short delays (i.e., 0-200 ms), children with ASD show improvements for both moderate and short delays (i.e. 0-300 ms). The solid line indicates continuous significant (p<.05) differences from zero. Error bars represent standard error of the mean (SEM).

Statistical Comparison	0 ms	50 ms	100 ms	150 ms	200 ms	300 ms	400 ms	500 ms
ASD to zero [t(15)(p-value)]	**2.47 (.02)**	**2.66 (.01)**	**2.29 (.03)**	**4.39 (<.001)**	**4.67 (<.001)**	**2.69 (.01)**	1.27 (.22)	1.95 (.07)
TD to zero [t(13)(p-value)]	0.31 (.38)	**2.29 (.02)**	**2.40 (.01)**	**1.93 (.03)**	1.41 (.09)	0.16 (.44)	0.67 (.26)	0.29 (.39)

Table 3.2: One-sample t-tests for improvements in performance accuracy at each SOA for both children with ASD and TD.

Statistical Comparison	0 ms	50 ms	100 ms	150 ms	200 ms	300 ms	400 ms	500 ms
ASD to zero [t(15)(p-value)]	**5.48 (<.001)**	**6.97 (<.001)**	**6.20 (<.001)**	**5.34 (<.001)**	**3.34 (.002)**	**2.43 (.02)**	0.05 (.96)	-.0.04 (.97)
TD to zero [t(13)(p-value)]	**3.07 (.01)**	**3.90 (<.001)**	**3.01 (.01)**	**2.50 (.02)**	**3.00 (.01)**	0.87 (.40)	-0.08 (.94)	0.85 (.41)

Table 3.3: One-sample t-tests for improvements in response time at each SOA for both children with ASD and TD.

Children with ASD showed significant improvements in accuracy from the 0 ms delay condition to the 300 ms delay condition. In contrast, children with TD showed significant improvements in accuracy from the 50 ms delay condition to the 150 ms delay condition (Table 3.2), a finding consistent with prior work in typical adults [26]. Lending additional support to the differences in temporal binding window size, children with ASD showed significantly more improvement in accuracy when compared to their typically developing peers for the 200 ms, t (28) = 2.64, p = .013, and 300 ms, t (28) = 2.18, p = .038 multisensory delay conditions (i.e., at multisensory delay conditions that were inside the temporal binding window for children with ASD, but outside the window for children with TD). Thus, the extent of the multisensory temporal window for improvements in accuracy in children with ASD was approximately doubled compared to children with TD.

With regard to response times, children with ASD showed faster responses from the 0 ms delay condition to the 300 ms delay condition. In contrast, children with TD showed improvements in response time from the 0 ms delay condition to the 200 ms delay condition (Table 3.3). Although children with TD showed significant improvements in response time over a greater range of delays relative to those for which they showed improvements in accuracy, children with ASD still showed improvements in response time for approximately 100 ms longer than children with TD.

Discussion

General Findings

The results of the current study validate and extend our previous finding of a prolonged temporal window of multisensory integration in autism spectrum disorders [23]. Previously, we demonstrated this expanded window of temporal integration within the context of a multisensory illusion (i.e., the sound-induced double flash [flash-beep] illusion). In the current study, we expand on this finding by establishing that children with ASD show gains in performance resulting from multisensory stimuli over a longer temporal window than typically-developing children on a temporal order judgment task. These performance gains manifest both as improvements in accuracy and as faster responses relative to the unisensory (i.e., visual) baseline condition across an increased range of multisensory delays. Together, these two studies provide converging evidence that multisensory temporal processing, and more specifically the multisensory temporal binding window, is significantly altered in ASD.

By measuring temporal processing both within and across sensory systems, the current study provides a perspective on the relative contributions of unisensory processing changes to alterations in multisensory function. Thus, whereas visual temporal acuity was comparable across groups as measured using a standard visual TOJ task, both auditory and multisensory function were significantly impacted in ASD. Our findings of intact visual temporal processing are among the first that indicate that basic visual temporal processing may be spared in children with ASD. In fact, there is very limited literature on basic visual temporal processing in ASD, relative to a fairly extensive literature on visual spatial processing in which intact and enhanced discrimination abilities are consistently found, particularly for simple stimuli (for review see [33]). This work on visual capabilities has been extended to motion perception (for review see [34]). Interestingly, it has been shown that detection of first-order motion appears to be intact in ASD, while second-order motion detection is impaired ([17]). In addition, deficits are seen when the motion is derived from higher-order (e.g., biological) cues likely to reflect greater integrative processes. The current study extends our knowledge of visual function in autism by providing the first evidence that spared perception for basic visual features may also extend to the temporal domain.

Alterations in Auditory Temporal Processing in ASD

The observed difference in auditory TOJ performance is consistent with prior psychophysical and electrophysiological studies of temporal processing conducted in individuals with ASD. Previous behavioral studies have shown that individuals with ASD have difficulties reproducing auditory stimuli of standardized duration (Szelag et al., 2004), as well as difficulties detecting duration changes among auditory stimuli (Lepsisto et al., 2006). In two separate studies, Lepisto and colleagues demonstrated reduced mismatch negativity in response to duration changes in non-speech sounds (Lepisto et al., 2005; Lepisto et al., 2006), providing electrophysiological evidence indicating atypical responses to the temporal structure of discrete auditory stimuli. Results of the present study extend these findings by suggesting that the ability to discriminate timing information between sequential stimuli is also impaired in ASD.

These differences in auditory temporal function could reflect a decreased ability of neurons in the primary auditory cortex of children with ASD to resolve differences in the onset of neural signals produced by the individual auditory stimuli. A delay in primary auditory cortical response would be consistent with findings from [35], who reported delayed latency of evoked potentials in superior temporal gyrus in response to tones of various pitch in individuals with ASD. Similarly, [36] demonstrated delayed mismatch negativity to both speech and non-speech sounds, suggesting that not only is the neural response to timing information in auditory stimuli atypical, but the timing of the brain's response itself is delayed in response to auditory input. At a mechanistic level, these delays may be the result of decreases in the signal-to-noise ratio of neural signaling processes for auditory cues in autism, resulting in poorer time-locking of neural responses to discrete sensory events [37]. Results from [38] support this hypothesis by showing that the ERP response to auditory speech stimuli in the absence of background noise for children with ASD was similar to that with background noise for children with TD, suggesting degraded response to auditory stimuli at baseline in ASD. Electrophysiological studies examining the neural response to timing differences between auditory stimuli could help clarify the potential contributions of a reduced signal-to-noise ratio to decreased auditory temporal acuity in ASD.

An alternate hypothesis related to our auditory TOJ findings is that poorer performance in children with ASD relative to children with TD on the auditory TOJ task may be the result of deficits in inter-hemispheric communication, rather than reflecting deficits in the basic encoding of auditory stimuli. Numerous studies have shown lateralization changes in autism [39-41]. Since participants in the current study were asked to distinguish between auditory stimuli presented to the left and right ears, disruptions in lateralization could play a substantive role in the differences observed between groups. Further studies are needed to clarify whether individuals with ASD show decreased temporal acuity for auditory tasks which do not rely on spatial information.

Comparisons with Prior Studies of Multisensory Processing in ASD

The current study further confirms previous findings of intact multisensory integration for low-level stimuli [23,24]. The results of these three studies stand in contrast to other published reports of disrupted audiovisual integration in the context of ASD [42,43]. In reviewing these studies, the most straightforward source of these differences seems to lie in the more complex and social nature of the auditory information (i.e., language) used in the latter set of studies. Deficits seen with the use of such stimuli could reflect processing problems at levels well upstream of the sensory and integrative processes being indexed by more simplistic audiovisual stimuli.

Mechanistic Implications: Toward the Brain Bases for Altered Multisensory Temporal Binding

As discussed previously [23], there are several possible neural mechanisms for the extended temporal window of multisensory integration in children with ASD. Rubenstein and Merzenich's decreased signal-to-noise ratio hypothesis described above within the auditory system could extend to the multisensory domain, where a protracted time window within which crossmodal stimuli can interact may emerge as a result of -- and possibly even as a compensatory mechanism for -- the imprecise time-locking of neural responses to stimuli within individual sensory domains. Alternatively, the current data are also consistent with the temporal binding deficit hypothesis proposed by [44], which suggests that activity within networks of interconnected sensory areas are not as strongly correlated in ASD, resulting in disruptions in the binding of perceptual information. It may be the case that these neural signals are not so drastically uncorrelated as to cause decoupling across regions (as initially hypothesized by Brock and colleagues), but instead occur in such a way as to necessitate an extended temporal binding window within which two stimuli can continue to be bound as part of one event. Further study is needed to provide additional support for one or the other of these theories, or to identify additional mechanistic possibilities. Such studies, if capable of employing neuroimaging tools such as fMRI and EEG/ERP, will be vital for improving our understanding of how the neural networks subserving multisensory integration may be disrupted in ASD and how these disruptions could result in an enlargement in the temporal window of multisensory integration.

Disrupted Temporal Multisensory Processing: A Common Disruption in Developmental Disorders?

An enlargement in the temporal window of multisensory integration has been found in other developmental disorders including developmental dyslexia (Hairston et al., 2005). Due to the multisensory nature of the relevant stimuli in the human environment, disruptions in the temporal fidelity with which auditory and visual stimuli are paired together and integrated could lead both to symptoms of dyslexia (e.g., difficulty mapping written words to their phonemic representation in speech) and of ASD (e.g., difficulty combining speech signals with visual cues from facial expressions and gestures to interpret others' communicative intent). However, it is important to note that, while both groups demonstrate an enlarged temporal binding window for audiovisual stimuli, some differences in the nature and extent of temporal processing abnormalities between the two disorders exist. For example, with regard to unisensory temporal processing, individuals with dyslexia show both auditory *and* visual temporal processing impairments (e.g., Hairston et al 2005; Laasonen, Service, and Visru, 2001), while our results suggest that individuals with ASD have impairment in auditory but *not* visual temporal processing. These differences may reflect divergent disorder-specific neural dysfunction related to temporal processing that ultimately results in similar disruptions of multisensory temporal processing. Along these lines, it has been proposed that autism results from local hyperconnectivity with long-range hypoconnectivity (Rippon, Brock, Brown, and Boucher, 2007), whereas dyslexia involves proximal hypoconnectivity but distal hyperconnectivity (Williams and Casanova, 2010). These opposite patterns might both result in atypical temporal multisensory function, but would likely result in divergent patterns of strengths and weaknesses in ASD and dyslexia. Alternatively, morphological or functional abnormality in one or more discrete brain regions that form these connected networks could contribute to the shared profile of an enlargement in the multisensory temporal binding window, while simultaneously giving rise to ASD- or dyslexia-specific dysfunction. Future research into the neural underpinnings of the enlarged temporal window in both disorders should be directed toward distinguishing convergent and divergent neural abnormalities that could impact temporal multisensory processing, and should include subcortical structures such as the cerebellum that have been implicated in both disorders and may contribute to optimizing the temporal integration of sensory inputs (Nicolson and Fawcett, 2005). Further investigation may elucidate different mechanisms resulting in similar patterns of multisensory temporal function, as well as clarify the specificity of altered temporal multisensory function in producing the divergent symptomology in developmental disorders.

Conclusions and Implications

We are constantly bombarded by information from all senses, and our brains must combine individual unisensory events that are temporally proximal and likely to have occurred together into a unitary multisensory percept. A disruption in the temporal precision with which a multisensory perception is created from its component unisensory parts is likely to be compounded at subsequent processing stages and lead to more pronounced disruptions in the understanding of complex stimuli such as speech, as have been reported in other studies. The extended temporal multisensory window described in the current study is likely to have far-reaching consequences for children with ASD and could account for core deficits in social and communication abilities, though the present study does not allow this to be tested empirically on an individual level since the multisensory TOJ task does not give an accurate estimate of the temporal window for individual participants. Nonetheless, enlargement of the temporal window during language acquisition could impair a child's ability to correctly associate the visual and auditory components of speech, thus delaying or (if severe enough) preventing the acquisition of language. With regard to core social deficits, numerous auditory and visual stimuli involved in a social interaction (e.g., subtle changes in tone of voice, facial expression, and body language) must all be integrated seamlessly for the interaction to be successful. Altered experiences with multisensory processing from early ages may have detrimental effects on subsequent development of complex social abilities such as empathy and reciprocity. Research into when and how enlargements of the temporal window for multisensory integration first emerge and how they might result in social communication deficits central to ASD should be an important focus of future studies, as altered multisensory temporal processing may serve as an early marker of later deficits or suggest potential targets for intervention.

In conclusion, this study demonstrates that the temporal processing of auditory and multisensory stimuli is disrupted in ASD, providing empirical evidence in support of the clinical and anecdotal literature that consistently reports sensory functioning impairments in ASD. A limitation of the study is the inherent bias toward high functioning ASD necessitated by the cognitive and attentional demands of the psychophysical tasks used. In fact, even in the high functioning population used in this study, many of the participants were not able to complete one or more of the tasks. Further research is needed to fully characterize the nature and extent of these unisensory and multisensory temporal processing differences in ASD, to elucidate their neural substrates, to clarify their profile in lower-functioning individuals, to assess their emergence early in development, and to relate these findings to the core deficits in ASD. It is anticipated that this line of investigation will ultimately contribute to a broader understanding of ASD and lead to more sensitive diagnostic instruments and more specific remediation strategies.

Acknowledgements

This work was supported by a Marino Autism Research Institute Discovery Grant (PI: MTW); National Institute of Child Health and Human Development T32 HD07226 and Dennis Weatherstone Pre-doctoral Fellowship for JHF; Meharry-Vanderbilt Alliance Training Grant for LDK; and the Vanderbilt Kennedy Center for Research on Human Development.

References

1. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

2. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217-250 (1943).

3. Cesaroni, L. & Garber, M. Exploring the experience of autism through firsthand accounts. *J Autism Dev Disord* **21**, 303-313 (1991).

4. O'Neill, M. & Jones, R. Sensory-perceptual abnormalities in autism: a case for more research? *Journal of Autism and Developmental Disorders* **27**, 283-293 (1997).

5. Sigman, M. & Capps, L. *Children with Autism: A Developmental Perspective*, (Havard University Press, Cambride, MA, 1997).

6. Talay-Ongan, A. & Wood, K. Unusual Sensory Sensitivities in Autism: A possible crossroads. *International Journal of Disability, Development and Education* **47**, 201 - 212 (2000).

7. Rogers, S. & Ozonoff, S. Annotation: What do we know about sensory dysfunction in autism? A critical review of the empirical evidence. *Journal of Child Psychology and Psychiatry* **46**, 1255-1268 (2005).

8. Iarocci, G. & McDonald, J. Sensory Integration and the Perceptual Experience of Persons with Autism. *Journal of Autism and Developmental Disorders* **36**, 77-90 (2006).

9. O'Riordan, M., Plaisted, K., Driver, J. & Baron-Cohen, S. Superior visual search in autism. *J Exp Psychol Hum Percept Perform.* **27**, 719-730 (2001).

10. Jolliffe, T. & Baron-Cohen, S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *J Child Psychol Psychiatry* **38**, 527-534 (1997).

11. Shah, A. & Frith, U. An islet of ability in autistic children: a research note. *J Child Psychol Psychiatry* **24**, 613-620 (1983).

12. Plaisted, K., O'Riordan, M. & Baron-Cohen, S. Enhanced Discrimination of Novel, Highly Similar Stimuli by Adults with Autism During a Perceptual Learning Task. *J. Child Psychol. Psychiat.* **39**, 765-775 (1998).

13. Ashwin, E., Ashwin, C., Rhydderch, D., Howells, J. & Baron-Cohen, S. Eagle-Eyed Visual Acuity: An Experimental Investigation of Enhanced Perception in Autism. *Biological psychiatry* **65**, 17-21 (2009).

14. Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E. & Bonnel, A. Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *J Cogn Neurosci.* **15**, 226-235 (2003).

15. Samson, F., Mottron, L., Jemel, B., Belin, P. & Ciocca, V. Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks? *J. Autism Dev Disord.* **36**, 65-76 (2006).

16. Mongillo, E., Irwin, J., Whalen, D., Klaiman, C., Carter, A. & Schultz, R. Audiovisual Processing in Children with and without Autism Spectrum Disorders. *J Autism Dev Disord* (2008).

17. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

18. Ghazanfar, A. & Schroeder, C. Is neocortex essentially multisensory? *Trends in Cognitive Sciences* **10**, 278-285 (2006).

19. Szelag, E., Kowalska, J., Galkowski, T. & Poppel, E. Temporal processing deficits in high-functioning children with autism. *British Journal of Psychology* **95**, 269-282 (2004).

20. Tecchio, F., Benassi, F., Zappasodi, F., Gialloreti, L., Palermo, M., Seri, S. & Rossini, P. Auditory sensory processing in autism: a magnetoencephalographic study. *Biol Psychiatry* **54**, 647-654 (2003).

21. Gomot, M., Bernard, F., Davis, M., Belmonte, M., Ashwin, C., Bullmore, E. & Baron-Cohen, S. Change detection in children with autism: An auditory event-related fMRI study. *NeuroImage* **29**, 475-484 (2006).

22. Bebko, J., Weiss, J., Demark, J. & Gomez, P. Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. . *J Child Psychology and Psychiatry* **47**, 88-98 (2006).

23. Foss-Feig, J., Kwakye, L., Cascio, C., Burnette, C., Kadivar, H., Stone, W. & Wallace, M. An extended multisensory temporal binding window in autism spectrum disorders. *Exp Brain Res.* **203**, 381-389 (2010).

24. Van der Smagt, M., Van Engeland, H. & Kemner, C. Brief report: can you see what is not there? Low-level auditory-visual integration in autism spectrum disorder. *J Autism Dev Disord* **37**, 2014-2019 (2007).

25. Hairston, W., Burdette, J., Flowers, D., Wood, F. & Wallace, M. Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Exp Brain Res.* **166**, 474-480 (2005).

26. Hairston, W., Hodges, D., Burdette, J. & Wallace, M. Auditory enhancement of visual temporal order judgment. *Neuroreport.* **17**, 791-795 (2006).

27. Morein-Zamir, S., Soto-Faraco, S. & Kingstonek, A. Auditory capture of vision: examining temporal ventriloquism. *Brain Res. Cogn Brain Res.* **17**, 154-163 (2003).

28. Wechsler, D. *WASI: Wechsler Abbreviated Scale of Intelligence*, (Harcourt Assessment, Inc., San Antonio, TX, 1999).

29. Woodcock, R., McGrew, K. & Mather, N. *Woodcock-Johnson Tests of Achievement – Third Edition*, (Riverside Publishing, Rolling Meadows, IL, 2001).

30. Lord, C., Risi, S., Lambrecht, L., Cook, E., Jr, Leventhal, B., DiLavore, P., Pickles, A. & Rutter, M. Autism Diagnostic Observation Schedule - Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* **30**, 205-223 (2000).

31. Lord, C., Rutter, M. & LeCouteur, A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* **24**(1994).

32. Rutter, M., Bailey, A. & Lord, C. *SCQ: Social Communication Questionnaire*, (Western Psychological Services, Los Angeles, CA, 2003).

33. Simmons, D., Robertson, A., McKay, L., Toal, E., McAleer, P. & Pollick, F. Vision in autism spectrum disorders. *Vision Research* **49**, 2705-2739 (2009).

34. Dakin, S. & Frith, U. Vagaries of Visual Perception in Autism. **48**, 497-507 (2005).

35. Roberts, T., mKhan, S., Rey, M., Monroe, J., Cannon, K., Blaskey, L., Woldoff, S., Qasmieh, S., Gandal, M., Schmidt, G., Zarnow, D., Levy, S. & Edgar, J. MEG detection of delayed auditory evoked responses in autism spectrum disorders: towards an imaging biomarker for autism. *Autism Research* **3**, 8-18 (2010).

36. Oram-Cardy, J., Flagg, E., Roberts, W. & Roberts, T. Delayed mismatch field for speech and non-speech sounds in children with autism. *NeuroReport* **16**, 521-525 (2005).

37. Rubenstein, J. & Merzenich, M. Model of autism: increased ratio of excitation/inhibition in key neural systems. Vol. 2 255-267 (2003).

38. Russo, N., Zecker, S., Trommer, B., Chen, J. & Kraus, N. Effects of Background Noise on Cortical Encoding of Speech in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* **39**, 1185-1196 (2009).

39. Escalante-Mead, P., Minshew, N. & Sweeney, J. Abnormal brain lateralization in high-functioning autism. *J Autism Dev Disord* **33**, 539-543 (2003).

40. Herbert, M.R., Ziegler, D., Deutsch, C., O'Brien, L., Kennedy, D., Filipek, P., Bakardjiev, A., Hodgson, J., Takeoka, M., Makris, N. & Caviness, V. Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. *Brain* **128**, 213-226 (2005).

41. Stroganova, T., G, N., Tsetlin, M., Posikera, I., Gillberg, C., Elam, M. & Orekhova, E. Abnormal EEG lateralization in boys with autism. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* **118**, 1842-1854 (2007).

42. Williams, J., Massaro, D., Peel, N., Bosseler, A. & Suddendorf, T. Visual-auditory integration during speech imitation in autism. *Research in Developmental Disabilities* **25**, 559-575 (2004).

43. Smith, E. & Bennetto, L. Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry* **48**, 813-821 (2007).

44. Brock, J., Brown, C., Boucher, J. & Rippon, G. The temporal binding deficit hypothesis of autism. *Development and Psychopathology* **14**, 209-224 (2002).

CHAPTER IV

TEMPORAL MULTISENSORY PROCESSING AND ITS RELATIONSHIP TO AUTISTIC FUNCTIONING

Abstract

Autism spectrum disorders (ASD) form a continuum of neurodevelopmental disorders characterized by deficits in communication and reciprocal social interaction, repetitive behaviors, and restricted interests. Sensory disturbances are also frequently reported in clinical and autobiographical accounts. However, few empirical studies have characterized the fundamental features of sensory and multisensory processing in ASD. A recently published study has shown that children with ASD can integrate low-level multisensory stimuli, but do so over an enlarged temporal window when compared to typically developing (TD) children. The current study sought to expand upon our previous findings by examining differences in the temporal processing of low-level multisensory stimuli in high-functioning (HFA) and low-functioning (LFA) children with ASD in the context of a simple reaction time task. Contrary to previous findings, children with both HFA and LFA showed decreased improvements in performance in response to multisensory stimuli as compared to their TD peers. Additionally, the temporal window of integration was not found to be larger for children with HFA or LFA. These findings add complexity to our understanding of the multisensory processing of low-level stimuli in ASD and may hold promise for the development of more sensitive diagnostic measures and improved remediation strategies in autism.

Introduction

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders which are diagnosed using the following triad of symptoms: impairments in social interaction, impairments in language, and restricted, repetitive, and stereotyped behavior, interests, and activities[1]. In addition to the diagnostic triad of symptoms, sensory and perceptual disruptions are frequently associated with ASD. In fact, the original depiction of autism published by Kanner in 1943 included descriptions of sensory abnormalities such as fascination with particular stimuli as well as aversions to innocuous stimuli [2] which have since been reported consistently in autobiographical, caregiver and clinical reports [3-6].

Many empirical studies have further investigated changes in sensory processing in ASD. Interestingly, some of these studies have shown superior unisensory perceptual discrimination in individuals with ASD relative to control subjects [7-9]. For example, discrimination of fine visual spatial detail has widely been found to be a relative strength in ASD [10-13]. Other studies suggest that these enhanced perceptual abilities are limited to simplistic stimuli and that relatively more complex stimuli result in perceptual disruptions [14,15].

In addition to disruptions in unisensory processing, there is evidence for alterations in the binding of information across sensory systems (i.e., multisensory integration)[16]; however, multisensory processing in autism has not been studied as extensively as unisensory processing. Accordingly, much less is known about whether deficits in the integration of information across modalities exist in autism and what the nature and degree of these disruptions may be. Interestingly, the multisensory studies published thus far suggest the same dichotomy between simple vs. complex/social or verbal stimuli seen for unisensory stimuli[16-19].

There has been some indication that the temporal aspects of both unisensory and multisensory information processing may also be impacted in ASD[20-23]. Previous chapters have explored whether disruptions in the temporal processing of multisensory information are present in children with ASD. In chapter two, we showed intact integration but an expanded temporal window of multisensory integration for a multisensory illusion in children with ASD[24]. In chapter three, we did not only replicate these findings by showing an increase in the temporal window of integration in a multisensory temporal order judgment task, but we also expanded upon our knowledge of multisensory processing in ASD by exploring the role of unisensory temporal processing in the multisensory temporal processing[25]. Together, these two studies provide converging evidence that multisensory temporal processing but not the ability to integrate low-level multisensory stimuli is significantly altered in high-functioning children with ASD.

Although our prior work was instrumental in defining the role of temporal multisensory processing in high-functioning children with ASD, our results from chapters two and three may not generalize to lower-functioning children. Additionally, although we have demonstrated an enlarged temporal window for two dissimilar multisensory tasks, both multisensory effects result from the influence of task-irrelevant auditory information on visual perception. Other multisensory tasks may be subserved by different neurological networks and thus may be differentially impacted in ASD. The goal of the current study was to expand upon our previous findings by examining whether there are differences in the temporal processing of low-level multisensory stimuli in high-functioning (HFA) and low-functioning (LFA) children with ASD. To this end, we have investigated the ability of children with typical development (TD), HFA, and LFA to benefit from the presentation of low-level audiovisual stimuli in a simple reaction time task[26-31].

Methods

Participants

Twenty-seven children with ASD and 34 with typical development (TD) comprise the study sample. Additionally, children with ASD were split into a high-function autism (HFA) and low-functioning autism (LFA) group based their cognitive functioning (i.e. children in the HFA group had Verbal IQ scores over 70; children in the low functioning group had Verbal IQ scores below 70) resulting in 16 children in the HFA group and 11 children in the LFA group. Eligibility criteria for children in all groups were as follows: a) age 6-17 years; b) normal or corrected-to-normal hearing and vision; and c) no evidence or past diagnosis of a specific reading disorder. Cognitive functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI[32]) unless a child had completed cognitive testing in the past year and the parents could provide the scores. Additional eligibility criteria for the ASD group required that children: a) have a confirmed diagnosis of Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified; and b) have no history of seizure disorders or identified genetic disorders (e.g., Fragile X, tuberous sclerosis). Children with ASD were not excluded based on use of psychotropic medication.

Children's prior ASD diagnoses were confirmed in the present study using gold-standard procedures: the Autism Diagnostic Observation Schedule (ADOS; [33]) was administered by a research-reliable examiner and DSM-IV-based clinical diagnoses were made by a licensed clinical psychologist on the basis of this information unless a child had completed diagnostic testing in the past year. Additional eligibility criteria for children with TD were as follows: a) no history of or current psychiatric, neurological, or learning disorders (e.g., depression, epilepsy, dyslexia) or symptoms of ASD; and b) no first-degree relatives with ASD. Parent report of ASD symptoms was obtained using the

Lifetime version of the Social Communication Questionnaire (SCQ; [34]); all children with TD had SCQ scores below the at-risk cutoff for ASD. No differences in age, gender, or Full Scale IQ score were found between the TD and HFA groups (Table 4.1). As expected, a significant group difference was found for parent report of ASD symptoms on the SCQ, t (48) = 9.81, p < .001. No differences in age, gender, or SCQ were found between the HFA and LFA groups. As expected, a significant group difference was found for Full Scale IQ scores, t (25) = 5.46, p < .001.

Table 4.1: Participant Demographics.

Measure	**TD**	**HFA**	**LFA**
Gender	23M;11F	13M;3F	10M;1F
Age (months)	136 (38.2)	129.6 (26.9)	118.5 (19.7)
Verbal IQ	112.6 (19.3)	117.7 (20.4)	62.8(7.3) *
Performance IQ	110.5 (13.2)	117.3(20.4)	74.2 (24.1) *
Full Scale IQ	112.2 (15.7)	117.5 (16.5)	67.8 (13.0) *
SCQ	2.82 (2.64) *	20.4 (8.0)	26.5 (11.1)

*-Indicate significant differences compared to the HFA group.

Parents of all participants gave informed consent and all children in both groups gave assent prior to participation in any component of this study. All children received compensation for their participation at each visit. All procedures were approved by the Vanderbilt University Institutional Review Board.

General Procedure

Participants sat in a light- and sound-attenuated room. Visual stimuli consisted of a brief presentation (60ms duration) of a round white owl (4.2 cm in diameter subtending 4.37° of visual space) and presented at 4 cm (4.17°) below the center of the fixation cross on a CRT monitor (Iiyama Vision Master Pro 513, 22 inch screen; 60 Hz refresh rate; 640x480 pixel resolution). Auditory stimuli consisted of a 1850 Hz tone presented for 60 ms (ramped on and off for 5ms) and were presented via speakers (Solio W30351) located in front of the participants at a level of 85 dB peak SPL. (Figure 4.1) This task explored the redundant signals effects wherein the presentation of multisensory stimuli

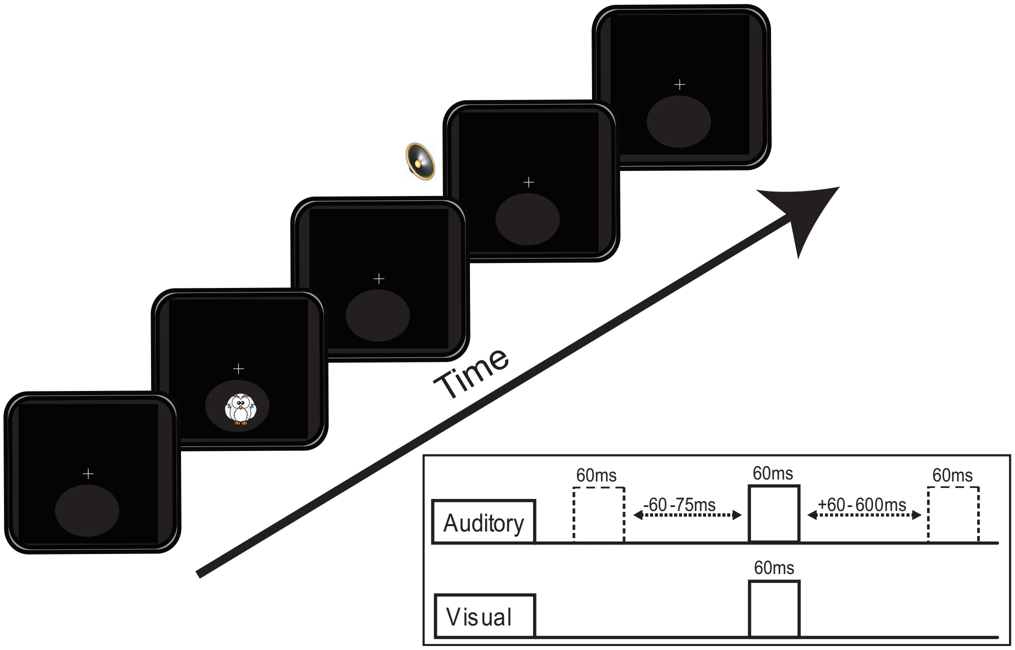


Figure 4.1: Task design. For simultaneous multisensory conditions, a small round owl is presented coincidentally with a beep. For positive SOA's, the beep is presented after the owl with variable delays (60-600ms). For negative SOA's, the beep is presented before the owl with variable delays (60-75ms).

results in speeded response times[26-31]. Trial types consisted of auditory only (auditory stimuli), visual only (visual stimuli), and multisensory (both visual and auditory stimuli). The stimulus onset asynchrony (SOA) ranged in multisensory trials between -75 ms (onset of auditory stimulus occurring 75 ms before the onset of the visual stimulus) to 600 ms (onset of the visual stimulus occurring 600 ms before the onset of the auditory stimulus). The SOA increments are as follows: -75, -60, 0, 60, 75, 100, 150, 200, 250, 300, 400, 500, 600 ms. All multisensory trials were repeated 30 times and unisensory trials were repeated 195 times thus equating the total number of unisensory and multisensory trials. The inter-trial interval varied randomly between 750 and 3000 ms. Stimuli were split into two blocks, and the participants were given a break between blocks. Stimulus presentation was controlled using E-Prime (Psychology Software Tools Inc., Pittsburgh, PA, USA). Responses were recorded via a Serial Response box (Psychology Software Tools Inc., Pittsburgh, PA, USA).

Participants were monitored continuously via closed-circuit video cameras to ensure that they were engaged in the tasks. On the rare occasions that a participant was not on-task, a variety of strategies were implemented to increase engagement (e.g., reminders to stay on task, additional breaks, parent in the testing room, etc). Participants were allowed to take breaks as necessary to increase compliance and maintain effort, motivation, and on-task behavior. All participants completed the study procedures described below within a single session.

Data analysis

Calculation of Response Times

Response timing data was recorded for each trial, and response times were calculated from this data as the amount of time between the onset of the first stimulus in the trial (i.e. the onset of the beep for negative SOA's or auditory only trials and the onset of the owl for positive SOA's or visual only trials) and the response. Response times less than 100ms or more than 800ms were considered unrelated to the stimulus presentation and excluded from analysis. If a participant responded more than once during a trial, the first response within the accepted time frame (between 100-800ms) was used to calculate response time. Multiple responses during a single trial were uncommon overall but occurred more frequently for multisensory trials with long SOA's in which participants may have been responding to the visual and auditory stimuli separately. An averaged response time was then calculated for each trial type for each participant.

Group Differences in Overall Performance

Given that cognitive functioning was not equated between the TD and LFA groups, the TD group was not compared directly to the LFA group. Instead, both the TD and LFA groups were compared separately to the HFA group. Response times for unisensory trials were compared using independent samples t-tests to examine any between-group differences in the detection of visual and auditory stimuli. In order to explore potential groups differences in performance on multisensory trials, an ANOVA was conducted for response time with SOA as the within-subjects variable and group as the between-subjects variable.

Differences in Improvement in Response Time for Multisensory Trials

The improvement in response time for multisensory trials was determined separately at each SOA by subtracting the average unisensory response time of the modality, which was presented first within the multisensory trial type from the average multisensory response time. For example, the average visual response time would be subtracted from the average response time for multisensory trials with an SOA of 75ms; however, the average auditory response time would be subtracted from the average response time for multisensory trials with an SOA of -75ms. SOA's that resulted in significant improvements in response time were determined by comparing the improvement in response time to an alternate value of 0 using one-sample t-tests separately for each group at each SOA. In order to explore potential groups differences in improvement in response time from the presentation of multisensory stimuli, an ANOVA was conducted for improvements in response time with SOA as the within-subjects variable and group as the between-subjects variable. Additionally, a global improvement in response time variable was calculated by averaging the improvements in response time across the shortest SOA's trials types which were the most likely to result in speeding of response time (i.e. -75 – 100ms). Independent samples t-tests were used to compare the global improvement in response time between the groups.

Differences In The Temporal Window Of Multisensory Integration

The temporal binding window for multisensory integration was determined individually for each participant by fitting a sigmoid curve to individual average response time by SOA data for positive SOA's only. Participants were only included in the analysis if the sigmoid function appropriately fit the participant's data ($R^2 > .4$). The temporal window was defined as the SOA, which corresponded to 50% of the maximum response time. Temporal window values were compared between groups using independent samples t-tests.

Performance on Unisensory Trials

To determine whether performance on visual and auditory trials differed in children with HFA as compared to children with TD and LFA, we determined the average response time for each participant for both the visual only and auditory only trials. Average response times for auditory-only trials were 295.9 ms for children with TD, 297.2 ms for children with HFA, and 311.4 ms for children with LFA. Average response times for visual-only trials were 303.4 ms for children with TD, 299.8 ms for children with HFA, and 324.1 ms for children with LFA. (Figure 4.2) Auditory and Visual response times did not significantly differ between the TD and HFA groups (auditory: t(48)=0.07, p=0.95; visual t(48)=0.19, p=0.85) or the HFA and LFA groups (auditory: t(25)=0.49, p=0.63; visual t(25)=0.89, p=0.38) indicating that all children responded within a similar time frame on unisensory trials.

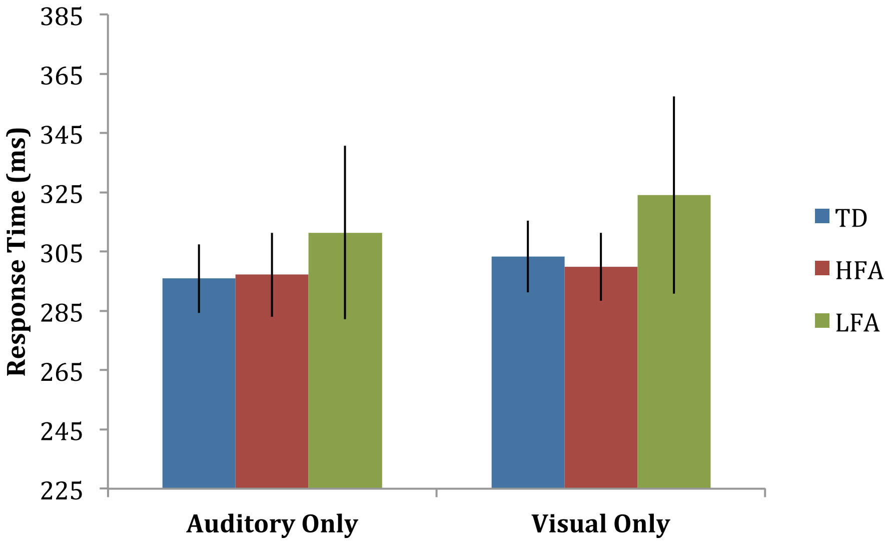


Figure 4.2: Average response times for visual only and auditory only trials. Children with TD, HFA, and LFA show similar response times for visual and auditory trials. Error bars represent standard error of the mean (SEM).

Temporal Dependence of Performance on Multisensory Trials

Performance on multisensory trials was compared between children with TD and HFA by conducting an ANOVA with SOA as the within-subjects factor and group as the between-subjects factor on averaged response times. Performance on multisensory trials was compared separately for children with HFA and LFA by conducting an ANOVA with the same factors. (Figures 4.3 and 4.4) The main effect of SOA was significant for both the comparison between children with TD and HFA (F(12,456)=9.23, p<.001) and the comparison between children with HFA and LFA (F(12,228)=4.47, p<.001) indicating that the temporal structure of multisensory stimuli had a strong effect on response times for all groups. Neither main effect of group nor the interaction between group and SOA were significant for either the comparison between children with TD and HFA (group: F(1,38)=0.08, p=.78; interaction: F(12,456)=0.73, p=.73) or the comparison between children with HFA and LFA (group: F(1,18)=0.73, p=.41; interaction: F(12,228)=1.34, p=.20) indicating that all groups responded over a similar time frame for each of the multisensory trial types. Similarly, independent samples t-tests did not reveal significant group differences between the HFA group and TD and LFA groups at any SOA.

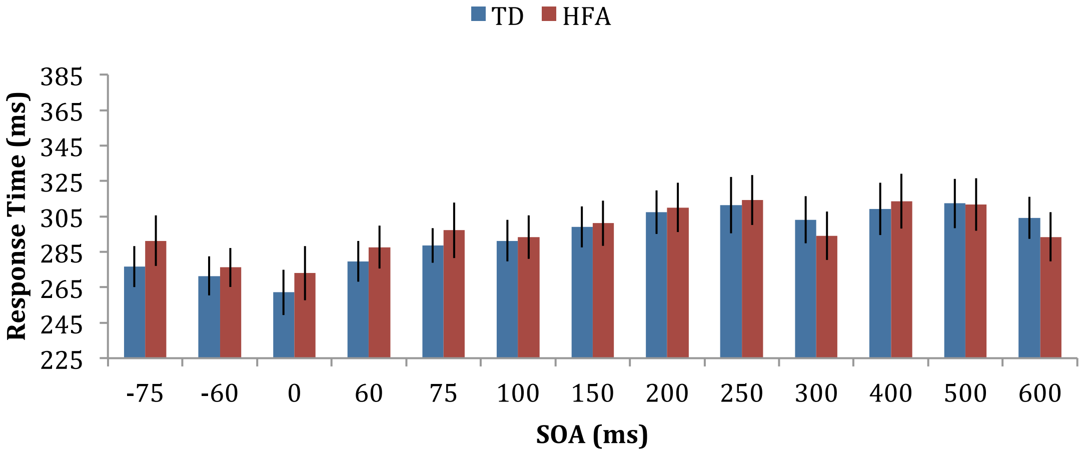


Figure 4.3: Response times for multisensory trials for TD and HFA groups. Multisensory SOA strongly influenced response times for both groups; however, the pattern of response times for multisensory trials did not significantly differ between groups. Error bars represent standard error of the mean (SEM).

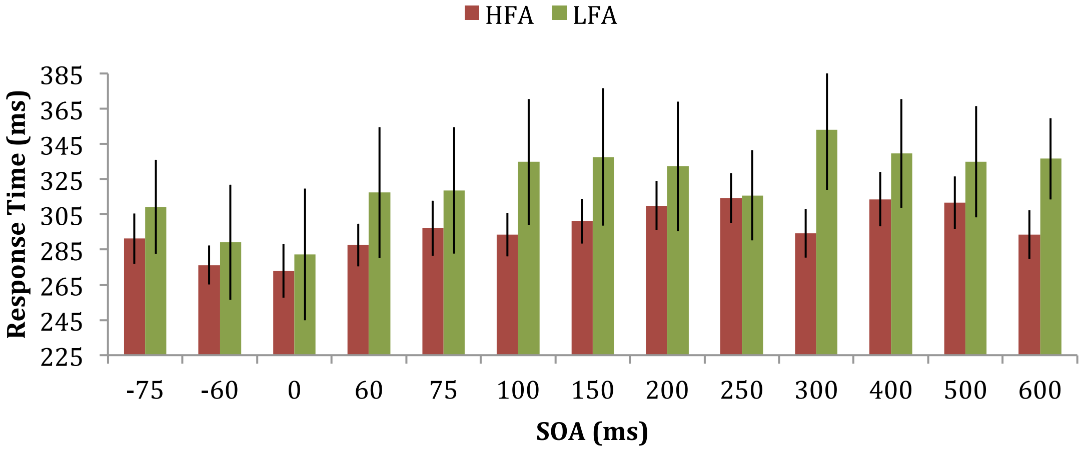


Figure 4.4: Response times for multisensory trials for HFA and LFA groups. Multisensory SOA strongly influenced response times for both groups; however, the pattern of response times for multisensory trials did not significantly differ between groups. Error bars represent standard error of the mean (SEM).

Improvements in Performance on Multisensory Trials

In accordance with previous studies, we found that the presentation of audiovisual stimuli resulted in significant improvements in response time as compared to unisensory stimuli over a limited range of SOA's. (Figures 4.5 and 4.6) Children with TD showed significant improvements in response time for the following SOA's: -75ms ($t(33)=3.66$, $p<0.05$), -60ms ($t(33)=3.97$, $p<0.05$), 0ms ($t(33)=4.67$, $p<0.05$), 60ms ($t(33)=5.32$, $p<0.05$), 75ms ($t(33)=2.12$, $p<0.05$), 100ms ($t(33)=2.64$, $p<0.05$). In contrast, children with HFA only showed significant improvements in response time for the following SOA's: -60ms ($t(15)=2.56$, $p<0.05$), 0ms ($t(15)=2.75$, $p<0.05$), 60ms ($t(15)=2.04$, $p<0.05$). Children with LFA only showed significant improvements for the 0ms SOA ($t(10)=2.76$, $p<0.05$).

Improvements in performance on multisensory trials were compared between children with TD and HFA by conducting an ANOVA with SOA as the within-subjects

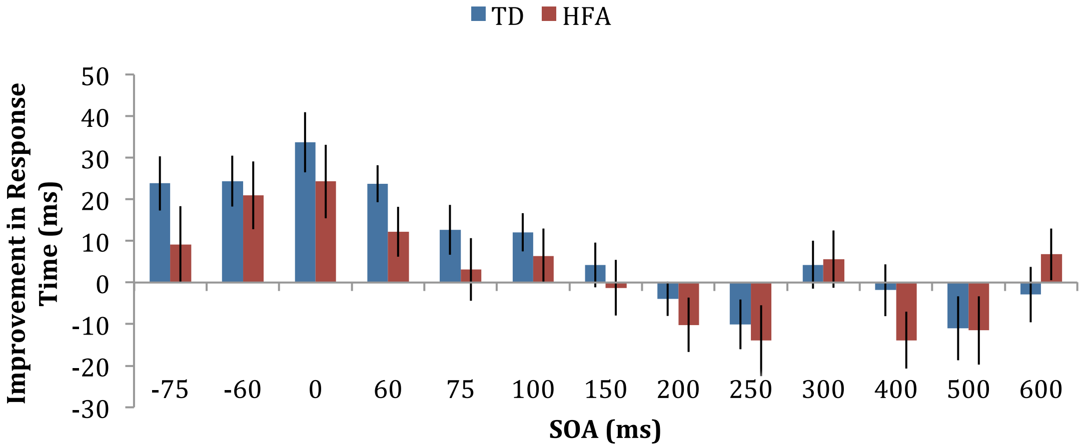


Figure 4.5: Improvement in response times for multisensory trials for TD and HFA groups. Whereas, children with TD show significant improvements in reaction times across SOA's ranging from -75 – 100ms, children with HFA only show significant improvements from -60 – 60ms. Error bars represent standard error of the mean (SEM).

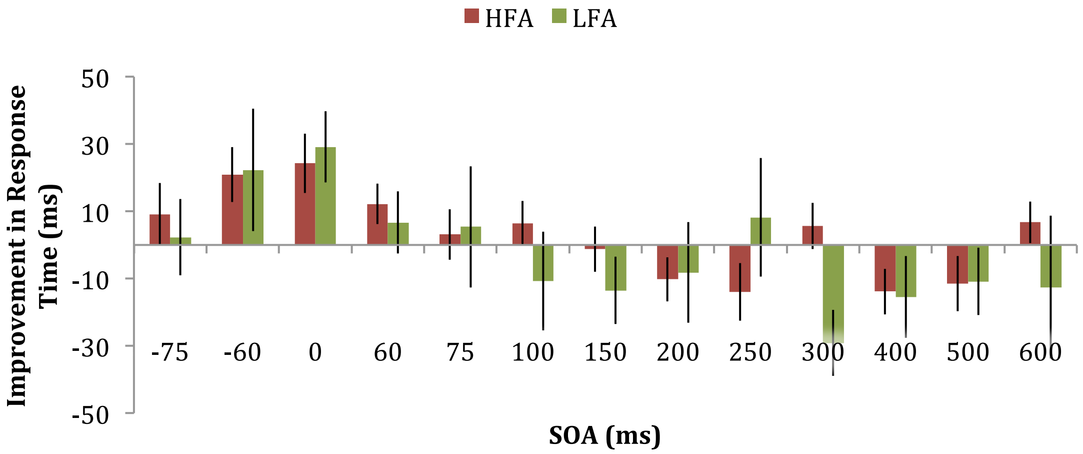


Figure 4.6: Improvement in response times for multisensory trials for HFA and LFA groups. Whereas, children with HFA show significant improvements in reaction times across SOA's ranging from -60 – 60ms, children with LFA only show significant improvements for simultaneous audiovisual presentations. Error bars represent standard error of the mean (SEM).

factor and group as the between-subjects factor on averaged response times. Performance on multisensory trials was compared separately for children with HFA and LFA by conducting an ANOVA with the same factors. (Figures 4.5 and 4.6) The main effect of SOA was significant for both the comparison between children with TD and HFA (F(12,456)=8.15, p<.001) and the comparison between children with HFA and LFA (F(12,228)=3.11, p<.001) indicating that the temporal structure of multisensory stimuli had a strong effect on improvements in response time for all groups. Neither main effect of group nor the interaction between group and SOA were significant for either the comparison between children with TD and HFA (group: F(1,38)=1.032, p=.32; interaction: F(12,456)=0..59, p=.85) or the comparison between children with HFA and LFA (group: F(1,18)=0..23, p=.64; interaction: F(12,228)=.95, p=.49). This lack of a significant difference indicates that all groups showed similar improvements in response time as a function of SOA; however, as was reported above, children with HFA and LFA showed significant improvements in response times across fewer SOA's than TD children. The ANOVA may not be revealing differences between groups because of the large variability in response times and the significant proportion of SOA's that do not result in significant improvements in response times. In order to optimize the ability to detect significant group differences, the improvements in response time were averaged for multisensory trials with short SOA's (-75ms – 100ms). On average, children with TD improved by 26.6 ms for multisensory trials with short SOA's. In contrast, children with HFA improved significantly less (13.3 ms (t(48)=2.08, p=.04). Children with LFA improved less than children with HFA (9.2 ms), but this difference was not significant (p(25)=.062, p=.54). (Figure 4.7)

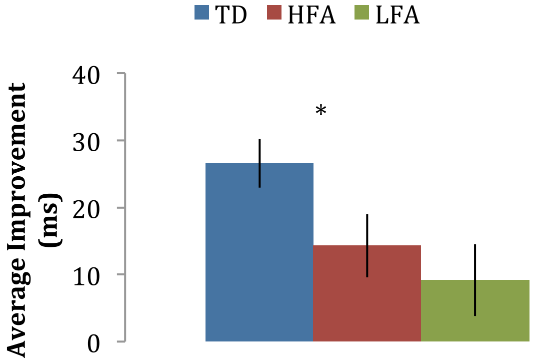


Figure 4.7: Average improvement in response times for multisensory trials with short SOA's. Children with HFA show significantly smaller improvements in response time as compared to TD children (asterisks represent $p < 0.05$). Children with LFA show similarly small improvements in response time. Error bars represent standard error of the mean (SEM).

Differences in the Temporal Window of Multisensory Integration

Individual estimates of the temporal window of multisensory integration were calculated to investigate differences in temporal multisensory processing in autism. A sigmoid curve was fit to individual response time by SOA data and the window of integration was defined as the SOA, which results in 50% of the maximum response time. Participants were only included in the analysis if the sigmoid function appropriately the participant's data ($R^2 > .4$). Twenty-two children with TD, 13 children with HFA, and 3 children with LFA were included in this analysis. Children with TD had an average window size of 93.2 ms and did not significantly differ from children with HFA (78.1ms). Children with LFA had much larger temporal windows (151.7ms); however, they did not differ significantly from children with HFA. (Figure 4.8)

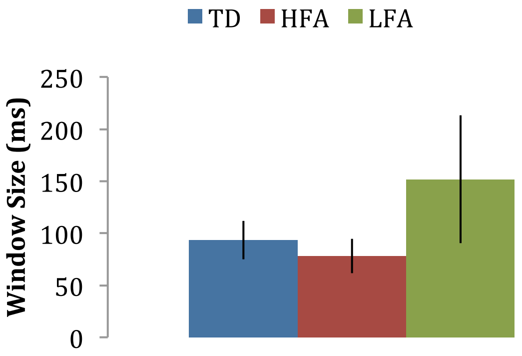


Figure 4.8: Temporal window of integration. Children with HFA do not differ from children with TD or LFA in the size of their temporal windows. Error bars represent standard error of the mean (SEM).

Discussion

The results of the current study suggest that the integration of low-level multisensory stimuli may be disrupted in children with both HFA and LFA during the completion of certain tasks, as evidenced by their decreased gains in performance resulting from multisensory stimuli. Furthermore, we showed that multisensory integration occurred over a similar range of SOA's for children with ASD and TD, suggesting that the temporal window of integration is not enlarged for children with ASD in this task. The results of this study are in direct conflict with our results from previous studies which showed intact multisensory integration over an extended range of SOA's both within the context of a multisensory illusion (flash-beep illusion)[24] and during the completion of a multisensory TOJ task[25]. This study adds complexity to our understanding of the integration of multisensory stimuli in autism by demonstrating that the context within which integration occurs strongly influences the nature of the behavioral disruptions resulting from altered multisensory processing.

Although our current results differ from our previous findings of intact multisensory integration over an enlarged temporal window, they are in accord with a recently published report by Russo and colleagues in which EEGs were recorded while children with autism and typical development were presented with low-level auditory and somatosensory stimuli. Waveforms in response to the multisensory stimuli were compared to the summed waveforms for the unisensory stimuli. The autistic children tended to show less pronounced and delayed (by approximately 200 ms) differences between the multisensory and summed waveforms indicating disrupted integration of low-level multisensory stimuli[35]. Although behavioral responses were not recorded, the results of this study imply that children with autism would receive a smaller benefit in response time for the multisensory stimuli, as we have shown in the current study. Interestingly, the differences in the temporal pattern of results in the Russo study suggest an intriguing explanation for our current finding of disrupted multisensory integration. Because responses to both unisensory and multisensory stimuli occur very quickly in detection tasks, delayed neurological integration of multisensory stimuli could occur too late to improve performance as strongly in children with autism as compared to TD children. In contrast, responses during the flash-beep and multisensory TOJ task occur much later and thus could still be strongly influenced by delayed processing of multisensory information.

Differences in the attentional modulation of multisensory processing in children with ASD may also explain the disruptions in multisensory integration observed in this study. In our prior studies utilizing the flash-beep and multisensory TOJ tasks, participants were instructed to focus on the primary visual task and to ignore the auditory stimuli[24,25]. However, in the current study, participants were asked to divide their attention between two modalities and detect both visual and auditory events. A prior study by Ciesielski and colleagues demonstrated that individuals with ASD showed disruptions in performance when their attention was divided between two modalities (i.e. decreased accuracy and response time for detecting separate visual and auditory targets) but not when asked to focus on one modality. Additionally, the slow negative wave component of their ERP waveforms did not show an attention-based modulation in amplitude for participants with ASD as was observed in participants with TD[36]. These observed differences in the interaction between attention and the processing of multisensory information in autism could lead to the decreases in gains in performance observed in the current study.

Given the discrepancy between our current finding of disrupted integration of low-level multisensory stimuli and our previous findings of intact integration of similar stimuli over an enlarged temporal window, future investigations into the temporal processing and integration of low-level stimuli in a variety of tasks may be necessary to adequately identify the primary disruption in multisensory processing in ASD. Additionally, studies investigating the role of attention in multisensory integration could determine whether the pattern of results observed in this study may be attributable to alterations in the interaction of attention and multisensory processing.

Although the results of the current study did not reveal significant differences in temporal multisensory processing and integration in children with LFA as compared to HFA, the disrupted integration of low-level multisensory stimuli observed in both groups differs from previous reports and thus may not be capturing the impact of functioning level on temporal multisensory processing which may exist for other tasks. To this end, further investigations into the temporal processing in both low- and high-functioning ASD are needed to clarify whether differences exist in this domain.

References

1. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

2. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217-250 (1943).

3. Cesaroni, L. & Garber, M. Exploring the experience of autism through firsthand accounts. *J Autism Dev Disord* **21**, 303-313 (1991).

4. O'Neill, M. & Jones, R. Sensory-perceptual abnormalities in autism: a case for more research? *Journal of Autism and Developmental Disorders* **27**, 283-293 (1997).

5. Sigman, M. & Capps, L. *Children with Autism: A Developmental Perspective*, (Havard University Press, Cambride, MA, 1997).

6. Talay-Ongan, A. & Wood, K. Unusual Sensory Sensitivities in Autism: A possible crossroads. *International Journal of Disability, Development and Education* **47**, 201 - 212 (2000).

7. Mottron, L., Dawson, M, Soulieres, I, Hubert, B, Burack, J Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord* **36**, 27-43 (2006).

8. O’Riodan, M., Passetti, F. Discrimination in Autism Within Different Sensory Modalities. *J Autism Dev Disord* **36**, 665-675 (2006).

9. Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. & Essick, G. Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study. *Journal of Autism and Developmental Disorders* **38**, 127-137 (2008).

10. O’Riordan, M., Plaisted, K., Driver, J. & Baron-Cohen, S. Superior visual search in autism. *J Exp Psychol Hum Percept Perform.* **27**, 719-730 (2001).

11. Jolliffe, T. & Baron-Cohen, S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *J Child Psychol Psychiatry* **38**, 527-534 (1997).

12. Shah, A. & Frith, U. An islet of ability in autistic children: a research note. *J Child Psychol Psychiatry* **24**, 613-620 (1983).

13. Plaisted, K., O'Riordan, M. & Baron-Cohen, S. Enhanced Discrimination of Novel, Highly Similar Stimuli by Adults with Autism During a Perceptual Learning Task. *J. Child Psychol. Psychiat.* **39**, 765-775 (1998).

14. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

15. Minshew, N., Hobson, JA. Sensory Sensitivities and Performance on Sensory Perceptual Tasks in High-functioning Individuals with Autism. . *J Autism Dev Disord* (2008).

16. Iarocci, G., McDonald, J Sensory integration and the perceptual experience of persons with autism. *J Autism Dev Disord* **36**, 77-90 (2006).

17. Mongillo, E., Irwin, J., Whalen, D., Klaiman, C., Carter, A. & Schultz, R. Audiovisual Processing in Children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* **38**, 1349-1358 (2008).

18. Smith, E.G. & Bennetto, L. Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry* **48**, 813-821 (2007).

19. Van der Smagt, M., Van Engeland, H, Kemner, C. Brief report: can you see what is not there? Low-level auditory-visual integration in autism spectrum disorder. . *J Autism Dev Disord* **37**, 2014-2019 (2007).

20. Szelag, E., Kowalska, J, Galkowski, T, Poppel, E. Temporal processing deficits in high-functioning children with autism. *Br J Psychol* **95**, 269-282 (2004).

21. Gomot, M., Bernard, FA, Davis, MH, Belmonte, MK, Ashwin, C, Bullmore, ET, Baron-Cohen, S. Change detection in children with autism: an auditory event-related fMRI study. *Neuroimage* **29**, 475-484 (2006).

22. Tecchio, F., Benassi, F., Zappasodi, F., Gialloreti, L.E., Palermo, M., Seri, S. & Rossini, P.M. Auditory sensory processing in autism: a magnetoencephalographic study. *Biological Psychiatry* **54**, 647-654 (2003).

23. Bebko, J., Weiss, JA, Demark, JL, Gomez, P. Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *J Child Psychology and Psychiatry* **47**, 88-98 (2006).

24. Foss-Feig, J., Kwakye, L., Cascio, C., Burnette, C., Kadivar, H., Stone, W. & Wallace, M. An extended multisensory temporal binding window in autism spectrum disorders. *Exp Brain Res.* **203**, 381-389 (2010).

25. Kwakye, L.D., Foss-Feig, J.H., Cascio, C.J., Stone, W.L. & Wallace, M.T. Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in Integrative Neuroscience* **4**(2011).

26. Sperdin, H.F., Cappe, C.I., Foxe, J.J. & Murray, M.M. Early, low-level auditory-somatosensory multisensory interactions impact reaction time speed. *Frontiers in Integrative Neuroscience* **3**(2009).

27. Noesselt, T., Bergmann, D., Hake, M., Heinze, H.-J. & Fendrich, R. Sound increases the saliency of visual events. *Brain Research* **1220**, 157-163 (2008).

28. Odgaard, E., Arieh, Y. & Marks, L. Cross-modal enhancement of perceived brightness: Sensory interaction versus response bias. *Perception & Psychophysics* **65**, 123-132 (2003).

29. Stein, B.E., London, N., Wilkinson, L.K. & Price, D.D. Enhancement of Perceived Visual Intensity by Auditory Stimuli: A Psychophysical Analysis. *Journal of Cognitive Neuroscience* **8**, 497-506 (1996).

30. Forster, B., Cavina-Pratesi, C., Aglioti, S. & Berlucchi, G. Redundant target effect and intersensory facilitation from visual-tactile interactions in simple reaction time. *Experimental Brain Research* **143**, 480-487 (2002).

31. Lovelace, C.T., Stein, B.E. & Wallace, M.T. An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Cognitive Brain Research* **17**, 447-453 (2003).

32. Wechsler, D. *WASI: Wechsler Abbreviated Scale of Intelligence*, (Harcourt Assessment, Inc., San Antonio, TX, 1999).

33. Lord, C., Risi, S., Lambrecht, L., Cook, E., Jr, Leventhal, B., DiLavore, P., Pickles, A. & Rutter, M. Autism Diagnostic Observation Schedule - Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* **30**, 205-223 (2000).

34. Rutter, M., Bailey, A. & Lord, C. *SCQ: Social Communication Questionnaire*, (Western Psychological Services, Los Angeles, CA, 2003).

35. Russo, N., Foxe, J.J., Brandwein, A.B., Altschuler, T., Gomes, H. & Molholm, S. Multisensory processing in children with autism: high-density electrical mapping of auditory–somatosensory integration. *Autism Research* **3**, 253-267 (2010).

36. Ciesielski, K., Knight, JE, Prince, RJ, Harris, Rj, Handmaker, SD. Event related potentials in cross-modal divided attention in autism. *Neuropsychololia* **33**, 225-246 (1995).

CHAPTER V

DISRUPTED FREQUENCY FILTERING IN AUDITION AND VISION IN AUTISM SPECTRUM DISORDERS

Abstract

Autism spectrum disorders (ASD) are characterized by disrupted social interactions, disordered language and communication, and by restrictive interests and repetitive behaviors. Although not part of the main diagnostic criteria, alterations in sensory responsiveness and perception are also prevalent in autistic individuals. Etiological theories such as the increased excitation/inhibition ratio theory and the minicolumnopathy theory implicate a reduced capacity for neurons in the autistic brain to filter sensory information as precisely as neurons in a typically developing brain. To investigate whether individuals with ASD show changes in sensory filtering, we determined the critical bandwidth for auditory and visual stimuli separately by measuring the threshold of detecting a 2 kHz pure tone (auditory) and a 3 c/d gabor patch (visual) in a notched noise masker as a function of notch width in children with ASD and typical development (TD). Our results suggest that individuals with ASD do show disruptions in frequency filtering in the degree of masking (i.e. changes in the threshold for detecting the pure tone or gabor for the smallest notch widths only) but not the range of frequencies that are able to mask the pure tone or gabor (i.e. changes in the critical bandwidth). Furthermore, a comparison between children with high-functioning autism (HFA) and low-functioning autism (LFA) suggests that the degree and nature of these sensory filtering disruptions are related to functioning level and modality in autism. Whereas high-functioning children with ASD tend to show higher thresholds for the auditory task but lower thresholds for the visual task, lower functioning children with ASD

tend to show higher thresholds for both tasks when compared to typically developing children. These changes in sensory filtering capacities represent a unique way of looking at the nature of the sensory disturbances seen in autism, and may represent an important window into the etiology of autistic symptomology and its relationship to the core disrupted domains including communication and social interactions. Furthermore, these results are likely to provide important insights for the development of better interventional strategies for those living with autism.

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder which is characterized by impairments in social interactions and language, and restricted, repetitive, and stereotyped behavior, interests, and activities[1]. Although not part of the classic diagnostic triad of symptoms, sensory and perceptual disruptions are frequently associated with ASD. In fact, the original depiction of autism published by Kanner in 1943 included descriptions of abnormal reactions to sensory stimulation[2] which have since been shown to span all sensory domains and be nearly universal in ASD[3-10].

Many diverse aspects of visual processing have been studied ranging in complexity from simple detection of visual gratings modulated in contrast/luminance to processing of faces and complex scenes. Many studies have shown intact and even superior performance on such tasks (among others) lending support to the hypothesis that the autistic brain may be more adept at processing simple visual information[11-18]. Bertone et al tested this hypothesis by altering the complexity of the stimulus to be discriminated. In this task, participants were asked to discriminate the orientation of a grating which could be luminance-defined (lower order) or texture defined (higher order). Individuals with ASD were superior at identifying orientation for luminance-defined gratings but inferior at identifying orientation for texture-defined gratings indicating that visual stimulus complexity has an inverse relationship with perceptual performance in autism[19]. The pattern of relative strengths and weaknesses in visual perception in autism suggest unique disruptions in the neural networks which subserve visual processing in the brain.

Investigations into the perception and processing of auditory stimuli are less numerous than studies of visual processing; however, these studies follow the same pattern of intact or enhanced perception of simple stimuli but disrupted perception of more complex stimuli. For example, several studies have shown that high-functioning individuals with autism were superior in discriminating pitch[20,21]. This is directly comparable to enhanced discrimination of visual gratings and strongly suggests a general change in the way that sensory information in processed in different modalities. In further accordance with studies of visual processing, individuals with autism show disruptions in the perception of complex auditory stimuli such as speech including a reduced ability to discriminate different speech sounds, phonemes, and syllables. For example, discrimination of a particular vowel sound may be disrupted while in the context of a word or phoneme but not disrupted in isolation[22].

One theory which has important implications for sensory processing in ASD is the minicolumnopathy theory proposed by Cassanova. This theory is based on anatomical observations of reductions in the architecture of minicolumn in the neocortex in postmortem tissue of individuals with autism[23-25]. Importantly Cassanova et al have proposed that these anatomical alterations will result in decreased lateral inhibition in autism. The authors further propose that decreased lateral inhibition could account for the dichotomy seen between performance of tasks using simple vs. complex stimuli and that it has important implications for the "filtering capacity of the neocortex[24,26]."

A second proposed neural mechanism for ASD which is also suggestive of disrupted filtering in ASD is founded on a decreased signal-to-noise ratio in neural encoding (Rubenstein and Merzenich 2003). Under typical conditions, neural responses are sharply tuned to particular features of sensory stimulation. This precise tuning has been clearly shown to depend on a delicate balance between excitatory and inhibitory transmission within the center-surround receptive field structure in the cortex. The decreased ratio of excitation/inhibition theory proposes that autism is characterized by disruptions in this balance. Specifically, Rubenstein and Merzenich propose that a decrease in inhibitory processing in autistic cortex results in less precision in the tuning of sensory neurons to specific sensory features[27].

A direct perceptual consequence of altered inhibition within minicolumns is a disruption in a person's ability to filter extraneous sensory information to improve task performance[28]**.** One method for approximating the filtering capabilities in a sensory system is by measuring the critical bandwidth which was originally demonstrated by Fletcher (1940) in the auditory modality. He showed that the detection of a sinusoidal signal was increasingly disrupted by increasing the bandwidth (BW) of narrowband noise until a particular BW (the critical BW) beyond which further increases in noise BW did not produce decrements in performance[29]. A similar observation was reported for visual stimuli by Pelli (1981) and Stromeyer and Julesz (1972) who demonstrated that increasing the spatial frequency BW of visual noise resulted in increased thresholds for detecting sinusoidal gratings until a critical BW, beyond which increases in the BW of the noise did not result in increased thresholds[30,31]. Conversely, the critical band can be ascertained by notching white noise (removing a range of frequencies centered at the target frequency) and measuring resulting changes in the accuracy of detecting a target tone[32].

The current study sought to examine differences in unisensory frequency filtering by measuring changes in the threshold for detecting sinusoidal signals (pure tone (auditory modality) and gabor (visual modality)) in noise of varying notch BW's in children with ASD and typical development (TD). Additionally, we investigated differences in the critical bandwidth for both the visual and auditory modalities in children with ASD and TD. Futhermore, we investigated the impact of functioning level in ASD by determining whether unisensory frequency filtering differs in children with high-functioning (HFA) and low-functioning (LFA) autism.

Methods

Participants

Twenty-seven children with ASD and 31 with typical development (TD) comprise the study sample and overlap with the participants from chapter four. Additionally, children with ASD were split into a high-function autism (HFA) and low-functioning autism (LFA) group based their cognitive functioning (i.e. children in the HFA group had IQ scores over 70; children in the low functioning group had IQ below 70) resulting in 16 children with HFA and 11 children with LFA. Eligibility criteria for children in both groups were as follows: a) age 6-17 years; b) normal or corrected-to-normal hearing and vision; and c) no evidence or past diagnosis of a specific reading disorder. Cognitive functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI[33]) unless a child had completed cognitive testing in the past year and the parents could provide the scores. Additional eligibility criteria for the ASD group required that children: a) have a confirmed diagnosis of Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder-Not Otherwise Specified; and b) have no history of seizure disorders or identified genetic disorders (e.g., Fragile X, tuberous sclerosis). Children with ASD were not excluded based on use of psychotropic medication.

Children's prior ASD diagnoses were confirmed in the present study using gold-standard procedures: the Autism Diagnostic Observation Schedule (ADOS[34]) was administered by a research-reliable examiner and DSM-IV-based clinical diagnoses were made by a licensed clinical psychologist on the basis of this information unless a child had completed diagnostic testing in the past year. Additional eligibility criteria for children with TD were as follows: a) no history of or current psychiatric, neurological, or learning disorders (e.g., depression, epilepsy, dyslexia) or symptoms of ASD; and b) no first-degree relatives with ASD. Parent report of ASD symptoms was obtained using the Lifetime version of the Social Communication Questionnaire (SCQ[35]); all children with TD had SCQ scores below the at-risk cutoff for ASD. No differences in age, gender, or Full Scale IQ score were found between the TD and HFA groups (Table 5.1).

Table 5.1: Participant Demographics.

Measure	**TD**	**HFA**	**LFA**
Gender	23M;11F	13M;3F	10M;1F
Age (months)	136 (38.2)	129.6 (26.9)	118.5 (19.7)
Verbal IQ	112.6 (19.3)	117.7 (20.4)	62.8(7.3) *
Performance IQ	110.5 (13.2)	117.3(20.4)	74.2 (24.1) *
Full Scale IQ	112.2 (15.7)	117.5 (16.5)	67.8 (13.0) *
SCQ	2.82 (2.64) *	20.4 (8.0)	26.5 (11.1)

*-Indicate significant differences compared to the HFA group.

As expected, a significant group difference was found for parent report of ASD symptoms on the SCQ, t (56) = 11.75, p < .001. No differences in age, gender, or SCQ were found between the HFA and LFA groups. As expected, a significant group difference was found for Full Scale IQ scores.

Parents of all participants gave informed consent and all children in both groups gave assent prior to participation in any component of this study. All children received compensation for their participation at each visit. All procedures were approved by the Vanderbilt University Institutional Review Board.

General Procedure

Participants sat in a light- and sound-attenuated room. Visual stimuli were presented on a gamma corrected CRT monitor (Iiyama Vision Master Pro 513, 22 inch screen; 60 Hz refresh rate; 1280x1040 pixel resolution). Auditory stimuli were presented via speakers (Solio W30351) located in front of the participants. Stimulus presentation and response recording was controlled using MATLAB and the Psychophysics Toolbox[36]. Participants responded via a touchscreen using a stylus (Magic Touch, Keytec). Participants were monitored continuously via closed-circuit video cameras to ensure that they were engaged in the tasks. On the rare occasions that a participant was not on-task, a variety of strategies were implemented to increase engagement (e.g., reminders to stay on task, additional breaks, parent in the testing room, etc). Participants were allowed to take breaks as necessary to increase compliance and maintain effort, motivation, and on-task behavior. Participants could complete each of the tasks described below within a single session, or they could complete the visual CB task in one session and the auditory CB task in a separate session.

Tasks

Visual Critical Bandwidth Task

The visual critical bandwidth (CB) task was used to test the capacity of the visual system to filter spatial frequency information. In this task, participants were asked to find a Gabor patch (2°x2°, 3 c/d, vertical orientation) on a computer monitory, which could be located at the top or bottom of the screen. The Gabor was embedded in notched spatial-frequency filtered noise (with the notch centered at 3c/d, 20% root-mean-square contrast) which varied in the BW of the notch. Six notch BW levels were selected (0,1,1.5,2,3, and 4 octaves) to maximize the potential of observing group differences as well as to incorporate the CB for the majority of participants. (Figure 5.1)

Participants completed a minimum of 10 practice trials (Gabor of 20% contrast)

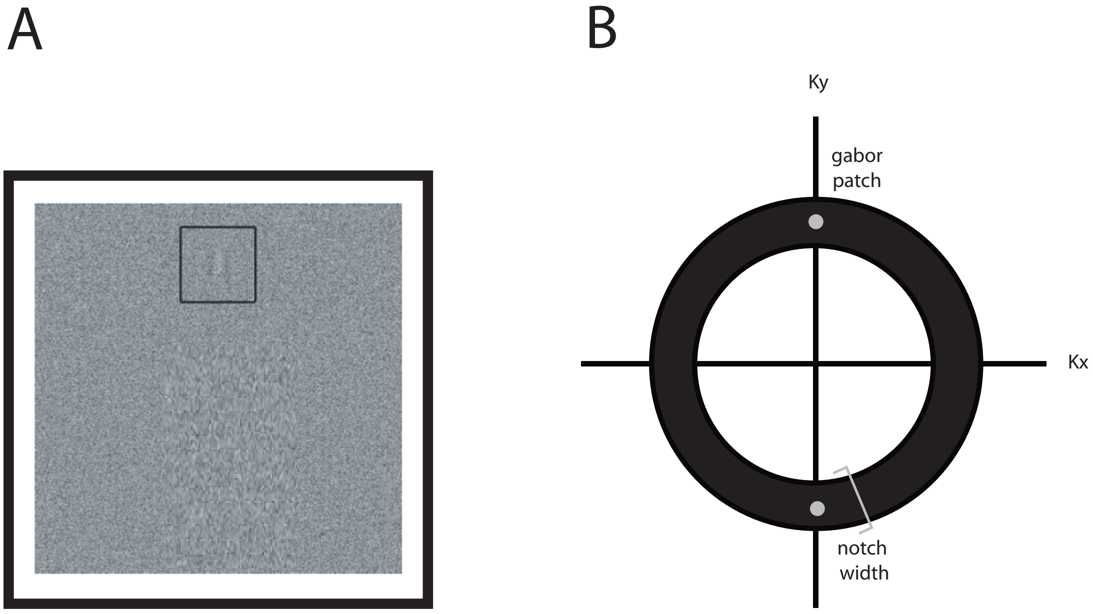


Figure 5.1: Visual CB task and stimuli. (A) Children touched the location of a vertically oriented Gabor embedded in notched visual noise using a touchscreen. (B) Fourier representation of visual notched noise. The black ring indicates the spatial frequencies which have been removed for all orientations. Gray dots indicated the Gabor.

before completing the full task. The practice ended when participants were able to obtain an accuracy rate of 90% on the last 10 trials. After practicing the task, an adaptive staircase procedure was used to determine the threshold percent contrast necessary for each participant to perform the visual CB task between 70 and 75% accuracy for each notch BW level. The initial step size (i.e. amount by which the percent contrast was adjusted) was 5% contrast, which was decreased to 1% contrast after three reversals in response accuracy and decreased again to .5% contrast after an additional six reversals. The percent contrast increased one step (i.e., became more visible) after each incorrect response, and decreased one step (i.e., became less visible) after two consecutive correct responses. Each staircase terminated after sixteen reversals in response accuracy and after an accuracy rate of at least 60% was reached for the last five reversals. An average was then calculated from the last five reversals to produce the threshold percent contrast.

Auditory CB Task

The auditory critical bandwidth (CB) task was used to test the capacity of the auditory system to filter frequency information. In this task, participants were presented

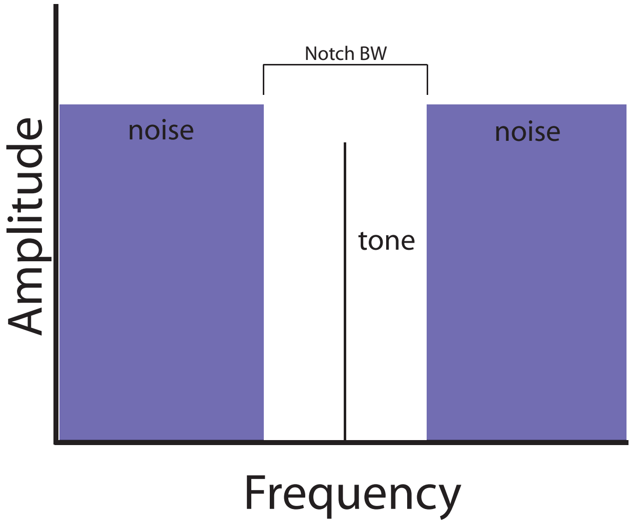


Figure 5.2: Frequency representation of auditory stimuli. Notched noise was composed of two broad noise bands position symmetrically about the target frequency (2kHz).

with two sequential intervals (200ms each, spectrum level of 40 dB) of notched noise separated by 1000ms. The notched noise was created using procedures described by Patterson in 1976[32] and was composed of two broad noise bands positioned symmetrically about the target tone (2kHz,100ms). Six notch BW levels were selected (10,200,400,800,1200, and 1600 Hz) to be consistent with previous studies of auditory filtering using notched noise[32]. (Figure 5.2) The target tone was presented during either the first or second interval of noise. To aid in task comprehension, the noise intervals were paired with differently colored fish (first interval was always paired with the yellow fish and the second interval was always paired with green fish) presented on the monitor. The children were told that the target tone was the sound of the fish singing and that the noise was the sound of the ocean. The children were then instructed to identify which

Figure 5.3: Auditory CB task. Intervals of noise were paired with the appearance of differently colored fish. The target tone was presented during either the first or second interval of noise. Children were instructed to touch the fish that "was singing" (i.e. the interval during which the target tone was presented) using a touchscreen.

fish they heard sing. (Figure 5.3) Participants completed a minimum of 10 practice trials (tone level of 80 dB) before completing the full task. The practice ended when participants were able to obtain an accuracy rate of 90% on the last 10 trials. After practicing the task, an adaptive staircase procedure was used to determine the threshold level necessary for each participant to perform the auditory CB task between 70 and 75% accuracy for each notch BW level. The initial step size was 2 dB, which was decreased to 1 dB after three reversals in response accuracy and decreased again to .5 dB after an additional six reversals. The level of the tone increased one step (i.e., became louder) after each incorrect response, and decreased one step (i.e., became softer) after two consecutive correct responses. Each staircase terminated after sixteen reversals in response accuracy and after an accuracy rate of at least 60% was reached for the last five reversals. An average was then calculated from the last five reversals to produce the threshold level.

Estimation of the Critical Bandwidth in Vision and Audition

An additional staircase was used to estimate the CB in each participant for both the visual and auditory tasks. The threshold value for the smallest notch (0 octaves for vision; 10 Hz for audition) was used to determine the signal to noise ratio for the CB staircase. After completing all of the threshold percent contrast (vision) or threshold level (audition) staircases, an adaptive staircase procedure was used to determine the notch BW necessary for each participant to perform the CB task between 90 and 95% accuracy for both the visual and auditory tasks. The initial step size was 30 Hz for the auditory and .1 octaves for the visual, which was decreased to 10 Hz for the auditory, and .05 octaves for the visual after three reversals in response accuracy and decreased again to 2 Hz for the auditory and .01 octaves for the visual after an additional six reversals. The notch BW increased one step (i.e., wider) after each incorrect response, and decreased one step (i.e., became narrower) after four consecutive correct responses. Each staircase terminated after sixteen reversals in response accuracy and after an accuracy rate of at least 85% was reached for the last five reversals. An average was then calculated from the last five reversals to produce the CB level.

Data Analysis

Given that cognitive functioning was not equated between the TD and LFA groups, the TD group was not compared directly to the LFA group. Instead, both the TD and LFA groups were compared separately to the HFA group. In order to explore potential groups differences in filtering capacity for the visual and auditory CB tasks, an ANOVA was conducted for thresholds with notch BW as the within-subjects variable and group as the between-subjects variable. Independent samples t-tests were also conducted at each notch BW to determine group differences in threshold values specific to notch BW.

Results

Influence of Notch Bandwidth on Visual Thresholds

Thresholds for the detection of a 3 c/d gabor embedded in notched visual noise were measured via an adaptive staircase for six notch bandwidths (0,1,1.5,2,3, and 4 octaves). To test for differences in the ability of children with TD, HFA, and LFA to filter extraneous spatial frequency information, we conducted a repeated measures ANOVA with notch BW as the within subjects factor and group as the between subjects factor. Notch BW was found to have a significant effect on visual thresholds (F(5,255)=57.15, p<.001) confirming the expected decrease in visual thresholds with increasing notch BW. Importantly, the main effect of group was also significant (F(2,51)=9.57, p<.001), indicating that children with TD, HFA, and LFA differed in their ability to filter frequency information in the visual modality. The interaction between notch BW and group was not significant (F(10,55)=1.13, p=0.34), indicating that the three groups did not differ in the relationship between notch BW and visual thresholds. (Figure 5.4) To test for group differences at each notch BW, we conducted independent samples t-tests between the TD and HFA groups and between the HFA and LFA groups. This analysis revealed that children with HFA had significantly lower thresholds for detecting gabors embedded in notched visual noise with a notch BW of one octave (t(46)=2.25, p=0.03), indicating that visual spatial frequencies spectrally similar to the target frequency (of the gabor) are less able to mask the gabor in HFA. Interestingly, the children with LFA showed a marked

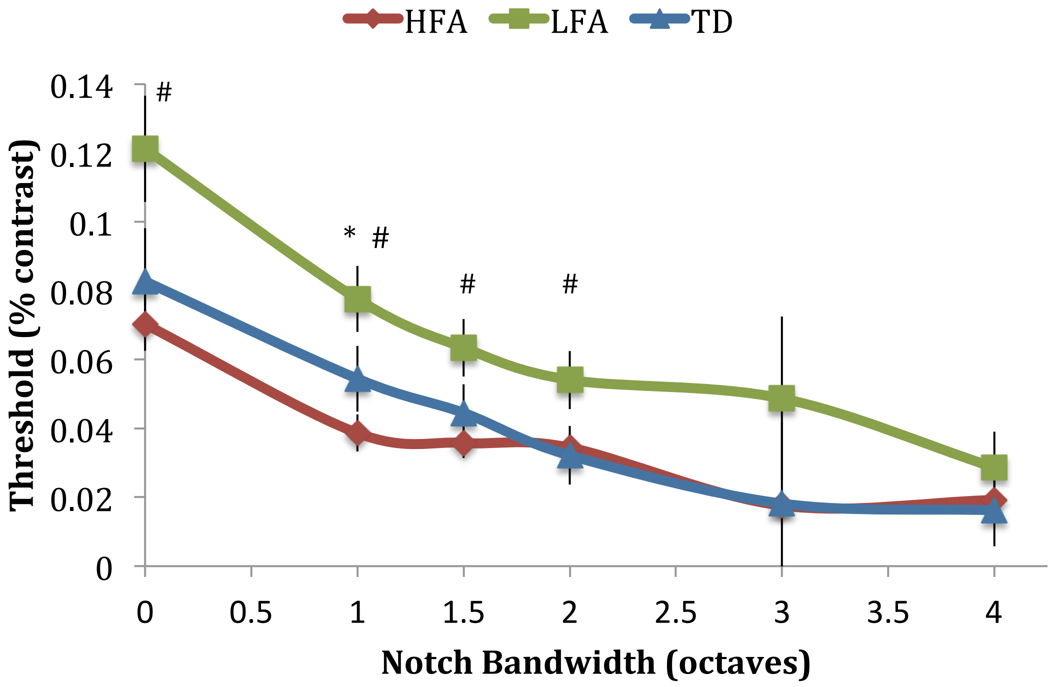


Figure 5.4 Visual thresholds as a function of notch bandwidth. Children with HFA show significantly lower thresholds at notch BW's of one octave as compared to children with TD. Asterisks indicate significant differences between HFA and TD ($p < 0.05$). Children with LFA show significantly higher thresholds for notch BW's between zero and two octaves as compared to children with HFA. Pound signs indicate significant differences between HFA and LFA ($p < 0.05$). Error bars represent standard error of the mean (SEM).

increase in their visual thresholds as compared to children with HFA across the four smallest notch BW's: 0 octaves (t(25)=3.25, p=.003), 1 octave (t(25)=3.83, p<.001), 1.5 octaves (t(25)=3.06, p=.005), (t(25)=2.49, p=0.02). Whereas children with HFA were less affected by spatial frequencies spectrally similar to the target frequency, children with LFA were much more affected by a larger range of frequencies.

Differences in the Visual Critical Bandwidth

The width of the visual critical bandwidth (CB) was estimated via a staircase which adaptively altered the width of the notch BW for each participant. Individual thresholds for the zero octaves notch BW condition were first determined and used to set the signal to noise ratio for the CB staircase. On average, children with HFA had a visual CB of 1.26 octaves, whereas children with TD had a visual CB of 0.93 octaves, a difference which was marginally significant (t(45)=1.76, p=0.09), indicating that a larger range of spatial frequencies may disrupt the detection of a gabor in HFA as compared to TD. The visual CB was approximately 1.52 octaves in LFA and not statistically different from HFA, indicating that a similar range of frequencies are able to mask a gabor in children with HFA and LFA. (Figure 5.5)

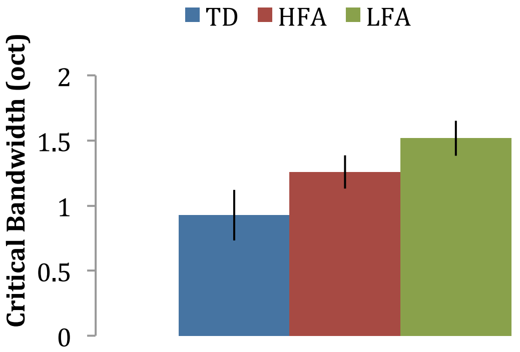


Figure 5.5 Visual CB values. Children with HFA show marginally larger visual CB's as compared to children with TD. The visual CB's for children with LFA do not statistically differ from children with HFA. Error bars represent standard error of the mean (SEM).

Influence of Notch Bandwidth on Auditory Thresholds

Thresholds for the detection of a 2 kHz tone presented in notched noise were measured via an adaptive staircase for six notch bandwidths (10, 200, 400, 800, 1200, and 1600 Hz). Due to the difficulty and the high attentional demands required to completely this task, only one participant with LFA was able to successfully complete all study procedures for the auditory CB tasks. The comparison with LFA was excluded from the auditory task because of the inability to conduct statistical analyses with only one data point. Several children with TD and HFA were also not able to complete the auditory CB task and have been excluded from further analyses. The study population for the auditory CB is comprised of 16 children with HFA and 29 children with TD.

To test for differences in the ability of children with TD and HFA to filter extraneous frequency input, we conducted a repeated measures ANOVA with notch BW as the within subjects factor and group as the between subjects factor. Notch BW was found to have a significant effect on auditory thresholds (F(5,180)=69.5, p<.001) confirming the expected decrease in auditory thresholds with increasing notch BW. The main effect of group was not significant (F(1,36)=0.97, p=0.33), indicating that children with TD and HFA were similarly able to filter frequency information in the auditory modality. The interaction between notch BW and group was not significant (F(5,180)=0.55, p=0.74), indicating that children from both groups did not differ in the relationship between notch BW and visual thresholds. (Figure 5.6) To test for group differences at each notch BW, we conducted independent samples t-tests between the

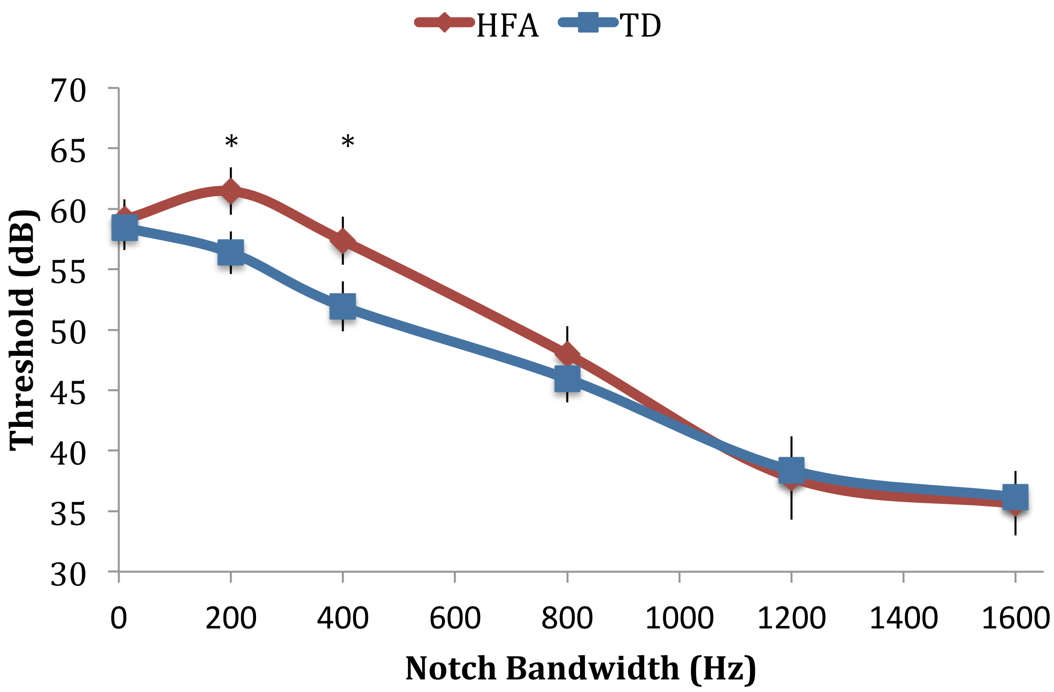


Figure 5.6 Auditory thresholds as a function of notch bandwidth. Children with HFA show significantly higher thresholds at notch BW's of 200 Hz and 400 Hz as compared to children with TD. Asterisks indicate ($p < 0.05$). Error bars represent standard error of the mean (SEM).

TD and HFA groups. This analysis revealed that children with HFA had significantly higher thresholds for detecting pure tone targets presented in notched noise with a notch BW of 200 Hz (t(44)=2.07, p=0.05) and 400 Hz (t(44)=2.35, p=0.03), indicating that frequencies spectrally similar to the target frequency mask the perception of the target to a greater extent in HFA.

Differences in the Auditory Critical Bandwidth

The width of the auditory critical bandwidth (CB) was estimated via a staircase which adaptively altered the width of the notch BW for each participant. Individual thresholds for the 10 Hz notch BW condition were first determined and used to set the signal to noise ratio for the CB staircase. On average, children with HFA had an auditory CB of 242.2 Hz, whereas children with TD had an auditory CB of 305.9 Hz, a difference which did not reach significance (t(44)=-1.08, p=0.30), indicating that a similar range of frequencies are able to mask the detection of a pure tone in HFA as compared to TD. (Figure 5.7)

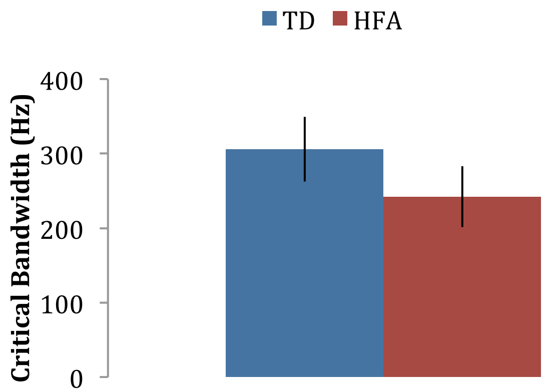


Figure 5.7 Auditory CB values. Children with HFA show similar auditory CB values as compared to children with TD. Error bars represent standard error of the mean (SEM).

Discussion

Our results suggest that individuals with ASD do show disruptions in frequency filtering in the degree of masking (i.e. changes in the threshold for detecting the pure tone or gabor for the smallest notch widths only) but not the range of frequencies that are able to mask the pure tone or gabor (i.e. changes in the critical bandwidth). Furthermore, a comparison between children with high-functioning autism (HFA) and low-functioning autism (LFA) suggests that the degree and nature of these sensory filtering disruptions are related to functioning level and modality in autism. Whereas high-functioning children with ASD tend to show higher thresholds for the auditory task but lower thresholds for the visual task, lower functioning children with ASD tend to show higher thresholds for both tasks when compared to typically developing children.

The finding of improved filtering ability in the visual modality for high-functioning children with ASD but disrupted filtering in low-functioning children with ASD adds complexity to our understanding of the minicolumnopathy and increased ratio of excitation/inhibition theories[23,27]. Disruptions in lateral inhibition may not be uniform in autism. Instead, differences in the degree of disruptions may result in divergent alterations in frequency filtering for high- as compared to low-functioning ASD. This possibility will be discussed in detail in the following chapter.

Our finding of disrupted filtering of auditory information in ASD may be attributable to the temporal content of the auditory stimuli. Whereas the target stimulus in the visual task remained on the screen until participants made a response, the auditory target was presented for a short period of time (100 ms). Given our finding of altered temporal processing in the auditory system, the disruption in auditory frequency filtering observed in ASD may result from the intersection of altered processing of frequency and temporal information in the auditory system.

Our finding of improved filtering ability in high-functioning ASD is consistent with previous psychophysical reports of superior perception and discrimination of simple visual stimuli in ASD[11-19]. Perhaps a small increase in the excitability of neurons in lower visual cortices improves the filtering capacity of the visual system for simple aspects of visual information such as spatial frequency thus improving the ability of individuals with high-functioning ASD to discriminate fine spatial detail in visual stimuli.

References

1. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

2. Kanner, L. Autistic disturbances of affective contact. *Nervous Child* **2**, 217-250 (1943).

3. Leekam, S., Nieto, C, Libby, SJ, Wing, L, Gould, J. Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord.* **37**, 894-910 (2007).

4. Omitz, E.M., Guthrie, D., & Farley, A. J. . The early development of autistic children. *Journal of Autism and Childhood Schizophrenia* **7**, 207-209 (1977).

5. Omitz, E.M., Guthrie, D., & Farley, A. J. . The early symptoms of childhood autism. in *Cognitive defects in the development of mental illness* (ed. Serban, G.) 24-42 (Brunner/Mazel, New York, 1978).

6. Dunn, W., Myles, BS, Orr, S. Sensory processing issues associated with Asperger syndrome: a preliminary investigation. *Am J Occup Ther.* **56**, 97-102 (2002).

7. Kern, J.K., Trivedi, M.H., Garver, C.R., Grannemann, B.D., Andrews, A.A., Savla, J.S., Johnson, D.G., Mehta, J.A., Schroeder, J.L. The pattern of sensory processing abnormalities in autism. *Autism* **10**, 480-494 (2006).

8. Watling, R., Deitz, J, White, O. Comparison of Sensory Profile scores of young children with and without autism spectrum disorders. *Am J Occup Ther.* **55**, 416-423 (2001).

9. Rogers, S., Hepburn, S, Wehner, E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *J Autism Dev Disord.* **33**, 631-642 (2003).

10. Kientz, M., Dunn, W. A comparison of the performance of children with and without autism on the sensory profile. *Am J Occup Ther.* **51**, 530-537 (1997).

11. White, S. & Saldaña, D. Performance of Children with Autism on the Embedded Figures Test: A Closer Look at a Popular Task. *Journal of Autism and Developmental Disorders*, 1-8 (2011).

12. Lee, P.S., Foss-Feig, J., Henderson, J.G., Kenworthy, L.E., Gilotty, L., Gaillard, W.D. & Vaidya, C.J. Atypical neural substrates of Embedded Figures Task performance in children with Autism Spectrum Disorder. *Neuroimage* **38**, 184-193 (2007).

13. de Jonge, M., Kemner, C. & van Engeland, H. Superior Disembedding Performance of High-Functioning Individuals with Autism Spectrum Disorders and Their Parents: The Need for Subtle Measures. *Journal of Autism and Developmental Disorders* **36**, 677-683 (2006).

14. Joliffe, T. & Baron-Cohen, S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *J Child Psychol Psychiatry* **38**, 527-34 (1997).

15. Joseph, R.M., Keehn, B., Connolly, C., Wolfe, J.M. & Horowitz, T.S. Why is visual search superior in autism spectrum disorder? *Developmental Science* **12**, 1083-1096 (2009).

16. Baldassi, S., Pei, F., Megna, N., Recupero, G., Viespoli, M., Igliozzi, R., Tancredi, R., Muratori, F. & Cioni, G. Search superiority in autism within, but not outside the crowding regime. *Vision Research* **49**, 2151-2156 (2009).

17. Almeida, R.A., Dickinson, J.E., Maybery, M.T., Badcock, J.C. & Badcock, D.R. Visual search performance in the autism spectrum II: The radial frequency search task with additional segmentation cues. *Neuropsychologia* **48**, 4117-4124 (2010).

18. Jemel, B., Mimeault, D., Saint-Amour, D., Hosein, A. & Mottron, L. VEP contrast sensitivity responses reveal reduced functional segregation of mid and high filters of visual channels in Autism. *Journal of Vision* **10**(2010).

19. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

20. Bonnel, A., Mottron, L, Peretz, I, Trudel, M, Gallun, E, Bonnel, AM. Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *J Cogn Neurosci.* **15**, 226-235 (2003).

21. O'Riordan, M., Passetti, F. Discrimination in Autism Within Different Sensory Modalities. *J Autism Dev Disord* **36**, 665-675 (2006).

22. Lepisto, T., Kujala, T, Vanhala, R, Alku, P, Huotilainen, M, Naatanen, R. The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Res.* **1066**, 147-157 (2005).

23. Casanova, M., van Kooten, I., Switala, A., van Engeland, H., Heinsen, H., Steinbusch, H., Hof, P., Trippe, J., Stone, J. & Schmitz, C. Minicolumnar abnormalities in autism. *Acta Neuropathologica* **112**, 287-303 (2006).

24. Casanova, M.F., Buxhoeveden, D. & Gomez, J. Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim. *The Neuroscientist* **9**, 496-507 (2003).

25. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E. & Roy, E. Minicolumnar pathology in autism. *Neurology* **58**, 428-432 (2002).

26. Raghanti, M.A., Spocter, M.A., Butti, C., Hof, P.R. & Sherwood, C.C. A comparative perspective on minicolumns and inhibitory GABAergic interneurons in the neocortex. *Frontiers in Neuroanatomy* **4**(2010).

27. Rubenstein, J.L.R. & Merzenich, M.M. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior* **2**, 255-267 (2003).

28. Blake, R., Holopigian, K. & Wilson, H.R. Spatial-frequency discrimination in cats. *J. Opt. Soc. Am. A* **3**, 1443-1449 (1986).

29. Fletcher, H. Auditory Patterns. *Reviews of Modern Physics* **12**, 47-66 (1940).

30. Stromeyer, C. & Julesz, B. Spatial-Frequency Masking in Vision: Critical Bands and Spread of Masking. *JOSA* **62**, 1221-1232 (1972).

31. Pelli, D. Cambridge University (1981).

32. Patterson, R. Auditory filter shapes derived with noise stimul. *J. Aooust.S Oc.A m.* **59**, 640-654 (1976).

33. Wechsler, D. *WASI: Wechsler Abbreviated Scale of Intelligence*, (Harcourt Assessment, Inc., San Antonio, TX, 1999).

34. Lord, C., Risi, S, Lambrecht, L, Cook, EH, Jr, Leventhal, BL, DiLavore, PC, Pickles, A, Rutter, M Autism Diagnostic Observation Schedule - Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* **30**, 205-223 (2000).

35. Rutter, M., Bailey, A, Lord, C. *SCQ: Social Communication Questionnaire*, (Western Psychological Services, Los Angeles, CA, 2003).

36. The Psychophysics Toolbox. *Spatial Vision* **10**, 433-436 (1997).

37. Tolhurst, D.J. & Tadmor, Y. Band-limited contrast in natural images explains the detectability of changes in the amplitude spectra. *Vision Research* **37**, 3203-3215 (1997).

38. Spitzberg, R. & Richards, W. Broad band spatial filters in the human visual system. *Vision Research* **15**, 837-841 (1975).

39. Sowden, P.T. & Schyns, P.G. Channel surfing in the visual brain. *Trends in Cognitive Sciences* **10**, 538-545 (2006).

40. Oru√ß, ƒ.p. & Barton, J.J.S. Critical frequencies in the perception of letters, faces, and novel shapes: Evidence for limited scale invariance for faces. *Journal of Vision* **10**(2010).

41. Stromeyer Iii, C.F. & Klein, S. Spatial frequency channels in human vision as asymmetric (edge) mechanisms. *Vision Research* **14**, 1409-1420 (1974).

42. Majaj, N.J., Pelli, D.G., Kurshan, P. & Palomares, M. The role of spatial frequency channels in letter identification. *Vision Research* **42**, 1165-1184 (2002).

43. Tanskanen, T., N√ § s√ § nen, R., Montez, T., P√ § √ § llysaho, J. & Hari, R. Face Recognition and Cortical Responses Show Similar Sensitivity to Noise Spatial Frequency. *Cerebral Cortex* **15**, 526-534 (2005).

44. Jemel, B., Mottron, L. & Dawson, M. Impaired Face Processing in Autism: Fact or Artifact? *Journal of Autism and Developmental Disorders* **36**, 91-106 (2006).

CHAPTER VI

GENERAL DISCUSSION AND FUTURE DIRECTIONS

Summary of Results

The results presented in chapter two offered the first evidence that multisensory temporal processing is disrupted in ASD. Specifically, we found that children with ASD have an extended temporal window within which they bind together multisensory stimuli, as shown by their increased likelihood of reporting the flash-beep illusion across an extended range of temporal disparities between the component visual and auditory stimuli. Additionally, we showed that high-functioning children with ASD are able to effectively integrate information from low-level multisensory stimuli, in that they show a high incidence of illusory percepts.

The results presented in chapter three expanded upon these findings by demonstrating that children with ASD show gains in their performance resulting from multisensory stimuli on a temporal order judgment task over a longer temporal window than typically-developing children. These performance gains manifest both as improvements in accuracy and as faster responses relative to the visual only condition across an increased range of multisensory delays. By measuring temporal processing both within and across sensory systems, the results of chapter three also provide insight into the relative contributions of changes in unisensory temporal processing to alterations in multisensory functioning. Thus, whereas visual temporal acuity was equivalent across groups as determined using a visual TOJ task, both auditory and multisensory temporal processing were significantly disrupted in ASD. The difference in auditory TOJ performance is consistent with prior psychophysical and electrophysiological studies of temporal processing in individuals with ASD; however our findings of intact visual temporal processing are among the first that indicate that basic visual temporal processing may be spared in children with ASD. Additionally, a series of correlational analyses revealed that unisensory temporal acuity as measured by the TOJ tasks for both vision and audition was associated with both the strength of integration and the temporal window of integration in the flash-beep task such that participants who had higher thresholds for the visual and auditory TOJ tasks were more likely to report the flash-beep illusion over a longer range of audiovisual temporal disparities (SOA's) indicating that temporal processing within unisensory systems has a strong influence on the temporal dynamics of multisensory integration. Together, these results provide converging evidence that multisensory temporal processing but not the ability to integrate low-level multisensory stimuli is significantly altered in high-functioning children with ASD.

The results presented in chapter four added a layer of complexity to our findings from chapters two and three by examining changes in multisensory temporal processing into both high-functioning and lower-functioning children with ASD during the completion of a simple reaction time task. These results suggest that the integration of low-level multisensory stimuli may be disrupted in high- and low- functioning children with ASD during the completion of certain tasks, as evidenced by their decreased gains in performance resulting from multisensory stimuli. Furthermore, we showed that multisensory integration occurred over a similar range of SOA's for children with ASD and TD, suggesting that the temporal window of integration is not enlarged for children with ASD in this task. Though the results presented in chapter four differ from our results from chapters two and three, a difference in the temporal processing of multisensory stimuli may be able to account for our results from all three chapters. Though the nature of the alterations seen in multisensory processing may vary in different multisensory tasks, the results from chapters two, three, and four clearly demonstrate that disrupted multisensory processing and integration of low-level stimuli are core features in autism.

Our results from chapter five suggest that individuals with ASD do show disruptions in frequency filtering in the degree of masking (i.e. changes in the threshold for detecting the pure tone or gabor for the smallest notch widths only) but not the range of frequencies that are able to mask the pure tone or gabor (i.e. changes in the critical bandwidth). Furthermore, a comparison between children with high-functioning autism (HFA) and low-functioning autism (LFA) suggests that the degree and nature of these sensory filtering disruptions are related to functioning level and modality in autism. Whereas high-functioning children with ASD tend to show higher thresholds for the auditory task but similar thresholds for the visual task, lower functioning children with ASD tend to show higher thresholds for both tasks when compared to typically developing children. Additionally, a series of correlational analyses revealed several links between performance on the multisensory detection task and the critical band tasks. Notably, thresholds for detecting a pure tone embedded in noise with the largest range of frequencies removed (1600 Hz notch width) was positively correlated with the temporal window of integration for the detection task, whereas the auditory critical bandwidth was negatively correlated with the degree of improvement for the detection task. These correlations suggest that the efficiency of extracting relevant information in audition is associated with both the strength and temporal dynamics of multisensory integration. These changes in sensory filtering capacities represent a unique way of looking at the nature of the sensory disturbances seen in autism, and may represent an important window into the etiology of autistic symptomology and its relationship to the core disrupted domains including communication and social interactions which will be discussed in detail below.

Current Results in the Context of Established Theories of Sensory Functioning in Autism

As discussed previously, Rubenstein and Merzenich's decreased signal-to-noise ratio hypothesis proposes that autism is characterized by disruptions in the balance between excitatory and inhibitory transmission within the center-surround receptive field structure in the cortex and that this disruption alters the well-defined tuning of neural responses to particular features of sensory stimulation[1]. The minicolumnopathy theory is based on neuroanatomical findings and proposes that this disruption in the balance between excitation and inhibition functions within the minicolumns found in the cortex to disrupt the perception of sensory information[2-4]. The finding of intact filtering ability in the visual modality for high-functioning children with ASD but disrupted filtering in low-functioning children with ASD offers an interesting dilemma in assessing the relevance of this theory to autism. However, the divergent effects seen in high versus low functioning autism can still be encompassed by the intersection of this theory and the minicolumnopathy theory discussed previously. Many researchers have theorized that the anatomical disruptions observed in minicolumns are likely to result in local over-excitability[2,3,5]. It is possible that the balance in excitatory and inhibitory processing is undisturbed in high-functioning children with ASD but severely disturbed in low-functioning ASD. In the case of low-functioning autism, a severe disruption in inhibitory processing might result in a dramatic increase in local excitability thus extending the range of frequencies to which a neuron responds, decreasing its ability to filter extraneous frequency input.

The multisensory component of our results may also align with differential effects of the degree to which the balance of excitation and inhibition is disrupted. In the temporal realm, a briefly presented unisensory (e.g., auditory) stimulus typically results in a discrete neural response time-locked to the presentation of the stimulus[6]. In contrast, the same stimulus presented to an individual with ASD may result in a response whose neural signature is less clearly time-locked to the stimulus event. Extending this theory into the multisensory domain, it can be envisioned that increased temporal variability in the unisensory responses could necessitate a compensatory enlargement in the time interval over which multisensory stimuli can influence one another. Although our results may be explainable by the decreased ratio of excitation/inhibition, this theory must be refined to be able to account for differences in the filtering capacity of individuals with high functioning versus low functioning autism.

The data presented in this document are strongly supportive of the temporal binding deficit hypothesis which states that perceptual binding is a result of strongly correlated activity among a network of interconnected brain regions, and alterations in these patterns of correlation in ASD result in concomitant reductions in binding[7]. These neural signals may not be so drastically uncorrelated as to cause decoupling across regions (as was initially hypothesized by Brock and colleagues), but instead the time constants between brain regions may be altered in such a way so as to continue to support binding, but over an atypically large set of temporal intervals. However, the temporal binding of multisensory stimuli may be disrupted in certain multisensory tasks as was found in chapter four. It is possible that the multisensory networks underlying different multisensory tasks may be characterized by different degrees of disruption in temporal binding such that an enlargement in the temporal window of integration results from slight perturbations but decreases in the ability to integrated information from multiple modalities results from large perturbations.

Our results offer indirect support that disrupted functional connectivity between brain regions is an important etiological factor in disrupted sensory processing in autism[8-11]. The precise temporal correspondence of neuronal activity within sensory networks (functional connectivity) within multisensory networks has been shown to be an important factor in multisensory integration[12-16]. The disruption in multisensory processing observed in our studies is likely to be the result of dysfunctional connectivity within the multisensory network subserving the integration in each of the tasks. Similar to the temporal binding deficit hypothesis, a slight dysfunction in the connectivity of multisensory networks might only alter the accuracy of multisensory processing in the temporal realm leading to the enlargement of the temporal window. A much stronger dysfunction in connectivity in could impair the networks ability to integrate multisensory information leading to weaker benefits from the perception of multisensory stimuli.

Potential Hierarchical Neurobiological Model of Observed Sensory Disruptions in Autism

Many of the neurological theories for sensory disruptions in autism are not mutually exclusive of each other. Instead they attempt to explain differences in the brains of individuals with autism at varying levels of neural processing[1,7,8]. This section proposes a model for the sensory disruptions presented in this document that encompasses a broad range of neural processing levels. Disrupted functional connectivity[8,9,17] is at the core of this model and posits that dysfunction in the connectivity between unisensory and multisensory brain areas reduces the ability of multisensory networks to appropriately integrate multisensory information. The binding of component unisensory information into a unified multisensory construct is disrupted in autism by the lack of precise temporal correspondence within brain areas comprising the multisensory network.

There are many anatomical dysfunctions which could result in disruptions in functional connectivity in neural networks. A disruption in the balance of excitatory and inhibitory processing within a specific brain area could strongly affect the temporal properties of the output of that area[1,3]. As discussed previously, inhibition is essential in both the tuning and the shaping of a neuron’s response to external sensory input[3]. Neurons do not continuously fire in response to a stimulus. Instead, precise inhibitory feedback results in a discrete neural response[18]. Disruptions in inhibition could alter the temporal pattern of neuronal activity within a sensory region in response to a stimulus which in turn would convey temporally degraded information to other sensory areas in its network. The temporally “noisy” output of sensory information from brain regions comprising a multisensory network would lead to disruptions in the synchronization of these brain regions and impair their ability to effectively integrate information across the network[16,19]. Thus disruptions in the balance of excitation and inhibition may alter the connectivity within multisensory networks as well as the filtering capacity of individual neurons as discussed above.

Another anatomical alteration that could result in disrupted connectivity is a disorganization in the structure of axonal connections between areas. As discussed in chapter one, DTI, MRI, and post-mortem studies have revealed that the integrity and organization of white matter is disrupted in autism[20-22]. Decreases in the volume of major white matter structures, as has been shown in several studies of autism, could represent a reduction in the number of axons connecting distant brain regions. The functional connectivity of a network is strongly dependent on the structural connectivity between individual nodes in the network[23]. Thus a deficit in the structural connectivity between brain regions could lessen the ability of these regions to effectively drive other regions within its network. Additionally, disorganization in the connections within a network could severely degrade the quality of information transmitted. For example, a multisensory network that serves to integrate visual and auditory spatial information would be greatly disrupted if the spatial maps encoded in the unisensory structures did not precisely overlap in the multisensory structures within the network[24].

The reduction in the integrity of white matter in autism as shown in DTI studies[21,25,26] strongly implicates alterations in the development of myelin as a causative factor in sensory disruptions in autism[27]. Myelin is composed of fatty tissue that wraps around and electrically insulates axons thus speeding the transmission between neurons[27]. Inconsistency in the extent of myelination of individual axons within a fiber tract connecting two brain regions could produce greater variability in the timing of input from one region to another. This variability could manifest on a trial by trial basis such that a given stimulus may activate a slightly different subset of neurons whose axons are myelinated to varying degrees. Alternatively, increased variability in the timing of inputs from individual axons between areas could result in an increase in the amount of time over which information is transmitted from one area to another thus decreasing the temporal precision in the communication between the two areas. As was discussed in chapter four, a recent event-related potential (ERP) study of multisensory integration in ASD revealed a delay in the multisensory interactions of ERP waveforms[28] potentially representing delayed neural multisensory interactions. This delay in multisensory integration may be a factor in the decreased ability of children with both high- and low-functioning ASD to benefit from the presentation multisensory stimuli in a simple reaction task. Disruptions in myelination may be an etiological cause of this observation and represent another aspect of altered temporal processing of multisensory information in autism. Disruptions in myelination are important factors in several recent animal models of autism, highlighting its potential importance in our understanding of the neurological basis of sensory disruptions in autism[29,30].

As discussed in chapter one, autism is an extremely heterogeneous disorder that is caused by a complex interplay between many genetic and environmental factors[31-35]. These factors may converge to disrupt a common neurological process such as the appropriate connectivity between distant brain regions by selectively impairing one or more aspects of neuronal processing and/or neuroanatomical dysfunction. The degree to which the functioning of an individual with autism is impaired may be due to the severity of disruption of a specific neuronal process (e.g. imbalanced inhibitory and excitatory processing) or by a weaker impact on several neuronal processes. Adding a layer of complexity, the neuronal processes described above do not function in isolation. Instead, highly complex interactions between each of the processes exist such that particular pairs of neuronal/anatomical alterations may more strongly influence sensory disruptions in autism.

Contributions of the Processing of Simple Stimuli to the Perception of Complex Stimuli in Autism

By using simple stimuli and tasks, we can isolate fundamental differences in sensory perception in autism. However, we rarely encounter such simple stimuli in our environment. Instead, our brains deconstruct the complex stimuli that we perceive into their constituent components that are then processed separately and ultimately reconstructed in higher brain centers[36]. Thus alterations in the processing of simple stimuli are likely to be a factor in the processing of the integral features of complex stimuli including their spectral and temporal content. The disruptions in basic sensory processing in autistic individuals described in this document are likely to have a strong impact on the perception of complex unisensory and multisensory stimuli such as speech and social cues. For example, because both auditory and visual speech stimuli contain complex congruent temporal information[16,37-39], deficits in the temporal processing of simple multisensory stimuli are likely to contribute to the decreased integration of audiovisual speech stimuli observed in autism[40]. Similarly, frequency channels in audition and vision are vital in the perception of socially relevant stimuli such as speech, faces, and letters[41-46]. Thus, alterations in the width of these filters will distort the perception of these social stimuli and may be contribute to their disrupted perception in autism.

Potential Impact of Observed Disruptions in Sensory Processing to Autistic Symptomology

We live in a world rich in information from many sensory modalities. Each event in our environment can usually be perceived through more than one sense with different senses adding unique perceptual information to our understanding of the happenings in the world around us. Our ability to accurately combine information from multiple senses has evolved to strongly improve our functioning in many ways ranging from increasing our basic survival (avoiding dangers and locating vital objects) to improving our ability to communicate with each other[47]. Given the immense importance of multisensory integration in our daily lives, the disruptions in multisensory processing as described in previous chapters could have far reaching consequences for individuals with autism. In fact, each of the characteristic symptoms of autism comprising the diagnostic triad is inextricably linked to multisensory integration. Communication is strongly enhanced by our ability to accurately integrate visual and auditory speech information. For example, lip-reading greatly improves our understanding of speech in a noisy environment[16]. Social information is also presented in multiple modalities. Facial expressions, prosody, and gestures all convey important social cues that must be appropriately combined to comprehend another person's intentions, beliefs, and understanding[48]

Disruptions in the integration and temporal processing of multisensory information could have a strong impact on autistic symptomology. Not only would a decrease in the ability to integrate multisensory information impede the vital benefit in understanding speech and social stimuli[16,48], but the inappropriate binding of the simple components of complex stimuli such as speech and social cues could actually serve to confuse the perception of these stimuli in individuals with autism. Furthermore, indiscriminant binding of unisensory information in the environment into an inappropriate multisensory percept could cause the experience of the world to be incredibly chaotic for individuals with autism. An intense need for structure, organization, and limited experiences could be a natural result of such a chaotic environment.

Given the potential of disruptions in the precision of multisensory processing having detrimental effects on social functioning, communication, and behavioral responses to the environment, we must consider the possibility that disrupted multisensory integration could play a direct causative role in the etiology of autism. The likelihood of disrupted temporal multisensory processing being the sole cause of autism is extremely low considering both that altered temporal multisensory processing has been shown in other disorders such as dyslexia and schizophrenia which are quite distinct from autism[49,50] and that the extensive heterogeneity seen in autistic symptomology and genetic risk factors does not support the concept of any single etiological cause of autism[34,35,51]. Disruptions in multisensory processing are still likely to contribute to autistic symptomology in at least a subset of individuals with autism. For example, multisensory integration is vital in improving our perception of degraded unisensory information[16]. Just as multisensory integration improves our understanding speech in a noisy environment, an individual with autism who may have noisy neural processing of auditory speech information should be able to benefit from concurrent visual speech information if he was able to appropriate integrate the auditory and visual speech stimuli[16]. Thus, a decrease in the ability to appropriately integrate information from multiple modalities would remove one pathway which could compensate for disrupted perception of unisensory cues.

Future Directions

Drawing from the work presented in this document we can suggest several key studies that will expand our knowledge of sensory filtering and multisensory temporal processing in autism.

Potential Interactions between Temporal Processing and Frequency Filtering

Filtering and temporal processing do not function in isolation in the brain. Instead, both factors strongly interact to direct neural responses to sensory stimulation[52-54]. Given the disruptions in both the filtering and temporal domains in autism, elucidation of the interaction between these two factors could drastically improve our understanding of how sensory information is processed in autistic individuals. In human studies, it has been shown that both the spectral content and temporal proximity of noise influences the detectability of a target[55,56]. Moore et al demonstrated that the ability of a particular frequency to mask another frequency is not uniform in time. Instead the critical band narrows with increasing temporal disparity[57]. Individuals with autism may not show this pattern, adding insight into the nature of the interactions between the processing of temporal and frequency information in autism.

Another interesting area of investigation into the interactions between filtering and multisensory processing is the study of cross-modal filtering. In the case of audiovisual interactions, frequency is not an inherently associated feature between the auditory and visual systems. Particularly, spatial frequency in vision and spectral frequency in audition have no inherent relationship. However, frequency is a shared feature between the auditory and somatosensory systems (vibration in Somatosensation and pitch in audition) such that a range of frequencies is perceivable by both modalities[58-60]. Importantly, recent work by Yau and colleagues demonstrates that frequency channels in the auditory and somatosensory systems may be linked. Notably, they found that both pure tone and broadband auditory maskers were able to disrupt performance on a tactile frequency discrimination task only if the auditory and somatosensory stimuli were similar in frequency composition. This cross-modal “critical band” signifies an interesting intersection between the aspects of sensory processing which we have shown to be disrupted in autism[61]. A similar study in autism could reveal whether filtered unisensory information is integrated in the same manner in autistic individuals. This interaction would be particularly interesting to study between low- and high-functioning children with autism who differ in their ability to filter frequency information. Accordingly, low functioning children would be expected to show less disruption of the tactile task due to the auditory masker; however, a greater range of auditory frequencies may be able to disrupt tactile performance though to a lesser extent. A deviation from this pattern would suggest that filtering within one modality does not simply transfer to other modalities in autism.

Temporal Multisensory Processing and Filtering in Higher-Order Stimuli

Multisensory speech tasks such as the McGurk effect and the benefit in speech comprehension with the presentation of multisensory stimuli are also temporally constrained; however, the temporal window is typically larger for these tasks than for tasks involving simple stimuli[62]. Given the heightened deficits in sensory processing for complex stimuli both within and across all sensory modalities[63,64], children with autism may show a greater enlargement in the temporal window for the integration of complex stimuli than for simple (flash and tone) stimuli. However, if the primary cause of disrupted multisensory temporal processing is a shift in the locus of multisensory integration unisensory cortex to association cortex for low-level stimuli (as mentioned above), the temporal window of integration of complex social and speech stimuli would likely be similar in individuals with autism. These conflicting hypotheses can easily be tested by comparing the size of the temporal window on a variety of speech and non-speech tasks between children with ASD and TD.

In the filtering domain, frequency channels are known to play a vital role in the perception of complex stimuli such as faces, letters, and speech such that a specific frequency channel mediates the perception of a complex stimulus[41-46]. For example, Tanskanen et al showed that a specific range of spatial frequencies (11-16 cycles/image) were able to disrupt the identification of faces, highlighting the important role of this frequency channel in face identification[65]. Interestingly, Majaj et al demonstrated that the frequency channel used by an observer is selected bottom-up by stimulus features and not top-down by the observer. In this study, stimuli (e.g. letters of different fonts and sizes and visual gratings) were masked by low-pass or high-pass visual noise of varying cut off frequencies. The authors observed a sigmoidal relationship between cut off frequency and threshold for each stimulus. Interestingly, the width of the channels (as measured by the sigmoidal slope) did not vary amongst the stimuli. Instead, the center frequency of the channel varied between stimuli and was invariably associated with each stimulus over hundreds of trials[46]. A similar study could show whether individuals with autism use the same frequency channels as typical individuals for each stimulus and whether the channels have the same width. Additionally, a comparison of alterations in the width and center frequency of channels for letters versus faces could show a preferential deficit for the processing of faces within spatial frequency channels contributing to our understanding of disrupted facial processing in autism[66].

Influence of the Processing of Simple Stimuli on the Perception of Complex and Autistic Symptomology

As discussed above, the disruptions in the processing of simple stimuli observed in children with autism are likely to strongly influence their perception of complex speech and social stimuli and thus significantly contribute to autistic symptomology. By correlating individual measurements of the temporal window of multisensory integration with the degree of benefit from the presentation of audiovisual speech stimuli, we can determine whether there is a relationship between the degree of disruption in multisensory temporal processing and the ability to integrate complex multisensory stimuli. Similarly, we can investigate the impact of alterations in frequency filtering on the perception of complex stimuli such as speech and faces by correlating the width of the critical band to the accuracy of speech recognition and emotion recognition. Disruptions in the perception of complex speech and social stimuli are inherent aspects of autistic symptomology[31]; therefore, any influence of temporal multisensory processing and frequency filtering on the perception of complex stimuli is likely to extend to autistic symptomology. This hypothesis can also be tested by correlating individual measurements of the temporal window of integration and notch widths in both the visual and auditory modalities to measures of autistic symptomology in each of the three categories. Significant correlations would provide intriguing evidence of the importance of these basic sensory disruptions to autistic functioning and inform our understanding of the neurological mechanisms of autistic symptomology.

Role of Perceptual Learning in Remediation

Given the role of multisensory processing in everyday functioning as discussed in the section above, improvement in the ability of individuals with autism to accurately integrate temporal multisensory information could attenuate autistic symptomology or at a minimum offer a pathway to compensate for poor perception of unisensory social and speech stimuli. Powers et al recently showed that perceptual training could narrow the temporal window of multisensory integration in typical adults[67]. A similar training protocol could also narrow the temporal window for the integration of simple stimuli to a typical width in children with autism and thus could potentially both improve their ability to integrate complex multisensory stimuli and alleviate their autistic symptomology. Powers et al recently demonstrated that the plasticity underlying the narrowing of the temporal window takes place within a multisensory network comprised of both unisensory (visual and auditory cortex) and multisensory (STS) brain areas[68]. As was discussed in chapter one, the STS plays an integral role in the perception of many higher-order social stimuli such as biological motion and speech and is thought to be a major locus of dysfunction in autism[25,69-71]. An improvement in the temporal functioning of STS via perceptual training may be able to improve the perception and integration of social/complex multisensory stimuli such as speech.

As discussed above, perceptual training can narrow the temporal window of multisensory integration and may be effective in contracting the enlarged temporal window observed in autism to a typical width[67]. By measuring the severity of autistic symptomology both before and after training, we could assess whether perceptual training is a good tool for remediation in autism. Furthermore, a significant positive correlation between degree of narrowing of the temporal window and improvement in autistic symptoms would provide strong support of a causative role of temporal multisensory processing in autistic etiology. This study, however, would not be capable of revealing a relatively small influence of temporal multisensory processing on autism severity. A measure of the ability to integrate complex multisensory stimuli such as speech and social cues may be a more successful comparison with the temporal window than measures of autistic symptomology.

Use of Imaging Tasks in Identifying Neural Correlates of Disrupted Temporal Multisensory Processing in Autism

ERP's have proven to be an important tool for studying the neural correlates of multisensory integration at the perceptual level. ERP studies of the multisensory detection task described in chapter four have demonstrated super-additive multisensory ERP waveforms, showing similarity to multisensory interactions at the single neuron level[72,73]. These multisensory enhancements from audiovisual stimuli were observed over fronto-central and occipito-parietal electrode sites and occurred shortly after presentation of the multisensory stimuli (approximately 50 ms and 100 ms) indicating that the multisensory interactions arose at an early sensory processing stage[80]. Multisensory interactions in ERPs have also been shown to decrease with increased temporal disparity between the unisensory components, demonstrating that ERPs are useful in the study of temporal multisensory processing[14]. Many ERP studies have also localized the multisensory interactions seen in the ERP waveforms to specific areas in the brain[74-76]. Because ERP recordings mimic the multisensory interactions seen at the neuronal level, diminish with temporal disparity, and can be localized to specific areas of the brain, we think that this method could be extremely useful for studying the neurophysiological correlates of temporal multisensory integration in children with ASD and could improve our understanding of how the brains of autistic individuals process multisensory input. Additionally, studies of neural oscillations would be instrumental in testing the hypothesis that disruptions in connectivity within multisensory networks underlie the alterations in multisensory processing shown in previous chapters. As was discussed in chapter one, increases in the power and coherence of EEG oscillations have been strongly associated with multisensory integration[13,14,19,77-80] and have been shown to be influenced by temporal synchrony[14]. Analysis of oscillatory activity during the completion of multisensory tasks may reveal decreases in the amplitude and coherence of oscillations in children with ASD thus lending support to the hypothesis that connectivity plays a vital role in the disrupted integration of multisensory information in autism. Decreases in the inter-trial coherence of oscillatory activity in autistic individuals would indicate an increase in the variability of neural responses to multisensory stimuli, suggesting that the observed disruptions in multisensory processing may be due to “noisy” neural responses to sensory stimulation. An analysis of inter-electrode coherence could elucidate whether decreases in functional connectivity can account for the observed differences in multisensory processing. Alternatively, a decrease in coherence between electrode locations thought to be associated with multisensory integration in individuals with autism would indicate a decoupling of activity within a multisensory network. By comparing differences in inter-trial coherence and inter-electrode coherence, we can isolate the relative contributions of variability of neural responses to multisensory stimuli as compared to variability within a multisensory network.

As mentioned above, the observed disruptions in multisensory processing could be the result of an alteration in the network of brain regions subserving the integration multisensory information. Specifically, the locus of integration of low-level stimuli may shift from unisensory cortex to a higher-order association area. An analysis of differences in the topography of ERP activity could indicate a change in the multisensory network in autism. ERP source localization analyses such as the brain electrical source analysis (BESA) or the low-resolution electromagnetic tomography (LORETA) techniques may be able to identify the neural sources of ERP activity observed on the scalp in individuals with ASD vs TD[81]. Additionally, the concurrent recording of fMRI data could confirm whether a different network of brain regions are associated with multisensory integration in individuals with ASD.

The Use of Animal Models for Studying the Role of Disrupted Neuronal Functioning in Temporal Multisensory Processing and Frequency Filtering

Although psychophysical and imaging studies of the fundamental aspects of sensory functioning are vital in identifying key areas of disruptions in autism, they are unable to directly test the contribution of alterations in neuronal functioning, neural anatomy, and their interactions to disrupted sensory perception. Many animal models of autism exist which impact a specific aspect of neural processing and/or anatomy thought to be disrupted in autism. In fact, some of these animal models are based on emerging findings from genetic studies of autism which have identified and implicated candidate genes in autism. Importantly, animal models which show disruptions in inhibitory signaling[82], neural organization[83], and myelination[29,30,84] are currently being used to study autistic etiology. Animal models have also been extensively used to study the relationship between neuronal processing and sensory perception for both multisensory integration and frequency filtering[54,85-88]. With the current availability of animal models of specific aspects of sensory functioning and specific disruptions in neural processing thought to be involved in autism, future research could utilize a combinatorial approach of these two types of animal models to investigate the influence of specific alterations in neural processing and anatomy on multisensory processing and frequency filtering. For example, the temporal pattern of neuronal activity in response to the spectral content of auditory stimuli have been extensively studied using the spectro-temporal receptive field (STRF) in rodents[54,89,90]. Additionally, changes in an animal's behavioral performance have been linked to alterations in neuronal STRF's[91]. This model could be a powerful tool for investigating potential disruptions in the neural processing of frequency information in animal models of autism. This model could delineate the relative contributions of disrupted inhibitory signaling, neural organization, and myelination to alterations in frequency filtering as well identify specific potential neural substrates for these alterations (e.g. broader neuronal tuning of frequency, increased/decreased neuronal responsiveness to differing frequencies, increased variability of neuronal responses, and/or alterations in the temporal patterning of neuronal responses).

Conclusions

The work described in this document represents the first attempt to investigate disruptions in some of the basic aspects of unisensory and multisensory processing in autism spectrum disorders. Our results demonstrate that children with autism show both alterations in their ability to filter extraneous frequency information in both the visual and auditory modalities and disrupted temporal processing of both auditory and multisensory stimuli. Furthermore, we have shown that the functioning level in autism determines the nature and extent of the disruptions in frequency filtering and temporal multisensory processing. These results form the foundation of future studies wherein the neural correlates of these disruptions may be determined and the contributions of these disruptions to autistic symptomology may be defined. Finally, we hope that these results will provide important insights for the development of better interventional strategies for those living with autism.

References

1. Rubenstein, J.L.R. & Merzenich, M.M. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior* **2**, 255-267 (2003).

2. Casanova, M., van Kooten, I., Switala, A., van Engeland, H., Heinsen, H., Steinbusch, H., Hof, P., Trippe, J., Stone, J. & Schmitz, C. Minicolumnar abnormalities in autism. *Acta Neuropathologica* **112**, 287-303 (2006).

3. Casanova, M.F., Buxhoeveden, D. & Gomez, J. Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim. *The Neuroscientist* **9**, 496-507 (2003).

4. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E. & Roy, E. Minicolumnar pathology in autism. *Neurology* **58**, 428-432 (2002).

5. Raghanti, M.A., Spocter, M.A., Butti, C., Hof, P.R. & Sherwood, C.C. A comparative perspective on minicolumns and inhibitory GABAergic interneurons in the neocortex. *Frontiers in Neuroanatomy* **4**(2010).

6. Meredith, M., Nemitz, JW, Stein, BE. Determinants of Multisensory Integration in Superior Colliculus Neurons. I. Temporal Factors. *J Neuroscience* **7**, 3215-3229 (1987).

7. Brock, J., Brown, CC, Boucher, J, Rippon, G. The temporal binding deficit hypothesis of autism. *Development and Psychopathology* **14**, 209-224 (2002).

8. Geschwind, D., Levitt, P. Autism spectrum disorders: developmental disconnection syndromes. *Current Opinion in Neurobiology* **17**, 103-111 (2007).

9. Hughes, J.R. Autism: The first firm finding = underconnectivity? *Epilepsy & Behavior* **11**, 20-24 (2007).

10. Jou, R.J., Jackowski, A.P., Papademetris, X., Rajeevan, N., Staib, L.H. & Volkmar, F.R. Diffusion tensor imaging in autism spectrum disorders: preliminary evidence of abnormal neural connectivity. *Australian and New Zealand Journal of Psychiatry* **0**, 1-10.

11. Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K. & Minshew, N.J. Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an

Executive Function Task and Corpus Callosum Morphometry. *Cerebral Cortex* **17**, 951-961 (2007).

12. Ghazanfar, A.A., Chandrasekaran, C. & Logothetis, N.K. Interactions between the Superior Temporal Sulcus and Auditory Cortex Mediate Dynamic Face/Voice Integration in Rhesus Monkeys. *The Journal of Neuroscience* **28**, 4457-4469 (2008).

13. Senkowski, D., Schneider, T.R., Foxe, J.J. & Engel, A.K. Crossmodal binding through neural coherence: implications for multisensory processing. *Trends in Neurosciences* **31**, 401-409 (2008).

14. Senkowski, D., Talsma, D, Grigutsch, M, Herrmann, CS, Woldorff, MG. Good times for multisensory integration: Effects of the precision of temporal synchrony as revealed by gamma-band oscillations. *Neuropsychologia* **45**, 561-571 (2007).

15. Senkowski, D., Gomez-Ramirez, M, Lakatos, P, Wylie, GR, Molhom, S, Schroeder, CE, Foxe, JJ. Multisensory processing and oscillatory activity: analyzing non-linear electrophysiological measures in humans and simians. *Exp Brain Res.* **177**, 184-195 (2007).

16. Nath, A.R. & Beauchamp, M.S. Dynamic Changes in Superior Temporal Sulcus Connectivity during Perception of Noisy Audiovisual Speech. *The Journal of Neuroscience* **31**, 1704-1714 (2011).

17. Kleinhans, N.M., Richards, T., Sterling, L., Stegbauer, K.C., Mahurin, R., Johnson, L.C., Greenson, J., Dawson, G. & Aylward, E. Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain* **131**, 1000-1012 (2008).

18. Connors, B.W. & Gutnick, M.J. Intrinsic firing patterns of diverse neocortical neurons. *Trends in Neurosciences* **13**, 99-104 (1990).

19. Keil, J., Muller, N., Ihssen, N. & Weisz, N. On the Variability of the McGurk Effect: Audiovisual Integration Depends on Prestimulus Brain States. *Cerebral Cortex* (2011).

20. Mengotti, P., D'Agostini, S., Terlevic, R., De Colle, C., Biasizzo, E., Londero, D., Ferro, A., Rambaldelli, G., Balestrieri, M., Zanini, S., Fabbro, F., Molteni, M. & Brambilla, P. Altered white matter integrity and development in children with autism: A combined voxel-based morphometry and diffusion imaging study. *Brain Research Bulletin* **In Press, Corrected Proof**.

21. Noriuchi, M., Kikuchi, Y., Yoshiura, T., Kira, R., Shigeto, H., Hara, T., Tobimatsu, S. & Kamio, Y. Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder. *Brain Res* **1362**, 141-9 (2010).

22. Shukla, D.K., Keehn, B. & Müller, R.-A. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *Journal of Child Psychology and Psychiatry* **52**, 286-295 (2011).

23. Wass, S. Distortions and disconnections: Disrupted brain connectivity in autism. *Brain and Cognition* **75**, 18-28 (2011).

24. Meredith, M.A. & Stein, B.E. Spatial determinants of multisensory integration in cat superior colliculus neurons. *Journal of Neurophysiology* **75**, 1843-1857 (1996).

25. Barnea-Goraly, N., Kwon, H., Menon, V., Eliez, S., Lotspeich, L. & Reiss, A.L. White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biological psychiatry* **55**, 323-326 (2004).

26. Sundaram, S.K., Kumar, A., Makki, M.I., Behen, M.E., Chugani, H.T. & Chugani, D.C. Diffusion Tensor Imaging of Frontal Lobe in Autism Spectrum Disorder. *Cerebral Cortex* **18**, 2659-2665 (2008).

27. Assaf, Y. & Pasternak, O. Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review. *Journal of Molecular Neuroscience* **34**, 51-61 (2008).

28. Russo, N., Foxe, J.J., Brandwein, A.B., Altschuler, T., Gomes, H. & Molholm, S. Multisensory processing in children with autism: high-density electrical mapping of auditory–somatosensory integration. *Autism Research* **3**, 253-267 (2010).

29. Sakurai, T., Ramoz, N., Barreto, M., Gazdoiu, M., Takahashi, N., Gertner, M., Dorr, N., Gama Sosa, M.A., De Gasperi, R., Perez, G., Schmeidler, J., Mitropoulou, V., Le, H.C., Lupu, M., Hof, P.R., Elder, G.A. & Buxbaum, J.D. Slc25a12 Disruption Alters Myelination and Neurofilaments: A Model for a Hypomyelination Syndrome and Childhood Neurodevelopmental Disorders. *Biological psychiatry* **67**, 887-894 (2010).

30. Fatemi, S.H., Folsom, T.D., Reutiman, T.J., Abu-Odeh, D., Mori, S., Huang, H. & Oishi, K. Abnormal expression of myelination genes and alterations in white matter fractional anisotropy following prenatal viral influenza infection at E16 in mice. *Schizophrenia research* **112**, 46-53 (2009).

31. (APA), A.P.A. *Diagnostic and statistical manual of mental disorders-IV-TR*, (APA, Washington, DC, 2000).

32. (CDC), C.f.D.C.a.P. Prevalence of autism spectrum disorders – Autism and developmental disabilities monitory network. *Morbidity and Mortality Weekly Report Surveillance Summary* **56**, 12-28 (2007).

33. Abrahams, B.S. & Geschwind, D.H. Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* **9**, 341-355 (2008).

34. Grafodatskaya, D., Chung, B., Szatmari, P. & Weksberg, R. Autism Spectrum Disorders and Epigenetics. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 794-809 (2010).

35. State, M.W. The Genetics of Child Psychiatric Disorders: Focus on Autism and Tourette Syndrome. *Neuron* **68**, 254-269 (2010).

36. Treisman, A. The binding problem. *Current Opinion in Neurobiology* **6**, 171-178 (1996).

37. Beauchamp, M., Argall, BD, Bodurka, J, Duyn, JH, Martin, A. Unraveling multisensory integration: patchy organization within human STS multisensory cortex. *Nature Neuroscience* **7**, 1190-1192 (2004).

38. Beauchamp, M.S., Nath, A.R. & Pasalar, S. fMRI-Guided Transcranial Magnetic Stimulation Reveals That the Superior Temporal Sulcus Is a Cortical Locus of the McGurk Effect. *The Journal of Neuroscience* **30**, 2414-2417 (2010).

39. Magnee, M.J.C.M., Gelder, B.d., Engeland, H.v. & Kemner, C. Audiovisual speech integration in pervasive developmental disorder: evidence from event-related potentials. *Journal of Child Psychology and Psychiatry* **49**, 995-1000 (2008).

40. Anderson, S., Skoe, E., Chandrasekaran, B. & Kraus, N. Neural Timing Is Linked to Speech Perception in Noise. *The Journal of Neuroscience* **30**, 4922-4926 (2010).

41. Tolhurst, D.J. & Tadmor, Y. Band-limited contrast in natural images explains the detectability of changes in the amplitude spectra. *Vision Research* **37**, 3203-3215 (1997).

42. Spitzberg, R. & Richards, W. Broad band spatial filters in the human visual system. *Vision Research* **15**, 837-841 (1975).

43. Sowden, P.T. & Schyns, P.G. Channel surfing in the visual brain. *Trends in Cognitive Sciences* **10**, 538-545 (2006).

44. Oru√ß, ƒ.p. & Barton, J.J.S. Critical frequencies in the perception of letters, faces, and novel shapes: Evidence for limited scale invariance for faces. *Journal of Vision* **10**(2010).

45. Stromeyer Iii, C.F. & Klein, S. Spatial frequency channels in human vision as asymmetric (edge) mechanisms. *Vision Research* **14**, 1409-1420 (1974).

46. Majaj, N.J., Pelli, D.G., Kurshan, P. & Palomares, M. The role of spatial frequency channels in letter identification. *Vision Research* **42**, 1165-1184 (2002).

47. Green, A.M. & Angelaki, D.E. Multisensory integration: resolving sensory ambiguities to build novel representations. *Current Opinion in Neurobiology* **20**, 353-360 (2010).

48. Oberman, L., Ramachandran, VS. Preliminary evidence for deficits in multisensory integration in autism spectrum disorders: the mirror neuron hypothesis. *social neuroscience* **3**, 348-355 (2008).

49. Hairston, W., Burdette, J., Flowers, D., Wood, F. & Wallace, M. Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Exp Brain Res.* **166**, 474-480 (2005).

50. Magnee, M.J.C.M., Oranje, B., van Engeland, H., Kahn, R.S. & Kemner, C. Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia* **47**, 1728-1732 (2009).

51. Toro, R., Konyukh, M., Delorme, R., Leblond, C., Chaste, P., Fauchereau, F., Coleman, M., Leboyer, M., Gillberg, C. & Bourgeron, T. Key role for gene dosage and synaptic homeostasis in autism spectrum disorders. *Trends in Genetics* **26**, 363-372 (2010).

52. DeAngelis, G.C., Ohzawa, I. & Freeman, R.D. Spatiotemporal organization of simple-cell receptive fields in the cat's striate cortex. I. General characteristics and postnatal development. *Journal of Neurophysiology* **69**, 1091-1117 (1993).

53. Abeles, M., Bergman, H., Margalit, E. & Vaadia, E. Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. *Journal of Neurophysiology* **70**, 1629-1638 (1993).

54. Klein, D.J., Depireux, D.A., Simon, J.Z. & Shamma, S.A. Robust Spectrotemporal Reverse Correlation for the Auditory System: Optimizing Stimulus Design. *Journal of Computational Neuroscience* **9**, 85-111 (2000).

55. Recanzone, G.H. & Sutter, M.L. The biological basis of audition. *Annual review of psychology* **59**, 119-42 (2008).

56. Macknik, S.L. Visual masking approaches to visual awareness. *Progress in brain research* **155**, 177-215 (2006).

57. Moore, B.C., Poon, P.W., Bacon, S.P. & Glasberg, B.R. The temporal course of masking and the auditory filter shape. *The Journal of the Acoustical Society of America* **81**, 1873-80 (1987).

58. Wilson, E.C., Reed, C.M. & Braida, L.D. Integration of auditory and vibrotactile stimuli: effects of frequency. *The Journal of the Acoustical Society of America* **127**, 3044-59 (2010).

59. Wilson, E.C., Reed, C.M. & Braida, L.D. Integration of auditory and vibrotactile stimuli: effects of phase and stimulus-onset asynchrony. *The Journal of the Acoustical Society of America* **126**, 1960-74 (2009).

60. Butler, J.S., Molholm, S., Fiebelkorn, I.C., Mercier, M.R., Schwartz, T.H. & Foxe, J.J. Common or redundant neural circuits for duration processing across audition and touch. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **31**, 3400-6 (2011).

61. Yau, J.M., Olenczak, J.B., Dammann, J.F. & Bensmaia, S.J. Temporal Frequency Channels Are Linked across Audition and Touch. *Current biology : CB* **19**, 561-566 (2009).

62. Munhall, K., Gribble, P, Sacco, L, Ward, M. Temporal constraints on the McGurk effect. . *Percept Psychophys.* **58**, 351-362 (1996).

63. Bertone, A., Mottron, L., Jelenic, P. & Faubert, J. Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain* **128**, 2430-2440 (2005).

64. Mongillo, E., Irwin, J., Whalen, D., Klaiman, C., Carter, A. & Schultz, R. Audiovisual Processing in Children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* **38**, 1349-1358 (2008).

65. Tanskanen, T., N√ § s√ § nen, R., Montez, T., P√ § √ § llysaho, J. & Hari, R. Face Recognition and Cortical Responses Show Similar Sensitivity to Noise Spatial Frequency. *Cerebral Cortex* **15**, 526-534 (2005).

66. Jemel, B., Mottron, L. & Dawson, M. Impaired Face Processing in Autism: Fact or Artifact? *Journal of Autism and Developmental Disorders* **36**, 91-106 (2006).

67. Powers, A.R., III, Hillock, A.R. & Wallace, M.T. Perceptual Training Narrows the Temporal Window of Multisensory Binding. *J. Neurosci.* **29**, 12265-12274 (2009).

68. Powers, A.R., Hevey, M. & Wallace, M. Neural correlates of multisensory perceptual learning. *Nat Neurosci (In Revision)*.

69. Zilbovicius, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y. & Boddaert, N. Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences* **29**, 359-366 (2006).

70. Zilbovicius, M., Boddaert, N., Belin, P., Poline, J.-B., Remy, P., Mangin, J.-F., Thivard, L., Barthelemy, C. & Samson, Y. Temporal Lobe Dysfunction in Childhood Autism: A PET Study. *Am J Psychiatry* **157**, 1988-1993 (2000).

71. Boddaert, N., Chabane, N., Gervais, H., Good, C.D., Bourgeois, M., Plumet, M.H., BarthÈlÈmy, C., Mouren, M.C., Artiges, E., Samson, Y., Brunelle, F., Frackowiak, R.S.J. & Zilbovicius, M. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. *Neuroimage* **23**, 364-369 (2004).

72. Molholm, S., Ritter, W., Murray, M.M., Javitt, D.C., Schroeder, C.E. & Foxe, J.J. Multisensory auditory-visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Cognitive Brain Research* **14**, 115-128 (2002).

73. Perrault, T.J., Vaughan, J.W., Stein, B.E. & Wallace, M.T. Superior Colliculus Neurons Use Distinct Operational Modes in the Integration of Multisensory Stimuli. *Journal of Neurophysiology* **93**, 2575-2586 (2005).

74. Mishra, J., Martinez, A, Sejnowski, TJ, Hillyard, SA. Early Cross-Modal Interactions in Auditory and Visual Cortex Underlie a Sound-Induced Visual Illusion. *J Neurosci.* **27**, 4120-4131 (2007).

75. Mishra, J., Martinez, A. & Hillyard, S.A. Cortical processes underlying sound-induced flash fusion. *Brain Research* **1242**, 102-115 (2008).

76. Butler, J.S., Molholm, S., Fiebelkorn, I.C., Mercier, M.R., Schwartz, T.H. & Foxe, J.J. Common or Redundant Neural Circuits for Duration Processing across Audition and Touch. *The Journal of Neuroscience* **31**, 3400-3406 (2011).

77. Chen, Y.-H., Edgar, J.C., Holroyd, T., Dammers, J., Thönneßen, H., Roberts, T.P.L. & Mathiak, K. Neuromagnetic oscillations to emotional faces and prosody. *European Journal of Neuroscience* **31**, 1818-1827 (2010).

78. Yuval-Greenberg, S. & Deouell, L.Y. What You See Is Not (Always) What You Hear: Induced Gamma Band Responses Reflect Cross-Modal Interactions in Familiar Object Recognition. *The Journal of Neuroscience* **27**, 1090-1096 (2007).

79. Senkowski, D., Molholm, S., Gomez-Ramirez, M. & Foxe, J.J. Oscillatory Beta Activity Predicts Response Speed during a Multisensory Audiovisual Reaction Time Task: A High-Density Electrical Mapping Study. *Cerebral Cortex* **16**, 1556-1565 (2006).

80. Senkowski, D., Schneider, T., Tandler, F. & Engel, A. Gamma-band activity reflects multisensory matching in working memory. *Experimental Brain Research* **198**, 363-372 (2009).

81. Grech, R., Cassar, T., Muscat, J., Camilleri, K., Fabri, S., Zervakis, M., Xanthopoulos, P., Sakkalis, V. & Vanrumste, B. Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation* **5**, 25 (2008).

82. Samaco, R.C., Hogart, A. & LaSalle, J.M. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Human Molecular Genetics* **14**, 483-492 (2005).

83. Scott-Van Zeeland, A.A., Abrahams, B.S., Alvarez-Retuerto, A.I., Sonnenblick, L.I., Rudie, J.D., Ghahremani, D., Mumford, J.A., Poldrack, R.A., Dapretto, M., Geschwind, D.H. & Bookheimer, S.Y. Altered Functional Connectivity in Frontal Lobe Circuits Is Associated with Variation in the Autism Risk Gene CNTNAP2. *Science Translational Medicine* **2**, 56ra80 (2010).

84. Mostafa, G. & AL-Ayadhi, L. A lack of association between hyperserotonemia and the increased frequency of serum anti-myelin basic protein auto-antibodies in autistic children. *Journal of Neuroinflammation* **8**, 71 (2011).

85. Wallace, M.T., Meredith, M.A. & Stein, B.E. Multisensory Integration in the Superior Colliculus of the Alert Cat. *Journal of Neurophysiology* **80**, 1006-1010 (1998).

86. Stein, B.E., Huneycutt, W.S. & Meredith, M.A. Neurons and Behavior: the same rules of multisensory integration apply. *Brain Research* **448**, 355-358 (1988).

87. Stein, B.E., Meredith, M.A., Huneycutt, W.S. & McDade, L. Behavioral Indices of Multisensory Integration: Orientation to Visual Cues is Affected by Auditory Stimuli. *Journal of Cognitive Neuroscience* **1**, 12-24 (1989).

88. Blake, R., Holopigian, K. & Wilson, H.R. Spatial-frequency discrimination in cats. *J. Opt. Soc. Am. A* **3**, 1443-1449 (1986).

89. Elhilali, M., Fritz, J.B., Klein, D.J., Simon, J.Z. & Shamma, S.A. Dynamics of Precise Spike Timing in Primary Auditory Cortex. *The Journal of Neuroscience* **24**, 1159-1172 (2004).

90. Depireux, D.A., Simon, J.Z., Klein, D.J. & Shamma, S.A. Spectro-Temporal Response Field Characterization With Dynamic Ripples in Ferret Primary Auditory Cortex. *Journal of Neurophysiology* **85**, 1220-1234 (2001).

91. Fritz, J., Shamma, S., Elhilali, M. & Klein, D. Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex. *Nat Neurosci* **6**, 1216-1223 (2003).

APPENDIX

Description of Factors in Appendix

Key Factors from Chapters Two and Three

A_{TOJ}	Threshold for auditory temporal order judgment task in ms
V_{TOJ}	Threshold for visual temporal order judgment task in ms
TOJ_{win}	Temporal window for multisensory temporal order judgment task measured as the time span across which the participant showed improvement in accuracy greater than zero
TOJ_{max}	The maximum improvement in accuracy for the multisensory temporal order judgment task
FB_{win}	Temporal window for flash-beep task measured as the time span across which the participant showed reports of the flash-beep illusion greater than zero
FB_{max}	The maximum report of the flash-beep illusion

Key Factors from Chapters Four and Five

A_{rxn}	Average response time for auditory-only trials during the detection task
V_{rxn}	Average response time for visual-only trials during the detection task
Detect_{win}	Temporal window of integration for the multisensory detection task as determined using a sigmoid fit (see chapter four)
Detect_{imp}	Average improvement in response time for multisensory trials as compared to unisensory trials for -60 – 100 ms SOA’s (see chapter four)
A_{CB}	Auditory critical bandwidth as determined via staircase (see chapter five)
V_{CB}	Visual critical bandwidth as determined via staircase (see chapter five)
A_{min}	Auditory threshold for detecting pure tone at smallest notch width (10 Hz)
V_{min}	Visual threshold for detecting gabor at smallest notch width (0 octaves)
A_{max}	Auditory threshold for detecting pure tone at largest notch width (1600 Hz)
V_{max}	Visual threshold for detecting gabor at largest notch width (4 octaves)

Correlations

		A_{TOJ}	V_{TOJ}	TOJ_{win}	FB_{max}	FB_{win}
V_{TOJ}	r	**0.634****				
	p	**<0.001**				
TOJ_{win}	r	0.132	0.090			
	p	0.351	0.486			
FB_{max}	r	**0.434****	**0.350***	**0.028**		
	p	**0.009**	**0.031**	0.865		
FB_{win}	r	**0.487****	**0.476****	**0.012**	**0.549****	
	p	**0.003**	**0.003**	0.945	**<0.001**	
TOJ_{max}	r	0.157	0.091	**0.780****	0.186	-0.016
	p	0.271	0.483	**<0.001**	0.264	0.925

Figure A1. Correlational matrix for key factors from chapters two and three.

“r” indicates Pearson correlation coefficient.

$* \ p < 0.05$

$** \ p < 0.01$

		V_{rxn}	A_{rxn}	$Detect_{win}$	$Detect_{imp}$	V_{CB}	A_{CB}	V_{min}	V_{max}	A_{min}
A_{rxn}	r	**0.885****								
	p	**<0.001**								
$Detect_{win}$	r	0.144	0.048							
	p	0.390	0.775							
$Detect_{imp}$	r	0.193	**0.266***	0.010						
	p	**0.014**	**0.042**	0.953						
V_{CB}	r	-0.219	-0.255	-0.277	-0.281					
	p	0.244	0.174	0.238	0.133					
A_{CB}	r	-0.493	**-0.611***	-0.187	**-0.593***	0.150				
	p	0.073	**0.020**	0.581	**0.025**	0.610				
V_{min}	r	**0.306***	0.212	0.109	-0.278	**-0.644****	-0.206			
	p	**0.049**	0.177	0.579	0.075	**0.000**	0.544			
V_{max}	r	-0.109	-0.168	-0.061	-0.125	0.045	0.181	0.230		
	p	0.501	0.300	0.767	0.442	0.825	0.594	0.154		
A_{min}	r	0.076	0.178	0.136	-0.081	**0.423***	**-0.668***	-0.148	-0.088	
	p	0.647	0.278	0.508	.0623	**0.045**	**0.018**	0.402	0.628	
A_{max}	r	0.060	0.011	**0.454***	-0.280	0.269	0.174	0.251	0.122	0.096
	p	0.722	0.949	**0.020**	0.093	0.193	0.590	0.152	0.497	0.585

Figure A2. Correlational matrix for key factors from chapters four and five.

"r" indicates Pearson correlation coefficient.

* $p < 0.05$

** $p < 0.01$

Scatterplots of Significant Correlations

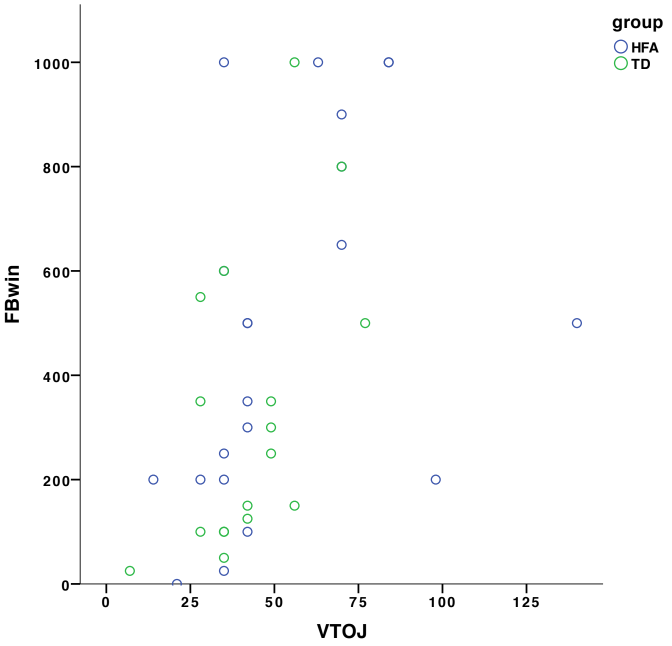


Figure A3. Scatterplot of $V_{TOJ\ and}$ $FB_{win.}$

Visual TOJ thresholds are positively associated with the temporal window of integration for the flash-beep task indicating that visual temporal acuity is associated with multisensory temporal processing.

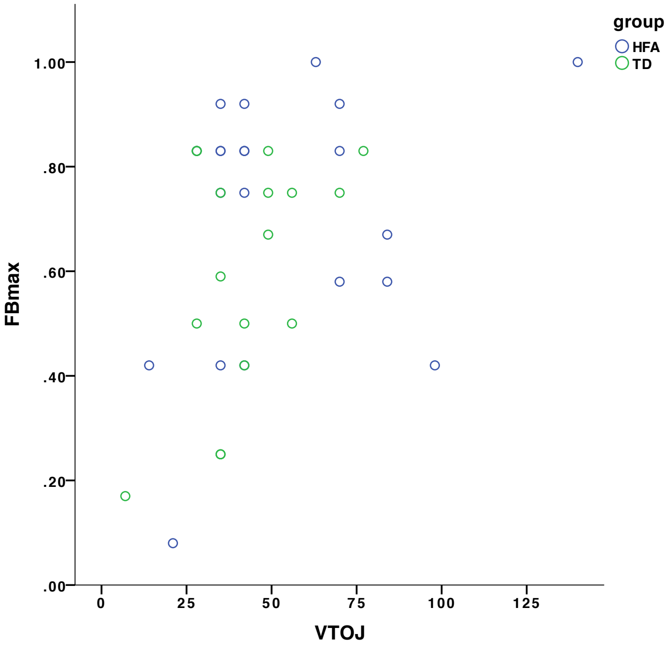


Figure A4. Scatterplot of $V_{TOJ\ and}$ $FB_{max.}$

Visual TOJ thresholds are positively associated with the maximum report of the flash-beep illusion indicating that visual temporal acuity is associated with the degree of multisensory integration.

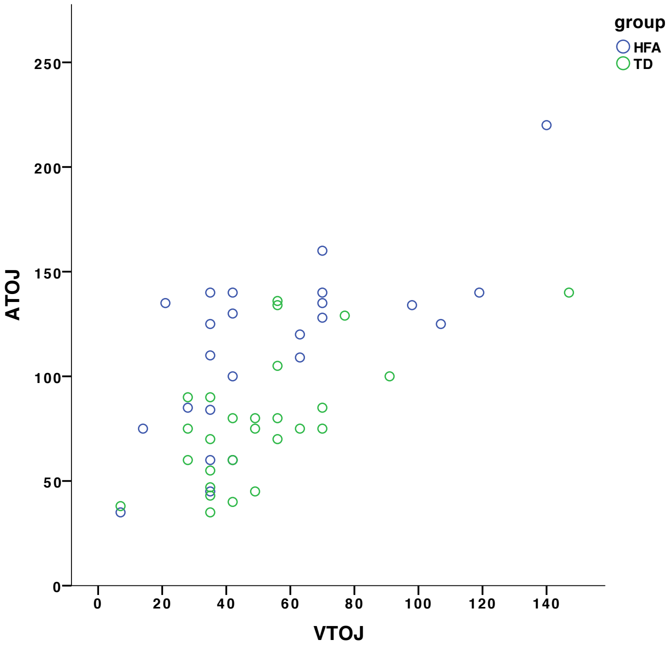


Figure A5. Scatterplot of V_{TOJ} and A_{TOJ}.

Visual TOJ thresholds are positively associated with auditory TOJ thresholds indicating that visual temporal acuity is associated with auditory temporal acuity.

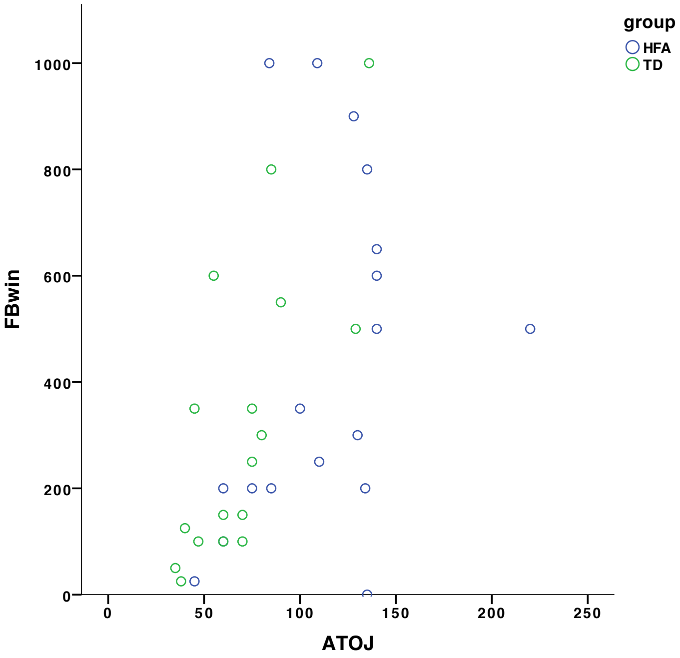


Figure A6. Scatterplot of A_{TOJ} and FB_{win}.

Auditory TOJ thresholds are positively associated with the temporal window of integration for the flash-beep task indicating that auditory temporal acuity is associated with multisensory temporal processing.

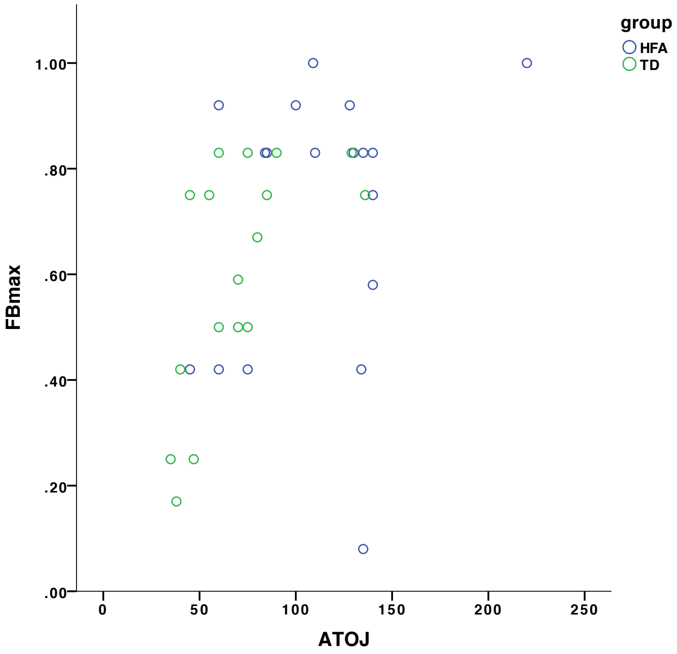


Figure A7. Scatterplot of A_{TOJ} and FB_{max}.

Auditory TOJ thresholds are positively associated with the maximum report of the flash-beep illusion indicating that auditory temporal acuity is associated with the degree of multisensory integration.

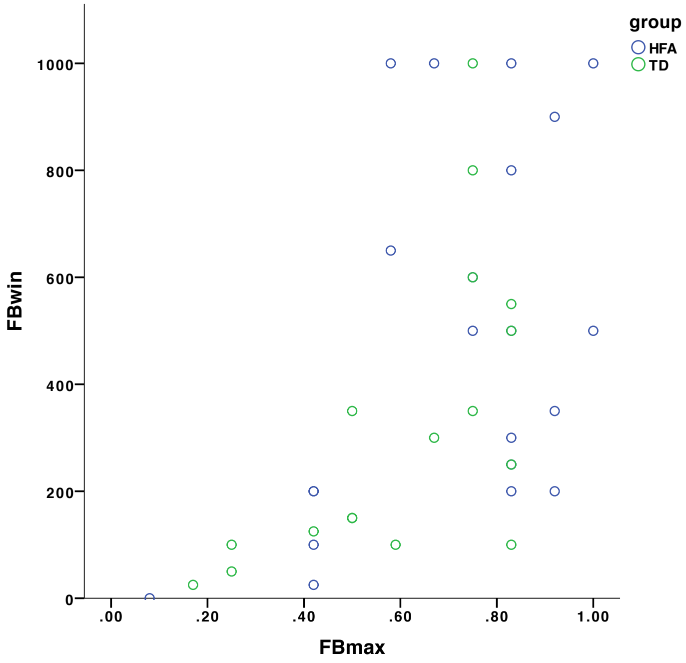


Figure A8. Scatterplot of FB_{win} and FB_{max}.

The temporal window of integration for the flash-beep task is associated with the maximum report of the flash-beep illusion indicating that the degree of multisensory integration is associated with the temporal processing multisensory information.

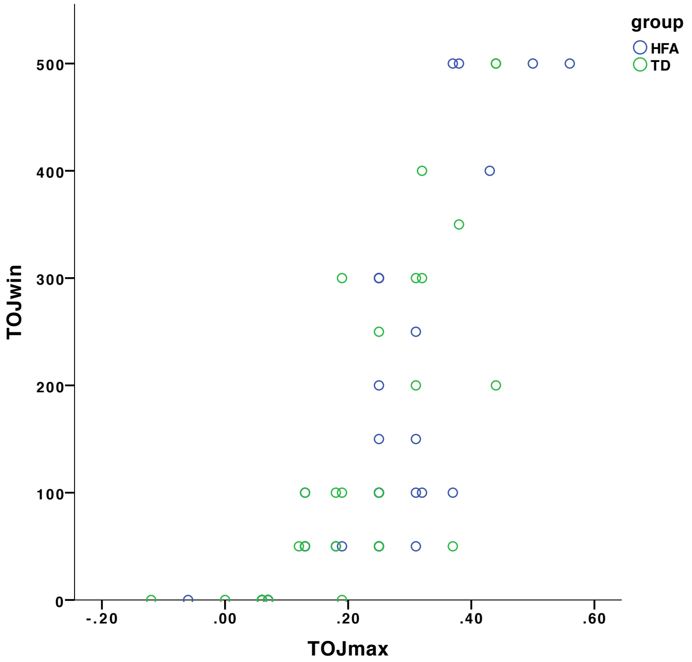


Figure A9. Scatterplot of TOJ$_{win}$ and TOJ$_{max}$.

The temporal window of integration for the multisensory TOJ task is associated with the maximum report of the flash-beep illusion indicating that the degree of multisensory integration is associated with the temporal processing multisensory information.

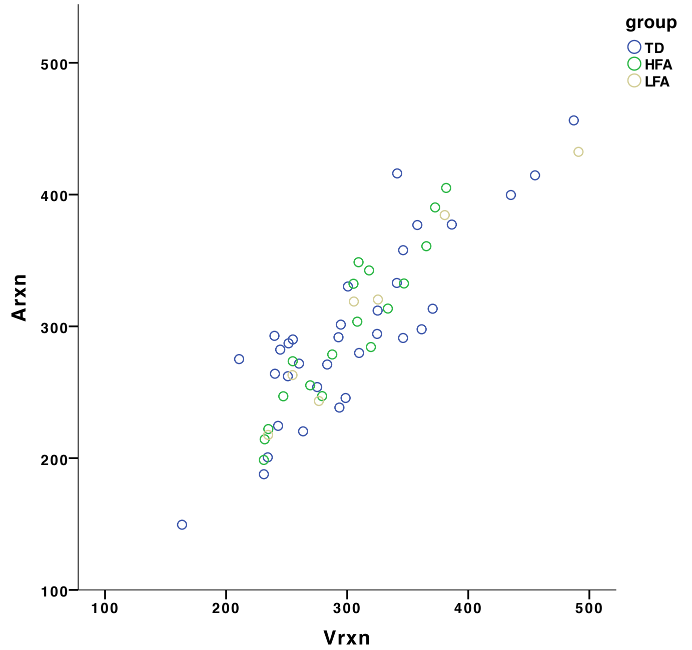


Figure A10. Scatterplot of V$_{rxn}$ and A$_{rxn}$.

The average response time for visual-only trials is highly correlated with the average response time for auditory-only trials in the detection task.

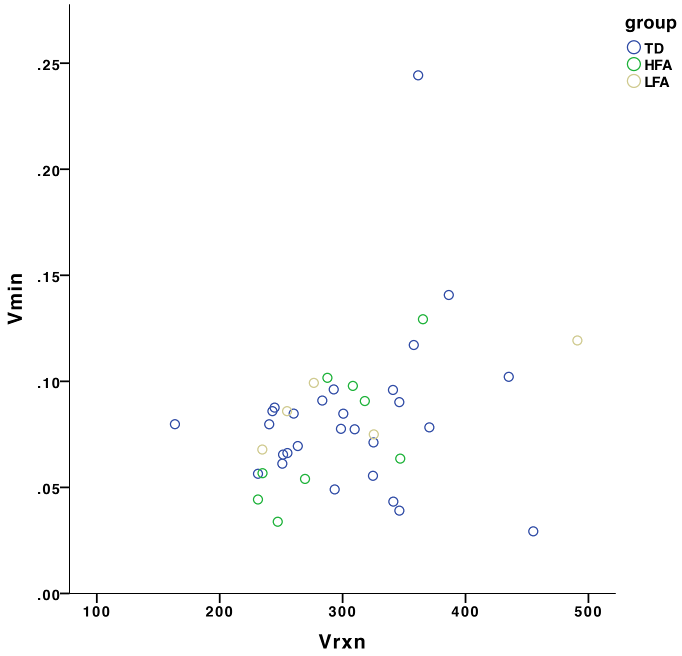


Figure A11. Scatterplot of V_{rxn} and V_{min}.

The average response time for visual-only trials for the detection task is associated with the threshold for detecting a gabor in visual white noise indicating that visual perceptual ability may general across tasks.

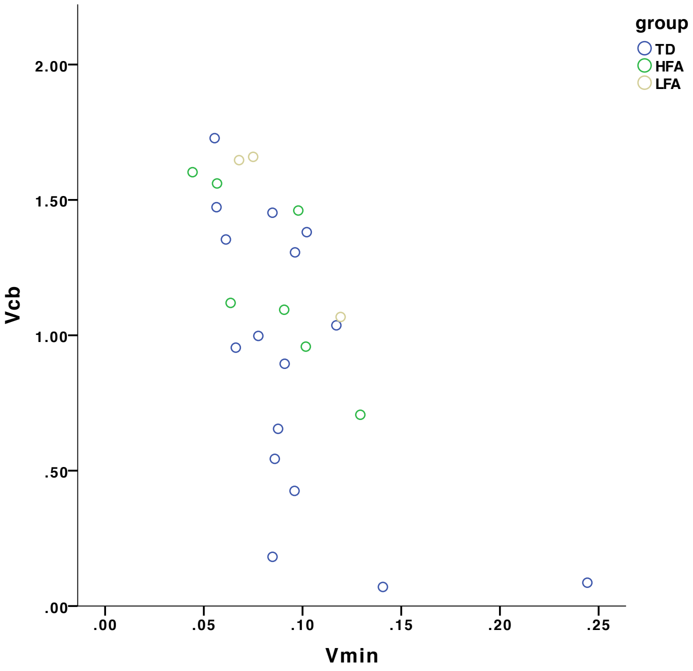


Figure A12. Scatterplot of V_{CB} and V_{min}.

The visual critical bandwidth is associated with the threshold for detecting a gabor in visual white noise indicating that the visual CB is associated with efficiency of extracting a visual signal from noise.

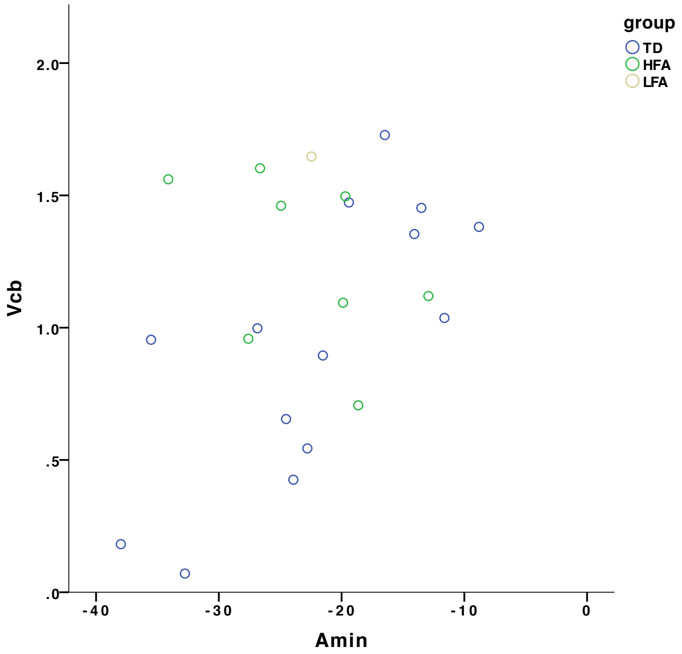


Figure A13. Scatterplot of $V_{CB\ and}\ A_{min.}$

The visual critical bandwidth is associated with the threshold for detecting a pure tone in filtered noise with the smallest notch width indicating that perceptual abilities may general across modalities.

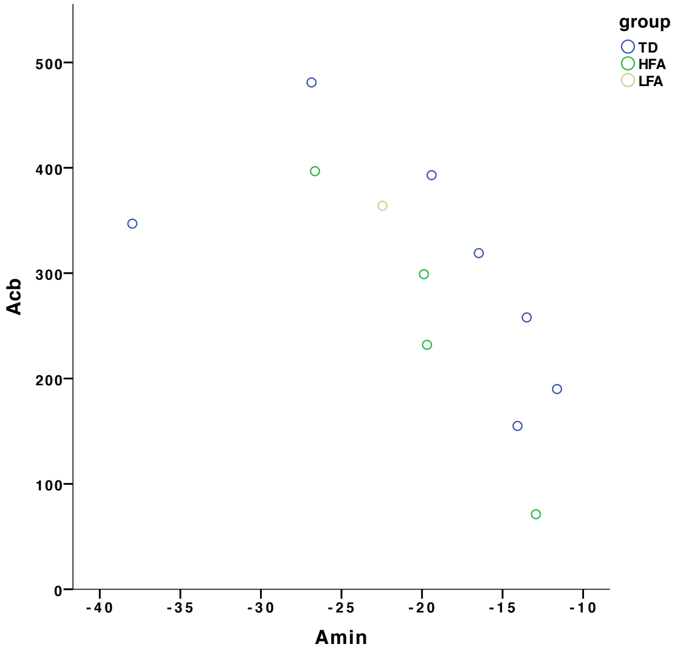


Figure A14. Scatterplot of $A_{CB\ and}\ A_{min.}$

The auditory critical bandwidth is associated with the threshold for detecting a pure tone in filtered noise with the smallest notch width indicating that the auditory CB is associated with efficiency of extracting an auditory signal from noise.

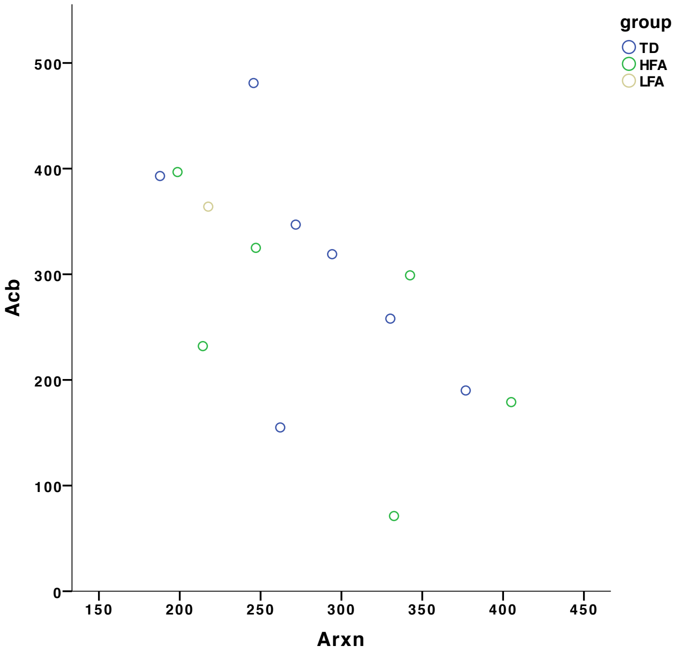


Figure A15. Scatterplot of A_{rxn} and A_{CB}.

The average response time for auditory-only trials for the detection task is associated with the auditory CB indicating that visual perceptual ability may general across tasks.

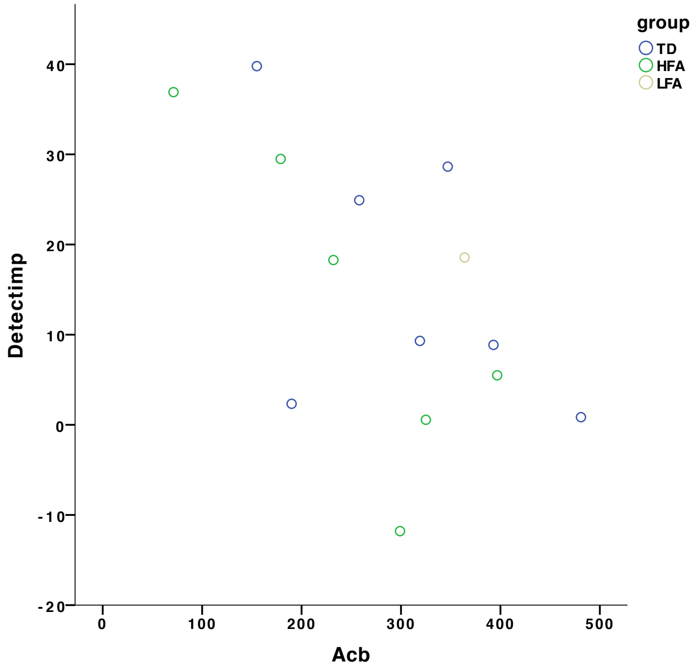


Figure A16. Scatterplot of A_{CB} and $Detect_{imp}$.

The auditory CB is associated with the average improvement in response time for multisensory trials with a short SOA indicating that the efficiency of processing within the auditory system is associated with the degree of multisensory integration.

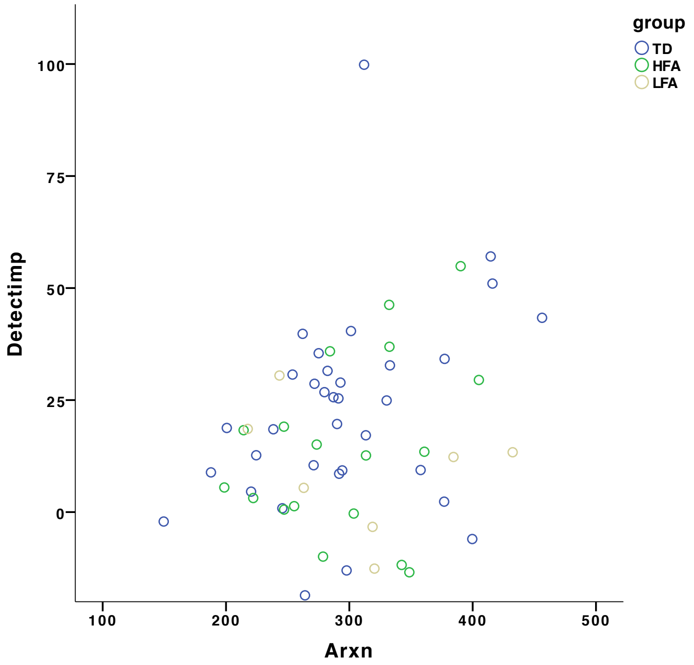


Figure A17. Scatterplot of A_{rxn} and $Detect_{imp}$.

The average improvement in response time for multisensory trials with a short SOA is associated with the average response time for auditory-only trials in the detection task indicating that longer unisensory response times may result in a greater potential for improvement with multisensory stimuli.

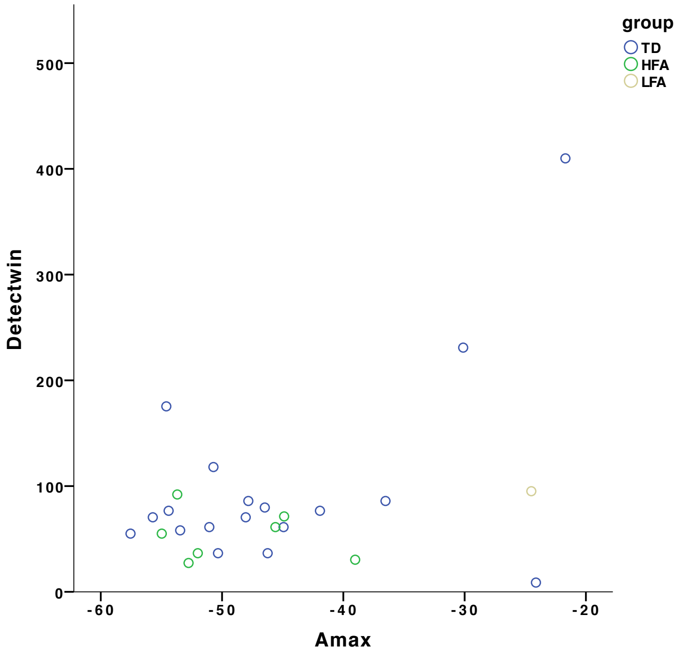


Figure A18. Scatterplot of A_{max} and $Detect_{win}$.

The threshold for detecting a pure tone in filtered noise with the largest notch width is associated with the temporal window of multisensory integration for the detection task indicating that the efficiency of the auditory system in extracting a signal from noise may be associated with temporal multisensory processing.

Skewness and Kurtosis of Key Factors

Factors	**Skewness**		**Kurtosis**	
	Statistic	Std. Error	Statistic	Std. Error
TOJ_{win}	**_1.138*_**	**_.297_**	.099	.586
A_{TOJ}	.438	.330	.242	.650
V_{TOJ}	**_1.186*_**	**_.304_**	**_1.308*_**	**_.599_**
TOJ_{max}	.031	.304	-.215	.599
FB_{win}	.645	.383	-.854	.750
FB_{max}	-.725	.383	-.282	.750

Figure A19. Characterization of the distribution of key factors from chapters two and three.

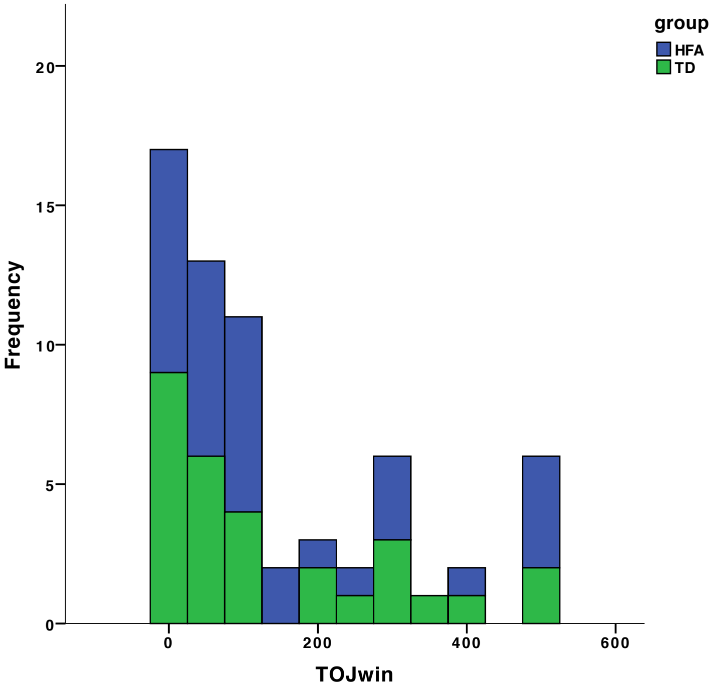
* indicates significant effect of either Skewness or Kurtosis in the distribution.

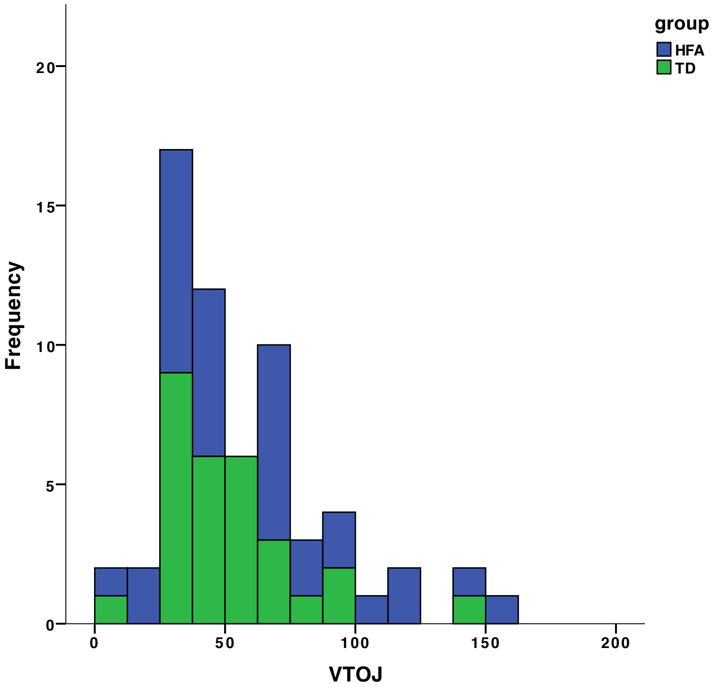
Factors	Skewness		Kurtosis	
	Statistic	Std. Error	Statistic	Std. Error
V_{rxn}	***.799****	***.311***	.847	.613
A_{rxn}	.316	.311	-.176	.613
Detect_{win}	***2.323****	***.383***	***6.474****	***.750***
Detect_{imp}	***.983****	***.311***	***2.595****	***.613***
V_{cb}	-.638	.427	-.612	.833
A_{cb}	-.249	.597	-.344	1.154
V_{min}	***2.327****	***.365***	***9.625****	***.717***
V_{max}	***2.083****	***.374***	***4.737****	***.733***
A_{min}	-.430	.378	-.663	.741
A_{max}	.716	.388	.031	.759

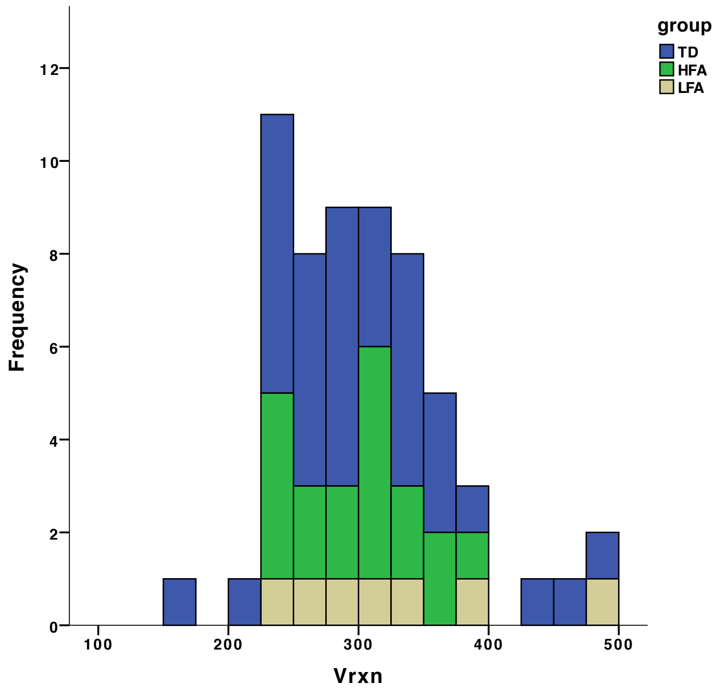
Figure A20. Characterization of the distribution of key factors from chapters four and five.

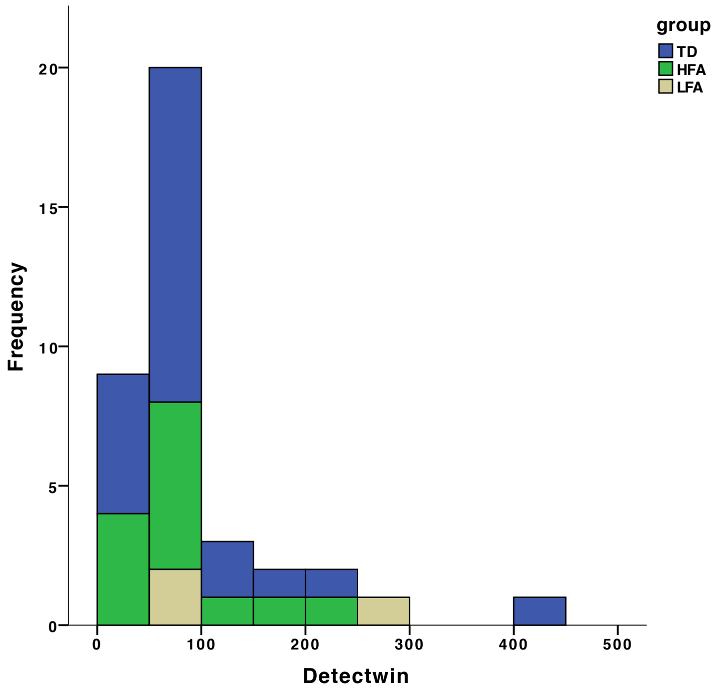
* indicates significant effect of either Skewness or Kurtosis in the distribution.

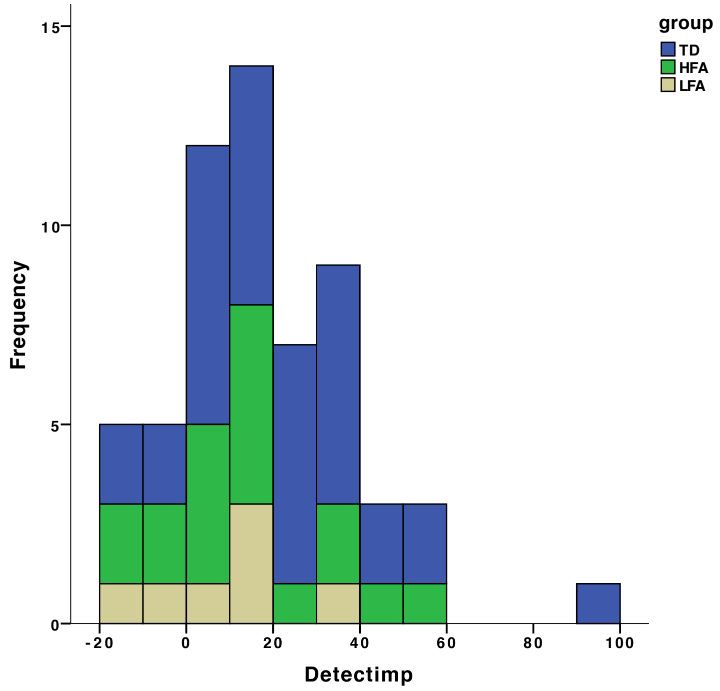
Histograms of Non-Normal Distributions



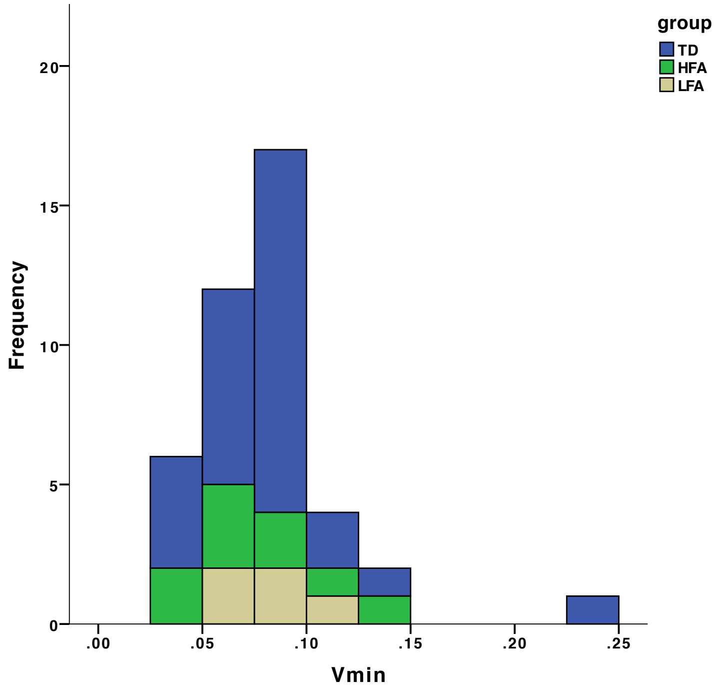



group
TD
HFA
LFA
Frequency
0
2
4
6
8
10
12
100
200
300
400
500
Vrxn

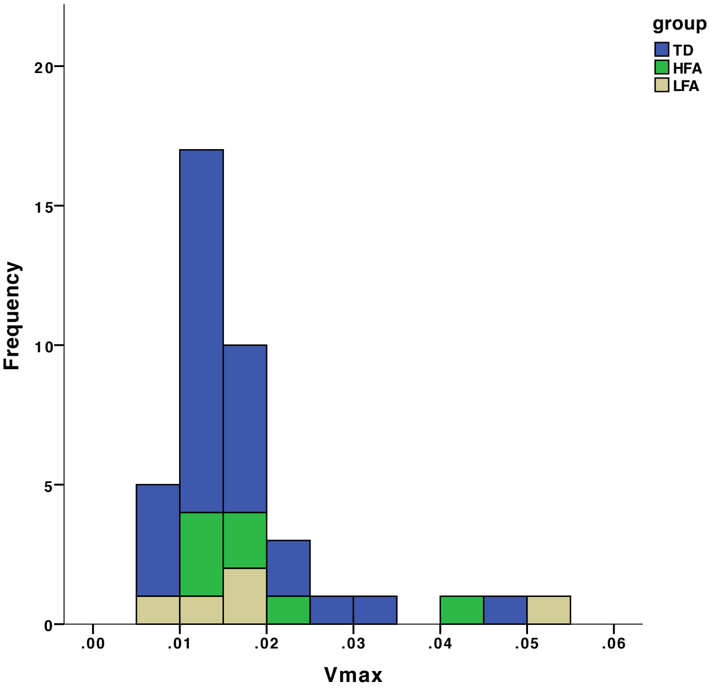

group
TD
HFA
LFA
Frequency
0
5
10
15
20
0
100
200
300
400
500
Detectwin



group
TD
HFA
LFA
Frequency
0
5
10
15
-20
0
20
40
60
80
100
Detectimp



group
TD
HFA
LFA
Frequency
0
5
10
15
20
.00
.05
.10
.15
.20
.25
Vmin


group
TD
HFA
LFA
Frequency
0
5
10
15
20
Vmax
.00
.01
.02
.03
.04
.05
.06