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Dissertation

CHARACTERIZATION OF CENTRAL AUDITORY PROCESSING IN MINIMALLY AND LOW VERBAL ADOLESCENTS WITH AUTISM

by

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B.S., Tufts University, 2012

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

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DEDICATION

This work is for every family of someone with autism who wants answers, including my own.

ACKNOWLEDGMENTS

Thank you to my advisors, Drs. Helen Tager-Flusberg and Barbara Shinn-Cunningham, for your tireless guidance and commitment to my success. I also want to give a special thank you to Dr. Le Wang for his incredible mentorship over the years. I am extremely grateful to Drs. Tyler Perrachione, Gerald Kidd, and Sudha Arunachalam for their support in this doctoral work. Thank you to those in the Graduate Program for Neuroscience, especially Dr. Shelley Russek, Dr. Sandi Grasso, and (almost Dr.) Terri Scott for your support and guidance throughout the past five (plus) years. Thank you to all the members of ANL, CARE, and CNR for your friendship and support through this process. A special shout out to all the research assistants who assisted in the collection of this data. Thank you also to my past advisors, Drs. Audrey Thurm, Ashura Buckley, Chip Gidney, and Richard Griffin for your efforts to enhance my training as an autism researcher. Thank you to my family and friends who have filled me with love in times of stress. This research would not have been possible without funding from the Graduate Program for Neuroscience, the National Science Foundation, the National Institutes of Health, and Autism Speaks. Finally, thank you to all who participated in the studies described – your commitment to the expansion of scientific research on ASD allowed this work to be possible.

CHARACTERIZATION OF CENTRAL AUDITORY PROCESSING IN MINIMALLY AND LOW VERBAL ADOLESCENTS WITH AUTISM

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Boston University School of Medicine, 2020

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder in which individuals demonstrate deficits in social communication and repetitive or restricted behaviors or interests. About one-third never attain fluent expressive language and remain minimally or low verbal (ASD-MLV). We hypothesized that central auditory processing is particularly disrupted in ASD-MLV given the shared neural substrates of sound processing and language. To address this hypothesis, we conducted four empirical studies designed to capture neural and behavioral correlates of central auditory processing in children and adolescents who were either typically developing (TD), verbally fluent with ASD (ASD-V), or ASD-MLV. Our first study established that adult-like neural indices of sound organization as measured by mismatch responses (MMRs) during a passive stream segregation task were not observable until adolescence in TD participants, ages 3 to 21 (N=65). Findings led us to focus subsequent studies on adolescents. In our second study, we conducted a meta-analysis of experiments that had compared MMRs between TD and ASD samples (N=721). We identified that while there was some evidence suggesting that perceptual sound organization (as evidenced by MMR) was more dysfunctional in those with ASD, more research was needed to validate

this pattern in adolescents and low verbal samples. In our third study (N=83), we determined that atypical auditory behaviors occurred most often in those with ASD with combined expressive and receptive language impairments; furthermore, the percentage of time exhibiting such behaviors was associated with weaker MMRs. In our final study (N=74), we quantified neural orienting responses to one's own name in a multispeaker setting – a task that requires higher-order stream segregation and social auditory attention – in adolescents. We found that responses were weaker in ASD-MLV compared to ASD-V and TD participants. In addition, strength of response in those with ASD was negatively correlated with parent-reported signs of auditory-specific attentional deficits, as measured by the Short Sensory Profile Auditory Filtering Subscale. With this dissertation, we found atypical neural indices of auditory processing in ASD-MLV adolescents and discuss theoretical implications for why central auditory processing might be particularly pronounced in the ASD-MLV phenotype.

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LIST OF COMMON ABBREVIATIONS

AEP ..... Auditory evoked potential

ASD ..... Autism spectrum disorder

ASD-MLV ..... Minimally and low verbal autism

ASD-V ..... Verbally fluent autism

CAPD ..... Disruptions in central auditory processing

EEG ..... Electroencephalography

EFR ..... Envelope following response

ERP ..... Evoked response potentials

IQ ..... Intelligence Quotient

LPP ..... Late posterior positive shift

MMN ..... Mismatch negativity

MMR ..... Mismatch response

NVIQ ..... Nonverbal Intelligence Quotient

OON ..... One's own name

PLV ..... Phase-locking value

PSD ..... Power spectral density

SN ..... Stranger's name

TD ..... Neurotypically developing

VIQ ..... Verbal Intelligence Quotient

CHAPTER ONE: INTRODUCTION

Disruptions in central auditory processing (CAPDs) are commonly noted in those with autism (ASD) (for review, see Ocak, Eshraghi, Danesh, Mittal, & Eshraghi, 2018). CAPDs in ASD are hypothesized to originate at least in part from difficulties perceptually organizing and orienting to sound – including the ability to differentiate and group acoustic features and prioritize groups of features that are important (Dawes & Bishop, 2008). This link between the CAPDs and ASD is based almost exclusively on research conducted with verbally fluent children and adults (ASD-V) (Ocak et al., 2018). However, given the shared neural substrates of sound processing and language, it is important to study CAPDs in those with severe language deficits. In this dissertation, I successfully test neural indices of central auditory processing in those who have historically not been included in studies on sound processing – minimally and low verbal adolescents with ASD (ASD-MLV). Furthermore, I provide evidence of atypical auditory processing mechanisms in ASD-MLV adolescents and pinpoint several features of the disorder that are associated with atypical neural indicators of sound processing.

In this chapter, I review several key ways in which humans typically organize sounds in complex auditory scenes and then describe ways in which we can use neuroimaging tools to quantify the neural systems underlying these processes. Next, I introduce ASD and describe what is required for researchers to address gaps in what is known about ASD-MLV. I then describe evidence that there are auditory processing deficits in ASD and what is known about those deficits specifically in ASD-MLV. I propose that atypical, low-level perceptual organization of sounds might be particularly

disordered in ASD-MLV and that this atypical organization is related to atypical receptive language and atypical auditory behaviors. Finally, I describe the objectives of each dissertation chapter and introduce the research conducted to meet those objectives.

Sound Organization and Stream Segregation

Successful central auditory processing requires the perceptual organization of sounds, in which humans effortlessly and automatically monitor their environment, grouping all incoming acoustic information into "auditory objects" based on the acoustic spectral and temporal content of the sounds (Teki, Chait, Kumar, von Kriegstein, & Griffiths, 2011). By directing our focus to whatever auditory object is important in the scene, we reserve our brain's computational power for the comprehensive processing of only that most relevant information. Therefore, the transfer of information from the cochlea, to the brainstem, to the thalamus, to the primary auditory cortex, and ultimately to associated areas for higher-order processing is optimized to ensure high spectral and temporal resolution of relevant auditory information by amplifying relevant information and suppressing extraneous information (Fritz, Elhilali, David, & Shamma, 2007; Shinn-Cunningham, 2008). If the organization and filtering of incoming signals fails at any point in this pathway, the information transferred to higher-order processing will include extraneous and unorganized information, resulting in a signal that is convoluted and difficult to decipher (Bregman, 1990).

This ability to listen to a mixture of sounds from distinct sources, select a single auditory object from that mixture, and then process that object to extract its meaning –

known as auditory scene analysis – is critical for humans to process aural language (Shinn-Cunningham, 2008). From birth, the ability to discriminate phonemes, stress patterns, and word boundaries provides a foundation for infants to acquire lexicon and syntax (Friederici, 2005). Making use of statistical regularities within one's auditory environment is likely an essential precursor to language development (Kujala, Lepistö, & Näätänen, 2013; Saffran, Newport, Aslin, Tunick, & Barrueco, 1997; Toro, Sinnett, & Soto-Faraco, 2005). These processes remains important when processing aural language after acquisition, as well, as humans must continue to detect subtle differences in sounds to parse language for semantic and pragmatic meaning (Friederici, 2011; Scott, 2005).

But, detection of such regularities likely relies on successful auditory scene analysis and it is through auditory scene analysis that humans successfully navigate complex auditory environments. For instance, in multispeaker settings, humans must identify and follow the content of one speaker's voice while filtering out other sounds in the environment, especially those that are similar temporally and/or spectrally. Humans must also passively monitor their environment so that their attention can be elicited and directed when they detect salient speech or other important sounds, even when they are not actively listening for auditory events.

Neural Measures that Assess the Organization and Orientation to Important Sounds

One can capture the electrical activity generated during tasks that require perceptual organization of sounds with a technique known as electroencephalography

(EEG). With this technique, electrode sensors are placed on the scalp to measure the voltage changes that result from neural activity. Some neural responses to sound can be observed even in passive settings, when the listener's attention is directed elsewhere.

Obligatory neural responses evoked by auditory stimuli are known as auditory evoked potentials (AEPs). AEPs originate from locations all along the auditory pathway, from the brainstem to primary auditory cortex to higher-order cortical regions. Within these automatic neural responses, there are components that occur when listeners detect changes in auditory patterns. This neural response is described as a mismatch response (also known as mismatch negativity and abbreviated as either MMR or MMN). Paradigms that measure auditory MMR are typically designed to have deviant, rare sounds that differ perceptually from standard, regularly occurring sounds on one or more acoustic features (such as intensity or pitch) (Näätänen, Gaillard, & Mäntysalo, 1978). The size of the MMR often indexes the degree to which a listener has built up a memory trace of an ongoing auditory pattern and detects a deviation from that trace (Näätänen et al., 1978). It can also can an index the extent to which a sound "grabs" the listener as salient or important (Näätänen, Kujala, & Winkler, 2011). This neural response is detected on the scalp's frontal-central midline from a young age and in general is quantified around 200 ms following stimulus onset (Haesen, Boets, & Wagemans, 2011). Measures of MMR have been associated with the discrimination of sounds in fundamental ways that guide language acquisition and language processing (Dehaene-Lambertz & Dehaene, 1994; Friederici, 2005).

The process of organizing sounds into perceptually distinct units, or sound

streams, identified as coming from distinct sources is often described as “stream segregation” (Bregman, 1990; Cherry, 1953; Wood & Cowan, 1995). Stream segregation can be quantified with measures of MMR when a second auditory stream complicates the scene. The extent to which a listener has successfully separated two streams as separate entities can be measured by the strength of an MMR in response to a deviant in one stream, despite other irregular, deviants occurring in a second, overlaid stream (Sussman, Bregman, Wang, & Khan, 2005).

In addition to the MMR, other neural indices can be used to measure the degree to which an individual has oriented to a salient sound. For instance, the P3, a positive parietal peak occurring approximately 250-500 ms after stimulus onset, and the LPP, a long-lasting late positive parietal shift from 300 to 800 ms, is evoked when individuals switch their attention towards a salient sound. Of note for this dissertation, the LPP is evoked in response to one’s own name (OON), in comparison to stranger’s names (SN), in both attentive and inattentive states (Höller et al., 2011; Fabien Perrin et al., 2005; Tacikowski, Brechmann, & Nowicka, 2013). Because these neural components are evoked so long after sound onset, they are thought to be more greatly impacted by top-down cognitive processes than earlier neural indices like the MMR.

Neural Indices of Central Auditory Processing in Neurotypical Children and Adolescents

The MMR index is a useful experimental measure to use with children because it does not require a high degree of overt attention or active participation from the listener.

In fact, the neural components that index the MMR have been reliably observed by researchers in infants (Choudhury, Parascando, & Benasich, 2015). Therefore, it should theoretically be possible to use the MMR in a dual-stream setting to assess processes of stream segregation in children. However, to our knowledge, the measurement of the MMR to assess automatic stream segregation has not been considered systematically across childhood (Werner, 2017).

We suspect that the process of automatic stream segregation might not be as stable and effortless in children as it is in adults. Between the ages of 7 and 12, there are known structural changes in synapse connections along the auditory pathway that make encoding and organization of sounds more efficient (Moore & Guan, 2001; Moore et al., 1995; Su et al., 2008). The hypothesis that the systems guiding stream segregation are not completely established in middle childhood is supported by evidence showing that school-aged children require a larger pitch separation to demonstrate adult-like MMRs during passive task performance, when attention is directed elsewhere, even though they show adult-like MMRs during active task performance, when attention is directed towards the sounds (Sussman & Steinschneider, 2009). Further investigation of age-related changes in the MMR during passive stream segregation is needed to confirm if or at what point in development this measure becomes a reliable indicator of successful automatic stream segregation.

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder estimated to affect 1 in 59 individuals in the United States (CDC, 2018). It is characterized in the Diagnostic Statistical Manual (5th Edition; DSM-5) by persistent deficits in social communication and atypical patterns of response to restricted interests and sensory inputs (American Psychiatric Association, 2013). Deficits are not obvious during infancy, but there are several early behavioral signs of the disorder in the first two years of life. These include: 1) reduced response to one's own name and atypical joint attention as demonstrated by reduced eye contact, pointing, and imitation, 2) low interest in social interaction and delayed acquisition of language, and 3) repetitive or restricted interests, play, and responses to sensory inputs. Identification of early signs of atypical development can help facilitate access to early intervention, but the disorder is not reliably diagnosed until at least 18 months.

Evaluation of ASD symptoms as defined by the DSM-5 is commonly determined with gold-standard measures like the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012). Diagnosis is sensitive to clinical judgment thresholds defined by clinicians and researchers. No brain-based test has yet been found that is sensitive enough to use for diagnostic purposes. With many delays in the identification of the disorder, the median age of diagnosis is around 4.5 years old in the United States (Estes, St John, & Dager, 2019). Challenges in identifying the disorder are only exacerbated by the extremely high variability in syndrome presentation and high overlap with other disorders. For instance, ASD has high comorbidity with attention-deficit/hyperactive

disorder (Joshi et al., 2013) and intellectual impairment (Matson & Shoemaker, 2011). Language disorders are also highly prevalent and are categorized as an accompaniment to the primary ASD diagnosis.

Uncovering the etiology of the disorder has been only further complicated by complex genetic traits and widespread disruptions to large-scale brain networks. Autism is characterized as a polygenetic disorder, with mutations in multiple genes leading to atypical microscopic synaptic development (Bourgeron, 2009; Ebrahimi-Fakhari & Sahin, 2015; Zikopoulos & Barbas, 2013). Aberrant synaptic development causes major, system-level global disruptions in neural activity that can be observed both during rest and during specific tasks directly related to social and sensory processing (Belmonte et al., 2004). Systems are often described as having an overarching imbalance of excitatory to inhibitory activity (Casanova, 2006; Rubenstein & Merzenich, 2003). It has been proposed that these disruptions originate from unsynchronized evoked cortical responses and a decreased inhibition of neural firing (Rubenstein & Merzenich, 2003), which leads to an excess of neural noise and ineffective signaling of information (Dinstein et al., 2012).

With respect to brain pathology in ASD, regions of interest include the brainstem and cerebellum, the limbic system, primary sensory cortices, and the superior temporal sulcus (Dinstein et al., 2012; Nickl-Jockschat et al., 2012). Abnormalities in the cerebellum and primary sensory cortices are promising explanations for low-level perceptual and sensory symptoms observed in the disorder (Marco, Hinkley, Hill, & Nagarajan, 2011). Limbic system abnormalities might explain differences in emotional

processing and social reward (Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010), along with sensory input processing. Abnormalities in the superior temporal sulcus are considered critical for other core symptoms of the disorder, including the interpretation of socially meaningful information and perception (e.g., understanding others' actions and mental states relative to one's own), language processing, and audiovisual integration and attention (Deen, Koldewyn, Kanwisher, & Saxe, 2015).

Minimally and Low Verbal Autism (ASD-MLV)

Despite the significant increase in ASD research over the past several decades, we know shockingly little about the third of individuals with ASD (roughly 1 in 180 people in the United States) who are minimally or low verbal (ASD-MLV) (Tager-Flusberg & Kasari, 2013). These are individuals who remain unable to communicate with fluent expressive language after the age of 5, when the critical window for language acquisition narrows (Tager-Flusberg & Kasari, 2013). Expressive language impairments are complex, and the origins are often unknown. It has been proposed that, for some, abnormal central auditory processing produces receptive language impairments, which then underlie expressive language deficits (Matsuzaki et al., 2019). Language deficits could also be caused by oral-motor deficits like apraxia (Chenausky, Brignell, Morgan, & Tager-Flusberg, 2019) and/or nonverbal cognitive deficits (Hinzen, Slušná, Schroeder, Sevilla, & Vila Borrellas, 2019; Luyster, Kadlec, Carter, & Tager-Flusberg, 2008; Thurm, Lord, Lee, & Newschaffer, 2007). There is also wide variability in receptive language abilities (Rapin, Dunn, Allen, Stevens, & Fein, 2009) and nonverbal

intelligence (Munson et al., 2008) within the ASD-MLV group. Attention disorders are pervasive in ASD-MLV individuals, and within this subgroup, nonverbal cognitive abilities negatively correlate with symptoms of attention-deficit/hyperactive disorder (Plesa Skwerer, Joseph, Eggleston, Meyer, & Tager-Flusberg, 2019). Furthermore, intervention on attentional skills related to social orienting and joint attention hold promise in facilitating social communication outcomes in ASD-MLV children (Goods, Ishijima, Chang, & Kasari, 2013).

Expansion of research on ASD-MLV is vital to improving the limited efficacy of clinical interventions available to ASD-MLV children and adults. However, our understanding about the etiology of this specific ASD subtype and the origins of severe language impairments in ASD is stalled because researchers do not include ASD-MLV participants in their research. There are various reasons for this exclusion. To start, it is difficult to be sure that participants with poor receptive language understand instructions and these participants cannot perform tasks that require expressive language. Experimental and standardized measures are often confounded by deficits in a participant's ability to understand or attend to task prompts. To address these issues, researchers have worked closely with clinicians to modify testing protocols (Tager-Flusberg et al., 2016). Adaptations include use of positive reinforcement procedures, supplemental aid materials, and measures that do not require substantial understanding of language prompts (Tager-Flusberg et al., 2016). However, more work is needed to develop clinically sensitive tools that can measure cognitive abilities in ASD-MLV (Trembath, Paynter, Sutherland, & Tager-Flusberg, 2019).

Further complicating matters, there are serious logistical challenges with placing testing demands on ASD-MLV individuals. Participants may feel frustrated when they are unable to use expressive language to communicate or when they feel that others are failing to understand their needs; such frustration may lead to disruptive behavioral aggressions (directed to self or others) (Bronsard, Botbol, & Tordjman, 2010). Other behavioral self-injurious aggressions occur regardless of emotional state (e.g., serve for sensory purposes) (Summers et al., 2017). Researchers must navigate the collection of research data while keeping all parties involved safe. To be prepared to meet these various challenges, researchers working with ASD-MLV participants require specialized training, creating yet another barrier to overcome.

Neuroimaging techniques can provide a window into the cognitive processes of ASD-MLV without requiring them to speak or understand language. With these techniques, we can measure brain activity even in the absence of an active task. In passive tasks, participants are not asked to actively respond to any prompt or stimulus, but rather, are distracted in some fashion (e.g., relaxing and watching an entertaining movie) while brain activity is recorded. Even so, there are challenges with administering these techniques in ASD-MLV. For instance, excessive movement can cause noise in measurements. Sensory issues are also of concern. Tactile sensitivity can make participants intolerant of an EEG cap, while auditory sensitivities may make loud and repetitive sounds from loud neuroimaging machinery (e.g., MRIs) or auditory experiments problematic to participants. Nonetheless, tremendous advances have been made by clinical experts to desensitize individuals to overwhelming sensory elements and

reduce excessive movement when conducting neuroimaging research (Nordahl et al., 2016; Tager-Flusberg et al., 2016)

Auditory Processing in ASD and Implications for Further Study in ASD-MLV

Atypical Auditory Behaviors

Atypical sensitivity to sounds is a diagnostic feature of ASD (American Psychiatric Association, 2013; Stiegler & Davis, 2010). Individuals with ASD exhibit paradoxical reactions to sounds in the environment, such as plugging their ears or requesting headphones on a regular basis, but also ignoring salient stimuli like one's own name (O'Connor, 2012; Tomchek & Dunn, 2007). Atypical reactions also include the auditory inspection of inanimate objects (e.g., fans) or humming to oneself (in a nonmusical way), despite the fact that sound content produced by these things does not lead to the type of spectral patterns that capture the interest of neurotypical (TD) listeners.

Currently, it is standard practice to assess atypical auditory behaviors and other sensory inputs with parent report and clinical observation (Ben-Sasson et al., 2009; Siper, Kolevzon, Wang, Buxbaum, & Tavassoli, 2017). Parent-report questionnaires include the Sensory Profile (Dunn, 1999), which asks parents about their child's sensitivity to noise, interest in sounds, and other behaviors indicative of sensitivity to other sensory inputs in other domains (e.g., vision, touch, and taste). Clinical judgment of these sensitivities is often documented using standardized assessments of ASD that group sensory sensitivities with repetitive and restricted interests (Lord et al., 2012; Rutter, Le Couteur, & Lord,

2003). More recently, elicitation procedures have been developed to quantify sensory symptomatology as well (Siper et al., 2017).

The causes of atypical auditory behaviors are unknown, although it is plausible that they originate from the way sounds are cortically processed. To test this hypothesis, we must first obtain more precise measures of atypical auditory behaviors and their neural correlates. Prior work has shown that, in ASD-V individuals, the strength of neural signatures to unexpected sound events (as measured by the MMR) is negatively correlated with measures of atypical sensory behaviors and sensory sensitivity to inputs, including those to sounds (Donkers et al., 2015; Ludlow et al., 2014). In a similar vein, ASD-V individuals who perform poorly on a perceptual task requiring the discrimination of tones based on intensity (i.e., loudness) and/or frequency exhibit more unusual sensory behaviors (Jones et al., 2009; Kargas, López, Reddy, & Morris, 2015). However, such associations have not been explored in ASD-MLV individuals, who may demonstrate even more atypical auditory behaviors than their ASD-V peers (Patten, Ausderau, Watson, & Baranek, 2013; Watson, Patten, Baranek, Poe, & Boyd, 2011).

Low-Level Auditory Perception

There is ample evidence that the processing of auditory information is atypical in many with ASD (for review, see O'Connor, 2012). This is apparent from a young age; neural response to deviant sounds, as measured through the MMR, are found to be atypical in infants at higher risk for autism and in young children recently diagnosed with ASD (Finch, Tager-Flusberg, & Nelson, 2018; Kuhl et al., 2005). Atypical responses continue across the lifespan. Many children and adults with ASD also exhibit similarly

atypical neural responses to salient sounds (Bomba & Pang, 2004; Jeste & Nelson, 2009; Marco et al., 2011). During active, psychoacoustic testing, individuals with ASD show deficits in their ability to differentiate auditory, but not visual, stimuli compared to TD controls (Foss-Feig, Schauder, Key, Wallace, & Stone, 2017). Overall, reports of group-level differences are inconsistent. Consistent differences may be better detected within specific subtypes of the disorder (Schwartz, Shinn-Cunningham, & Tager-Flusberg, 2018).

In addition, the ability to discriminate basic sound properties may be related to language ability. Researchers have shown that in ASD-V individuals, the ability to discriminate between nonspeech sounds based on single-feature changes (e.g., intensity) correlates with language abilities but not nonverbal IQ (Foss-Feig et al., 2017; Kargas et al., 2015). Furthermore, neural markers like the MMR are potential biomarkers for language impairment in ASD (Roberts et al., 2011). ASD-V children with language impairments show more atypical MMR responses to speech sounds than ASD-V children with normal-range language (Cardy, Flagg, Roberts, & Roberts, 2008; Roberts et al., 2011). These MMRs are even more atypical in ASD-MLV children (Matsuzaki et al., 2019). However, not all studies find an association between atypical MMR and language impairment; MMRs evoked by changes in pitch have been shown to be unrelated to receptive language in ASD-V children (Dunn, Gomes, & Gravel, 2008) and additional research is needed to resolve these discrepancies. In addition, more studies are needed to determine whether the associations between atypical MMRs and expressive or receptive language deficits are more pronounced in ASD-MLV individuals.

Prior work has also highlighted that some individuals with ASD show deficits in their ability to perceptually group sounds based on discriminating features that ultimately allow them to disentangle signal from noise. For instance, ASD-V participants are less effective in segregating sounds based on acoustic features like pitch than TD controls (Lepistö et al., 2009). Similarly, with respect to the segregation and encoding of a target from a masking signal, ASD-V children show less precise and robust responses to phonemes that are embedded in static noise (Russo, Zecker, Trommer, Chen, & Kraus, 2009). Within this ASD-V sample, the precise timing of cortical response to speech in noise correlated positively with core language skills – a finding that links language ability to low-level auditory processing (Russo et al., 2009). In addition, compared to their TD peers, children with ASD-V attending to speech in multispeaker settings require speech to be at a higher signal-to-noise ratio (Alcántara, Weisblatt, Moore, & Bolton, 2004). To our knowledge, only one study to date has compared two subtypes of children with ASD using an assessment to test speech recognition in background noise and auditory attention. The study found that children with high-functioning ASD (described as having social deficits with language delays) had poorer central auditory processing skills than children whom the study classified as having Asperger's (social deficits without language delays) (Boatman, Alidoost, Gordon, Lipsky, & Zimmerman, 2001).

Atypical Orienting to One's Own Name in Multispeaker Settings

Individuals with ASD are commonly described as failing to respond to hearing one's own name (OON) (Miller et al., 2017). However, only recently have *neural*

correlates of this weaker OON response been reported (Nijhof, Dhar, Goris, Brass, & Wiersema, 2018).

Decreased responsiveness to OON has been ascribed to degraded auditory perception (Lane, Dennis, & Geraghty, 2011). Just like deviant nonspeech and speech sounds, OON can elicit an MMR when it occurs unpredictably amongst other names (Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006). It can also elicit higher-level cognitive neural indices. Consequently, the MMR can act as a low-level perceptual measurement of a fairly complex cognitive construct (response to OON). There are compelling reasons to extend research to measure MMR with OON in ASD-MLV. First, the MMR has been proposed as a biomarker for language impairment (Roberts et al., 2011), and while one report found no MMR deficits to OON in ASD-V (Nijhof et al., 2018), deficits could nonetheless exist in ASD-MLV. Second, behavioral responses to social bids for attention (like responding to OON) are positively associated with language abilities in ASD (Bottema-Beutel, 2016; Dawson et al., 2004).

Decreased responsiveness to OON has also been described as a deficit in social orienting and selective auditory attention (Osterling, Dawson, & Munson, 2002) and a deficit in self-other differentiation (Nijhof et al., 2018) – processes that rely heavily on high-level cognitive processes and not simply auditory perception. This higher-level processing is evidenced by a later, long positive parietal shift around 300-800 ms, accompanied by a similar long negative frontal shift, in response to OON in TD children and adults (Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Pratt, Berlad, & Lavie, 1999). However, ASD-V adults show weaker late shift responses to OON, supporting the

claim that their brains respond atypically when engaging in tasks that require social orienting and self-other differentiation (Nijhof et al., 2018).

A plethora of psychoacoustic experiments confirm, both in children and adults, that neurotypical people quickly orient to the sound of their name when monitoring a complex, multispeaker scene (Newman, 2005; Wood & Cowan, 1995). However, to our knowledge, such experiments have not been done using neuroimaging methods. In this dissertation, we used EEG to measure response to hearing OON in a multispeaker setting, both in TD and ASD individuals. Because of the possible relationship between response to speech-in-noise and language ability in ASD (Boatman et al., 2001; Russo et al., 2009), testing how ASD-MLV individuals, in particular, respond to their name in multispeaker settings could provide valuable insights into whether they effectively filter out irrelevant noise and detect highly salient cues.

Overview of Empirical Chapters

To successfully capture the neural mechanisms that underlie atypical auditory processing in a complex and heterogeneous neurodevelopmental disorder like ASD, we must first establish a basis for these systems in neurotypical development. Prior research provides information about central auditory processing in neurotypical adults. However, for the purposes of understanding ASD (which is a *developmental* disorder), we must establish when components of these systems reach stable, adult-like states in neurotypical children. Unstable states in neural development are important to consider as we investigate aberrant systems within a developmental disorder like ASD in which systems

can follow drastically different developmental trajectories. *Chapter 2* focuses on age-related changes across typical development in the neural signatures believed to index perceptual organization of sounds. We capture these neural signatures with MMRs to intensity deviants presented in a single stream and in a pitch-separated stream.

Next, in *Chapter 3*, we systematically review existing evidence pertaining to whether individuals with ASD exhibit disordered central auditory processing. To do this, we conducted a meta-analysis based on all studies that compared amplitude and/or latency of MMRs in ASD and TD participants. Through this review, we were able to identify which participant groups were understudied and direct our focus towards these groups in *Chapters 4 and 5*. In addition, we identify specific methodological flaws to address in future research (again, in *Chapters 4 and 5*).

Prior work has suggested that atypical sensory behaviors and neural responses to sounds could be related to impaired language processing (Groen, Zwiers, van der Gaag, & Buitelaar, 2008). *Chapter 4* explores whether atypical sensory behaviors, either in response to sounds or in relation to sounds, are more pronounced in ASD individuals with severe expressive and receptive language deficits. In our first experiment, we compare the percent of time ASD-MLV children and adolescents engaged in atypical auditory behaviors relative to ASD-V peers. Motivated by these results, we then investigate how atypical auditory behaviors vary with receptive language within the ASD-MLV group. A final experiment considers how neural correlates of sound processing, as indexed by strength of MMR to an intensity deviant, relate to atypical auditory behaviors in ASD-MLV.

In *Chapter 5*, we expand upon prior sections of the dissertation that characterize neural processing of salient and rare sounds that elicit a listener's attention – in particular, response to one's own name (OON) – heard in multispeaker settings. We created a data-driven reference for spatial-temporal areas of interest based on a TD sample and then measured responses in a heterogeneous group of adolescents and young adults with ASD-V and ASD-MLV. Our hypothesis, as predicted in prior chapters, is that ASD-MLVs will show weaker MMRs to a salient cue – OON – compared to ASD-V and TD peers. We then evaluate the hypothesis that neural correlates of later cognitive processing previously found to be weak in ASD-V compared to TDs would be similarly weak in ASD-MLV. Finally, we test whether processing of OON in multispeaker settings correlates with parent report of how their child attends to important sounds while ignoring irrelevant sounds in noisy and multispeaker settings.

It should be noted that each of these empirical chapters are independent research papers and thus will have some degree of overlapping content.

CHAPTER TWO: THE EMERGENCE OF ADULT-LIKE AUDITORY STREAM SEGREGATION IN ADOLESCENCE

As adults, we experience a phenomenon known as the "Cocktail Party Problem," in which we must distinguish a single voice within a crowd. This problem arises not only in social settings with voices, but in any complex auditory scene. One way we work to solve this problem is by organizing sounds into perceptually distinct streams, perceiving each as originating from distinct sources with unique content (Bregman, 1990; Cherry, 1953; Wood & Cowan, 1995). Disentangling sounds in this way enables us to filter out background noise and retain important information. Adults do this quickly and effortlessly in diverse environments like restaurants, social gatherings, and work (Bregman, 1990; Sussman, 2005; Sussman et al., 2005).

Children face this problem too, yet it has not been determined if or at what point in development children engage in these same automatic and effortless processes to solve it (Werner, 2017). Children clearly do engage in some form of sound organization, as demonstrated by their ability to learn the subtle complexities of their native language and subsequently to comprehend orally presented information in educational settings (Hétu, Truchon-Gagnon, & Bilodeau, 1990; Klatte, Bergström, & Lachmann, 2013; Saffran, 2003). However, this process might not be as stable and effortless in children as it is in adults. During middle childhood, synaptic growth, synaptic pruning, and axonal myelination within structures along the auditory pathway occur, which ultimately make encoding and organization of sounds more efficient (Moore & Guan, 2001; Moore, Perazzo, & Braun, 1995; Su, Kuan, Kaga, Sano, & Mima, 2008). These structural

changes lead to morphological changes in the neural evoked responses to sound onsets (known as auditory evoked potentials, or AEPs). Between the ages of 7 and 12 years old, AEPs made of a single positive and negative peak (known as a P1-N2 complex) transition to AEPs made of two positive and negative peaks within the same time frame (known as a P1-N1-P2-N2 complex) (Johnstone, Barry, Anderson, & Coyle, 1996; Ponton, Eggermont, Don, et al., 2000; Sharma, Kraus, J. McGee, & Nicol, 1997).

These changes influence not only basic sound encoding, but also the central auditory processes that rely upon them. For instance, changes in AEP morphology can be observed during the elicitation of an auditory mismatch response (MMR), when a listener detects a change and that change detection results in an amplified AEP around 150 ms. During the same point in childhood that AEP morphology changes, MMRs switch in polarity from positive to negative as the N1 complex emerges (Oades, Dittmann-Balcar, & Zerbin, 1997; Shafer, Morr, Kreuzer, & Kurtzberg, 2000; Wetzel, Widmann, Berti, & Schroger, 2006). Large-scale changes in the neural generators responsible for central auditory processing arguably reflect a system that is not yet stable; this raises the question of how the neural markers of auditory stream segregation change across child development (Eggermont & Moore, 2012; Litovsky, 2015; Sussman, Wong, Horváth, Winkler, & Wang, 2007).

The neural signatures of children and adults during automatic stream segregation have been compared in a handful of studies (Lepistö et al., 2009; Sussman et al., 2005; Sussman & Steinschneider, 2006). Most commonly, researchers have used dual-stream mismatch response paradigms, in which brain responses are recorded while listeners hear

a target stream of repeating sounds that occasionally changes in a feature (like loudness), while simultaneously hearing a second, distractor stream of sounds that regularly changes in that same feature. With this paradigm, researchers leverage the fact that the feature change detection in a target stream of sounds may or may not be perceptually masked depending on whether the listener can effectively segregate the masking, overlaid stream. If the listener successfully segregates the two streams, that feature change will perceptually pop out to them and their brain will generate an MMR. If instead, the two streams are integrated together, this feature change will not be perceptually distinct and an MMR will not be generated. As a result, the MMR becomes a useful brain-based index of whether a listener has segregated two streams of sounds (Sussman, Ceponiene, Shestakova, Näätänen, & Winkler, 2001; Sussman & Steinschneider, 2009). Because MMR paradigms do not require active instruction or rely on any behavior from the listener, they are feasible when studying stream segregation across a wide age range of children, regardless of cognitive abilities (Lepistö et al., 2009; Näätänen, Gaillard, & Mäntysalo, 1978; Sussman, 2005). Prior work has investigated passive measures of stream segregation in discrete and narrow age ranges (Lepistö et al., 2009; Sussman et al., 2005; Sussman & Steinschneider, 2006), but differences have yet to be considered across childhood, in a comprehensive range of children, adolescents, and young adults.

In this study, we used the dual-stream mismatch paradigm described above to measure whether neural indicators of adult-like stream segregation were present in a sample of neurotypical participants ranging in age from 3 to 21 years old. We compared these responses to subcortical and cortical neural responses indicative of sound encoding

and deviance detection – stages of sound processing that precede stream segregation. We hypothesized that the presence of MMRs during an automatic stream segregation task would be contingent on auditory pathway maturation, as evidenced by the stabilization of an N1-P2 AEP complex.

METHODS

Participants

74 typically developing participants between the ages of 3 and 21 were enrolled in this study (M_{age}: 11.30, SD: 4.81, range: 3.14–21.19, 35 males). Prior to enrollment, we screened participants to confirm that they did not have a developmental disorder or learning difference that required educational accommodation, a known hearing impairment, or a history of traumatic brain injury. Following study enrollment, we used the Kaufman Brief Intelligence Test Second Edition (KBIT-2; Kaufman, 2004) or Wechsler Abbreviated Scales of Intelligence, Second Edition (WASI-2; Wechsler, 2011) to assess participant Full Scale Intelligence (IQ). Following cognitive testing, five participants were excluded from further analysis due to having an IQ below normal range (less than a standard score of 85). Two additional participants were excluded because their EEG data was not usable.

Analyses were conducted on the remaining 65 participants (**Table 1.1**, M_{age}: 11.45, *SD*: 4.79, *range*: 3;1–21;2, 33 males). Participants were assigned to one of five groups for cross-sectional age comparisons based on approximately defined stages of child development: early childhood (3-6 years), middle childhood (7-9 years), pre-

adolescent childhood (10-12 years), adolescence (13-16 years), and young adulthood (17-21 years).

EEG Paradigm

Neural activity was recorded from all participants using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR, sampling rate 1000 Hz). Participants sat in electrically shielded and sound-attenuated room. They were instructed to watch a self-selected soundless movie or television show with subtitles and to not worry about sounds they heard. Stimuli and paradigm design were adapted from work conducted by Lepisto and colleagues (2009). We presented 50 millisecond (ms) harmonic tone complex stimuli binaurally from two loudspeakers, placed +/- 45 degrees in front of the listener. We presented seven blocks of experimental conditions, with the order of block presentation randomized across participants. Six of the blocks were comprised of three, counterbalanced-stimuli MMR conditions (described as Oddball, Segregated, and Integrated conditions); the seventh block was a non-MMR, condition designed to evoke AEPs to standard complex tone onsets.

The Oddball condition was a classic one-stream MMR paradigm. In this condition, a standard, repeating sound was presented and interrupted semi-randomly (17% of the time) by a sound (called a “deviant”) that differed in intensity content. Both standards and deviants were complex tones composed of 10 harmonic frequencies, spaced evenly, with a fundamental frequency of 110 Hz. Standards and deviants differed on intensity and were presented at either 30 or 45 dB SPL, with stimulus intensity

counterbalanced across two blocks. There were always at least three standards between deviants. Stimulus onset asynchrony was 300 ms and interstimulus interval was 250 ms with a 40 ms jitter. We presented 1000 trials in each block.

The Segregated condition was similar to the Oddball condition but had an additional overlaid interfering distractor stream. Four 10-harmonic complex tones, all with fundamental frequencies of 634 Hz, were presented randomly and at equiprobability, at one of four intensities (25, 35, 40, 50 dB SPL). The resulting stimulus onset asynchrony was 100 ms and the interstimulus interval was 50 ms (with a jitter of 40 ms). This stream of sounds was designed to be perceptually separable in pitch from the target stream but similar in terms of intensity range.

The Integrated condition was similar to the Segregated condition, but the overlaid distractor stream was made of 10-harmonic complex tones with fundamental frequencies of 131 Hz. This stream of tones was closer in pitch to the target stream and therefore less easily perceptually separated.

Typical P1-N1-P2-N2 AEPs in response to standard tones in the prior conditions could be obscured by large oscillatory effects from the fast presentation of sounds (as was required to elicit a perceptual streaming effect in the six MMR condition blocks). To circumvent this issue, we presented a seventh, all-standard, non-MMR condition with a slower presentation rate (867 ms interstimulus interval with 218 ms jitter). This condition was comprised of 150 trials of 50 ms complex tones presented at 62 dB SPL. Tones were composed of 10 evenly spaced harmonic frequencies, centered around a fundamental frequency of 110 Hz.

EEG Measure 1: Passive Auditory Deviance Detection (MMR) in Oddball, Segregated, and Integrated Conditions

Responses to louder (45 dB SPL) standards and deviants were extracted from the six blocks of Oddball, Segregated, and Integrated conditions. Data were online digitally filtered with a 0.1 Hz highpass filter, and after acquisition, offline filtered at 1-35 Hz for analyses. Data were referenced to the average of the left and right mastoids and segmented into 700 ms epochs. Trials were rejected if neural amplitude at the primary channel of interest (mid-frontal channel Fz) or mastoids exceeded 100 microvolts, peak-to-peak. Trials were baseline corrected with respect to whole trial averages.

The remaining data consisted of an average of 167 deviant trials in each condition. Standard trials were randomly selected to provide an equal number of comparison trials for the deviants. Age groups did not differ in the number of accepted trials used for analyses (Oddball: $F(4,60) = 0.72$, $p = 0.59$; Segregated: $F(4,60) = 1.45$, $p = 0.23$; Integrated: $F(4,60) = 1.19$, $p = 0.32$).

To identify the latency windows in which there were significant differences between standard and deviant AEPs, we used nonparametric cluster-based permutation t-tests (Maris & Oostenveld, 2007). These tests allowed us to determine clusters of time in which, across participants within a given age group, deviant AEPs differed significantly from standard AEPs. This test was conducted at every time point for every participant in a predicted latency window of 75-300 ms post-stimulus onset. We set an arbitrary threshold of $t > 2.99$ and $p < 0.01$ to consider clusters significant. Next, we generated 1000 bootstrapped iterations of mock data (from random sampling of signals evoked by

deviants and standards) and generated a distribution of cluster values from that sampling. Finally, we selected clusters from the real dataset that were significant less than one percent of the time in the generated mock distribution. In addition to controlling for multiple comparisons, this method had the advantage of identifying MMRs across participant groups with different latency windows.

The MMRs were then calculated based on differences in response to 45 dB SPL standards and 45 dB SPL deviants. Average MMR amplitude was calculated with 30 ms average windows centered around the midpoints of two post-stimulus latencies ("Early": 104-134 ms and "Late": 152-182 ms). We selected these early and late latency windows because they were the windows during which standard and deviant AEPs significantly differed from one another during the Oddball condition in the youngest and oldest groups, as previously determined with cluster-based testing (**Figure 1.1.A, 1.1.B**). We conducted two separate 3x5 mixed ANOVAs to consider the effect of age group on MMR amplitude in the Oddball, Segregated, and Integrated conditions. ANOVAs that were significant were at the level of alpha less than 0.05 were followed up with Bonferroni-corrected pairwise comparisons.

EEG Measure 2: Subcortical Encoding of Complex Tones

We measured subcortical encoding of the presented complex tones to confirm adequate sensory coding of the sounds at the peripheral stages of sound processing. We looked at the evoked potentials generated from a selection of sounds presented during EEG Measure 1. This included 110 Hz complex tones presented at 30 dB SPL from all 6

MMR blocks, 110 Hz complex tones presented at 45 dB from all 6 MMR blocks, and 131 Hz complex tones presented at a mixture of four intensities (25, 35, 40, 50 dB SPL) during the two Segregated condition blocks. Data were online digitally filtered with a 0.1 Hz highpass filter and offline highpass filtered at 70 Hz. Like in EEG Measure 1, data were then baseline corrected to the left and right mastoids and mid-frontal channel Fz was selected for analyses. An average of 2837 trials were used for each analysis, with no significant difference in number of accepted trials across groups to each stimulus type ($F(4,60) = 2.04$, $p = 0.10$; $F(4,60) = 1.16$, $p = 0.34$; $F(4,60) = 1.41$, $p = 0.24$).

We operationalized subcortical encoding with measures of envelope following response (EFR) – in particular, phase-locking value (PLV) and power spectral density (PSD). PLVs across trials were calculated using a multitaper method, with our frequency range of interest between 50 and 1000 Hz and our time window of interest between 0 and 50 ms post-stimulus onset. PLV amplitude was calculated by taking a 20 Hz average window centered around the expected peak (e.g., for an EFR in response to a 110 Hz tone, a window of 100-120 Hz). Signal PSD was computed for the same frequencies within this same time window. (Time window calculation accounted for the 60 ms delay between with the timing of the EGI system trigger and sound presentation). ANOVAs were used to consider between-group effects in EFR as measured by PLV and PSD.

EEG Measure 3: Auditory Evoked Potential to a Standard Series of Complex Tones

Data from the control, all-standard block of 110 Hz complex tones were online digitally filtered with a 0.1 Hz highpass filter and were offline filtered at 0.5-20 Hz,

referenced to the left and right mastoids, and segmented into 700 ms epochs. Full AEP topography was considered in order to best capture morphological differences between the differently aged sample groups. Trials were rejected if any channel's amplitude exceeded 200 microvolts, peak-to-peak. In addition, channels along the cap's outer rim were excluded from analyses as they were more likely to be contaminated by noise. Trials were baseline corrected with respect to a 100 ms pre-stimulus baseline window. An average of 141 trials were used in these analyses, with no significant difference in the number of accepted trials across groups ($F(4,60) = 0.26$ $p = 0.91$).

RESULTS

EEG Measure 1: Passive Auditory Deviance Detection (MMR) in Oddball, Segregated, and Integrated Conditions

Each age group's average responses to standards and deviants during Oddball, Segregated, and Integrated conditions are displayed in **Figure 1.1A**. We identified significant differences between responses to standards and deviants during the Oddball condition across all groups except for the 7–9 year-old group (Group 3-6 years: 94–143 ms, Group 10–12 years: 142–187 ms, Group 13–16 years: 146–196 ms, Group 17–21: 140–194 ms). We also identified group differences between responses to standards and deviants during the Segregated condition in the oldest two groups (Group 13–16 years: 143–202 ms, Group 17–21: 141–194 ms). No group showed a significant difference between responses to standards and deviants during the Integrated condition.

Group by condition interaction effects for MMR amplitude are presented in **Table 1.2 and Figure 1.1**. Within the early latency window, we found a main effect of condition ($F(2,120) = 5.16$, $p = 0.007$) but no main effect of group ($F(4,60) = 2.56$, $p = 0.253$), as well as a condition by group interaction ($F(8,120)=2.16$, $p=0.036$). Post hoc analyses revealed that there were significant differences between the Oddball and both Segregated and Integrated conditions in the 3–6-year-olds, as well as significant differences between Oddball and Segregated conditions in the 7–9-year-olds. However, there were no significant differences between Segregated and Integrated conditions in the 3-6-year-olds or 7-9-year-olds. Conditions did not differ from one another in the 10–12, 13–16, or 17–21-year-old groups during this early latency window.

Within the late latency window, we found a main effect of group ($F(4,60) = 8.26$, $p < 0.001$) and a main effect of condition ($F(2,120) = 20.10$, $p < 0.001$). We also found a condition by group interaction ($F(8,120) = 3.83$ $p < 0.001$; **Figure 1.3.B**). Analyses revealed that Oddball, Segregated, and Integrated conditions did not differ from one another in 3–6- or 7–9-year-olds. Only 13–16-year-olds and 17–21-year-olds showed a significant difference between segregated and integrated conditions (**Table 1.2**).

EEG Measure 2: Subcortical Encoding of Complex Tones

Participants in all age groups produced similarly pronounced PLVs to the presented complex tones (**Figure 1.2.A**). There were no significant differences between groups in terms of their PLV amplitude surrounding the fundamental frequency in any of the three frequency/intensity combinations (110 Hz, 30 dB SPL: $F(4,60) = 2.19$, $p = 0.08$; 110 Hz,

45 dB SPL: F(4,60) = 1.53, p = 0.20; 131 Hz, 45 dB SPL: F(4,60) = 0.93, p = 0.45). There was also no difference between groups in PLV amplitude surrounding the second harmonic (110 Hz, 30 dB SPL: F(4,60) = 1.43, p = 0.24; 110 Hz, 45 dB SPL: F(4,60) = 0.85, p = 0.50; 131 Hz, 45 dB SPL: F(4,50) = 0.57, p = 0.68). Furthermore, there was no significant effect of age when EFR was measured with PSD in response to any of the three frequency/intensity combinations (110 Hz, 30 dB SPL: F(4,60) = 0.76, p = 0.56; 110 Hz, 45 dB SPL: F(4,60) = 0.37, p = 0.83; 131 Hz, 45 dB SPL: F(4,60) = 0.84, p = 0.50).

EEG Measure 3: Auditory Evoked Potential to a Standard Series of Complex Tones

As expected, AEPs (indicative of time-locked cortical responses to standard sound onsets) changed in morphology across the differently aged groups (**Figure 1.3**). Young children, ages 3–6, showed a P1-N2 morphology. They demonstrated a large frontal positive neural response in response to sounds that peaked around 150-200 ms, followed by a frontal negative peak around 125-175 ms. In contrast, adolescents and young adults showed a P1-N1-P2-N2 morphology. During middle and pre-adolescent childhood, there was a progressive emergence of the N1 in the 175-200 ms latency window that had previously been a part of an elongated P1. The P2, originating from positive voltages along central scalp electrodes around 225-250 ms, also emerged along a similar trajectory.

DISCUSSION

We found that, unlike adolescents and adults, children ages 3-12 did not show neural markers of automatic auditory stream segregation when listening to two widely separated pitch streams of sounds. This was observed from an interaction between group and condition, such that only adolescents and adults showed significantly larger MMRs to deviants during the Segregated condition than the Integrated condition. In contrast, groups did not differ in their MMRs during the two control, Oddball and Integrated conditions.

Automatic Stream Segregation

In adults, automatic segregation of auditory information is evidenced by MMRs in dual-stream settings. Our objective was to determine at what point during development children exhibit similar neural markers of automatic stream segregation. As predicted, we did not detect these markers in pre-adolescent children. For these children, neural responses to standards and deviants in a dual-stream, widely pitch-separated, Segregated condition were like those observed in a dual-stream, narrowly pitch-separated, Integrated condition. In contrast, children over the age of 13 exhibited neural responses indicative of successful segregation, showing significantly larger MMRs during the Segregated compared to the Integrated condition. Our findings suggest that the brain systems responsible for automatic stream segregation could be continuing to undergo developmental changes during childhood.

Our findings align with some prior studies on this topic (Sussman &

Steinschneider, 2008), but not all (Sussman, Ceponiene, Shestakova, Näätänen, & Winkler, 2001; Winkler et al., 2003). In contrast to our findings, some have reported that infants and children ages 7 to 10 do, in fact, show a strong neural response to intensity deviants heard in dual-stream, widely-pitch separated Segregation conditions (Lepistö et al., 2009; Sussman et al., 2001; Winkler et al., 2003). We suspect that the difference between those findings and our own may be attributable to the composition of the stimuli used in the respective studies and how the stimuli were processed. In our study, we presented complex tones, whereas prior studies presented pure tones (Lepistö et al., 2009; Sussman et al., 2001; Winkler et al., 2003). The pure, narrow-band tones presented in prior research could be separated to some extent by peripheral systems because they can be encoded on different sections of the basilar membrane of the cochlea, which is organized tonotopically by characteristic frequency. In contrast, the complex, broadband tones that we presented could not be encoded on any one section of the cochlea. As a result, the processes necessary for our participants to segregate sound streams relied more exclusively on central auditory processing systems. We postulate that, prior to adolescence, peripheral mechanisms aid in automatic stream segregation when sound inputs are not complex.

Preceding Stages of Sound Encoding

We isolated age-related changes specific to passive stream segregation by confirming that other, preceding components of sound processing had stabilized prior to adolescence. We found that the presence of neural responses resembling those in adults

during stream segregation emerged several years after major maturational changes in the auditory pathway, as indexed by the emergence of an N1-P2 AEP complex, while subcortical responses and MMRs to deviant tones were stable by early childhood. Our findings replicate reports that subcortical responses evoked by complex tones do not change considerably across childhood between the ages of 3 and 21 (Johnson, Nicol, Zecker, & Kraus, 2008). Our results were also consistent with prior reports that AEPs change in middle and pre-adolescent children from a P1-N2 to P1-N1-P2-N2 complexes (Bishop, 2007; Sharma et al., 1997; Wetzel et al., 2006) and MMR responses to oddball deviants, while present from a young age, change in morphology across child development simultaneously with morphological changes in AEPs (Oades et al., 1997; Ponton, Eggermont, Don, et al., 2000; Shafer et al., 2000). Our findings confirm that age-related differences in dual-stream MMR did not result from differences in preceding stages of sound processing (Eggermont & Moore, 2012; Werner, 2017). It is likely that changes observed in AEP morphology reflect the development of more specific, sensitive, and adaptive information processing (Čeponiene, Cheour, & Näätänen, 1998; Courchesne, 1990) driven both by biological changes and by experiences that strengthen neural connections involved in information processing. Given the observed developmental timeline, we propose that the stabilization of systems responsible for sound encoding precede the stabilization of systems responsible for auditory stream segregation. Future research should continue to investigate the maturational timelines of systems in the auditory processing pathway.

Limitations

This study measured neural responses to deviants under conditions in which only one pitch-separation cue was available to guide segregation. Thus, our findings, while significant, do not address how the degree of pitch separation might influence at what age neural pitch separation can be observed. It is possible that adult-like markers of segregation might appear in younger, pre-adolescent children if given a larger pitch separation (Sussman et al., 2007), or conversely, might appear in later adolescence if a smaller pitch separation were to be used. In addition, while it was in some respects useful to isolate a single major cue (pitch) for purposes of evaluating stream segregation, we acknowledge that in real life, people also rely on other relevant cues, like timbre and spatial location, to separate sound streams (Bronkhorst, 2015). Not only can each of these cues aid in the process of segregation, but the simultaneous availability of multiple cues allows for more accurate stream segregation when one is ambiguous (Shinn-Cunningham, 2008; Woods & Mcdermott, 2015). Future research should consider how multiple cues are simultaneously used to support successful stream segregation at different stages of child development.

Clinical Relevance

Even if the neural systems to guide automatic stream segregation are not stable by middle childhood, heightened attentional resources are likely recruited to mediate the organization of complex scenes until such processes become more automatic and less effortful (Shinn-Cunningham & Best, 2008; Sussman & Steinschneider, 2009; Wild et

al., 2012). During passive, dual-stream tasks in which attention is directed elsewhere, children require larger pitch separation than adults to demonstrate similar MMRs to target stream deviants (Sussman & Steinschneider, 2009). However, when actively attending to this stimuli, children and adults demonstrate similar MMRs to the target deviants with the same pitch separation (Sussman & Steinschneider, 2009). These findings could explain why some children have difficulty learning in complex auditory scenes (Hétu et al., 1990). In learning environments like classrooms, the cognitive load required to actively separate multiple voices and other noise can be high (Howard, Munro, & Plack, 2010; Shield & Dockrell, 2003). This would be particularly challenging for children with attentional impairments, insofar as they are unable to rely on attentional mechanisms in support of sound stream segregation (Corbett & Constantine, 2006; Shield & Dockrell, 2003; Tomchek & Dunn, 2007). Future research on this topic is needed to consider what additional cognitive resources children recruit to effectively segregate sounds prior to adolescence and how children cope if those resources are unavailable.

Conclusions

In this study, we measured a neural proxy for automatic stream segregation and found that well-established neural indices of adult-like automatic stream segregation were not detected in pre-adolescent children. Neural indices during stream segregation that resemble those of adults emerged during adolescence, shortly after major morphological changes in AEPs during middle and pre-adolescent childhood. From our results, we hypothesize that the auditory pathway is still undergoing development during pre-

adolescent childhood and that there is a sequential maturation of the neural mechanisms involved in central auditory processing (Ghinst et al., 2019; Ross et al., 2011; Werner, 2017). Future research should investigate what cognitive and automatic processes pre-adolescent children rely on to support the organization of complex auditory scenes.

Table 1.1. Demographics and behavioral performance. Means and Standard Deviations presented are based on normally distributed scores (*M*=100, *SD*=15).

	Age Group	**3-6 Years**	**7-9 Years**	**10-12 Years**	**13-16 Years**	**17-21 Years**	**Sig. (*p*)**
Sample	*N*	15	12	14	12	12	
Age (years)	*Mean (SD)*	5.23 (1.08)	8.77 (0.77)	11.39 (0.80)	14.91 (0.89)	18.50 (4.79)	
M:F	*Ratio*	8:7	4:8	8:6	5:7	8:4	*NS*
Race							*NS*
	Asian	2	0	0	2	1	
	Black/ African American	0	1	1	0	3	
	Caucasian	9	5	8	9	7	
	Multiple Races	3	3	5	1	1	
	Prefer not to respond	1	3	0	0	0	
Ethnicity							*NS*
	Hispanic	2	0	0	0	1	
	Non-Hispanic	13	9	14	11	11	
	Prefer not to respond	0	0	0	1	0	
IQ	*Mean (SD)*	107.87 (13.95)	119.83 (11.45)	111.50 (13.93)	113.75 (11.62)	112.58 (15.80)	*NS*

Table 1.2. Mean difference effects of condition on ERPs.

Latency Window	Age Group	Condition (I)	Condition (J)	Mean Diff. (I-J)	Sig. (*p*)	Cohen's d effect size [95% CI]
Early	3 to 6	Oddball	Segregated	1.61	*<0.01*	1.40 [0.56 – 2.15]
(104-134 ms)	7 to 9				*NS*	
	3 to 6	Oddball	Integrated	2.06	*<0.01*	1.29 [0.47 – 2.04]
	7 to 9			1.41	*0.05*	0.71 [-0.14 – 1.51]
	3 to 6	Segregated	Integrated		*NS*	
	7 to 9				*NS*	
Late	10 to 12	Oddball	Segregated	-0.99	*0.05*	-2.11 [-2.96 – -1.13]
(152-182 ms)	13 to 16				*NS*	
	17 to 21			-1.80	*<0.01*	-1.09 [-1.91 – -0.20]
	10 to 12	Oddball	Integrated	-1.52	*<0.01*	-1.01 [-1.76 – -0.20]
	13 to 16			-2.28	*<0.01*	-1.56 [-2.41– -0.60]
	17 to 21			-2.92	*<0.01*	-1.83 [-2.71 – -0.82]
	10 to 12	Segregated	Integrated		*NS*	
	13 to 16			-1.45	*<0.01*	-1.12 [-1.94 – -0.23]
	17 to 21			-1.12	*<0.01*	-1.28 [-2.10 – -0.36]

Figure 1.1.A. Standard-deviant difference windows across age and condition. Windows of significance are indicated with gray shading.

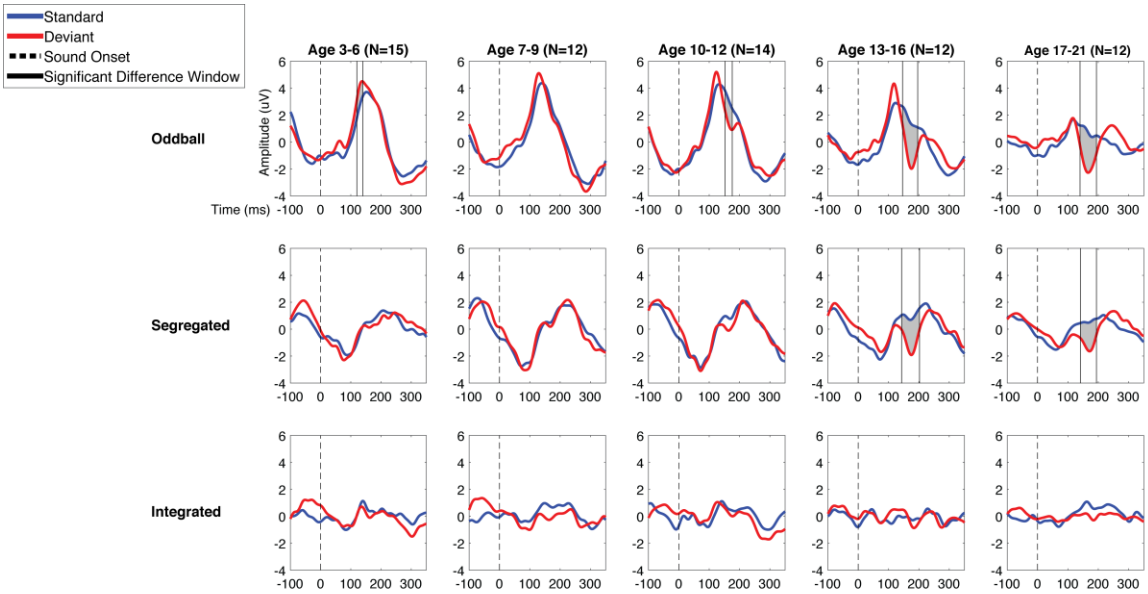


Figure 1.1.B. Mismatch response difference trace at channel Fz. Window shading corresponds to early (purple) and late (red) windows in figure.

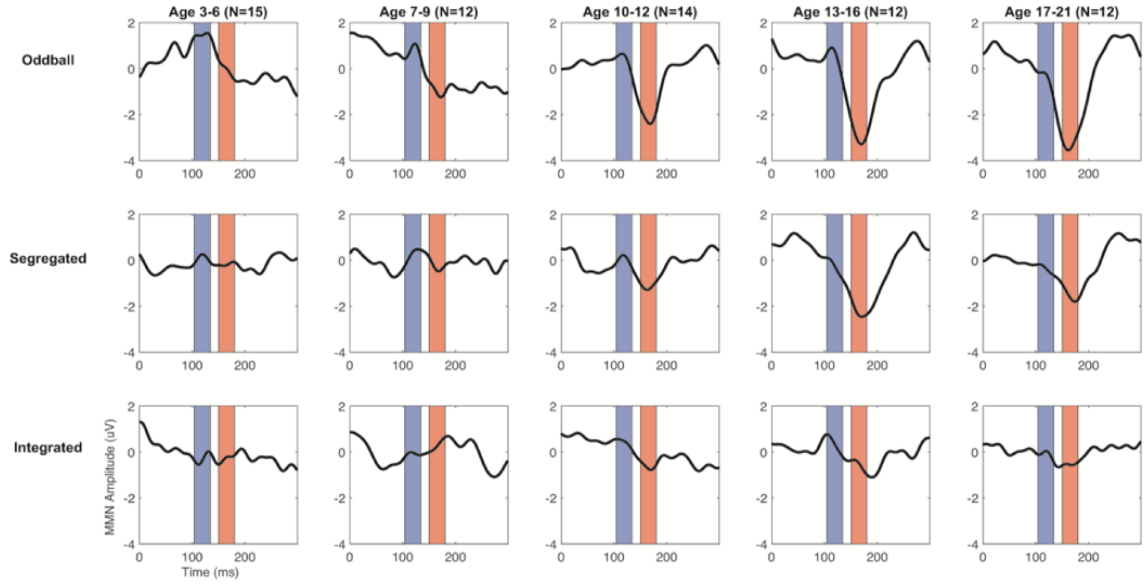


Figure 1.1.C. Average mismatch response during early and late windows for each age group.

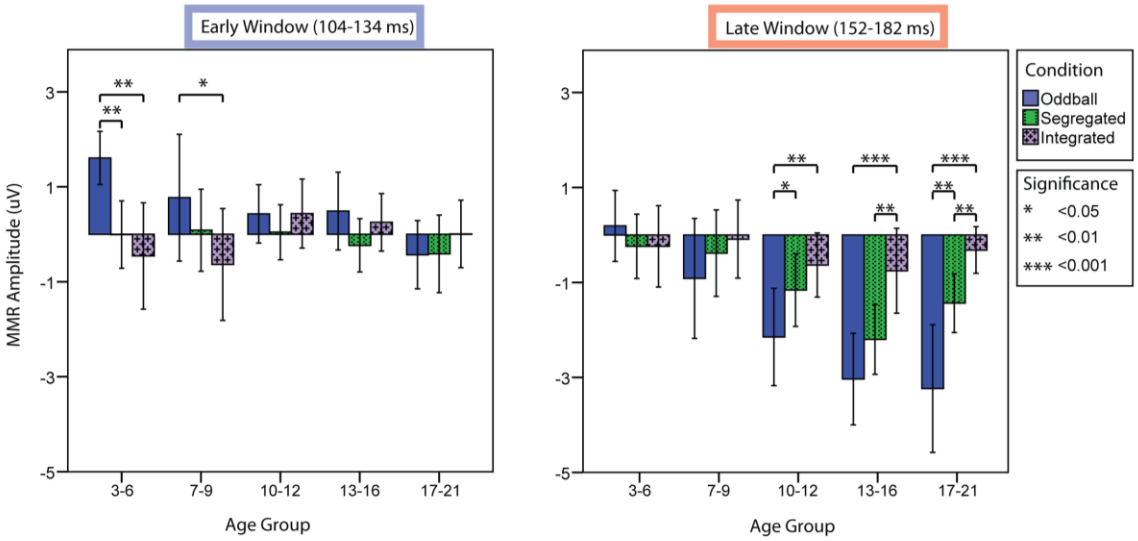


Figure 1.2.A. Subcortical envelope following response phase-locking values (PLVs). PLV amplitude relative to frequencies at fundamental frequency and its first two harmonics.

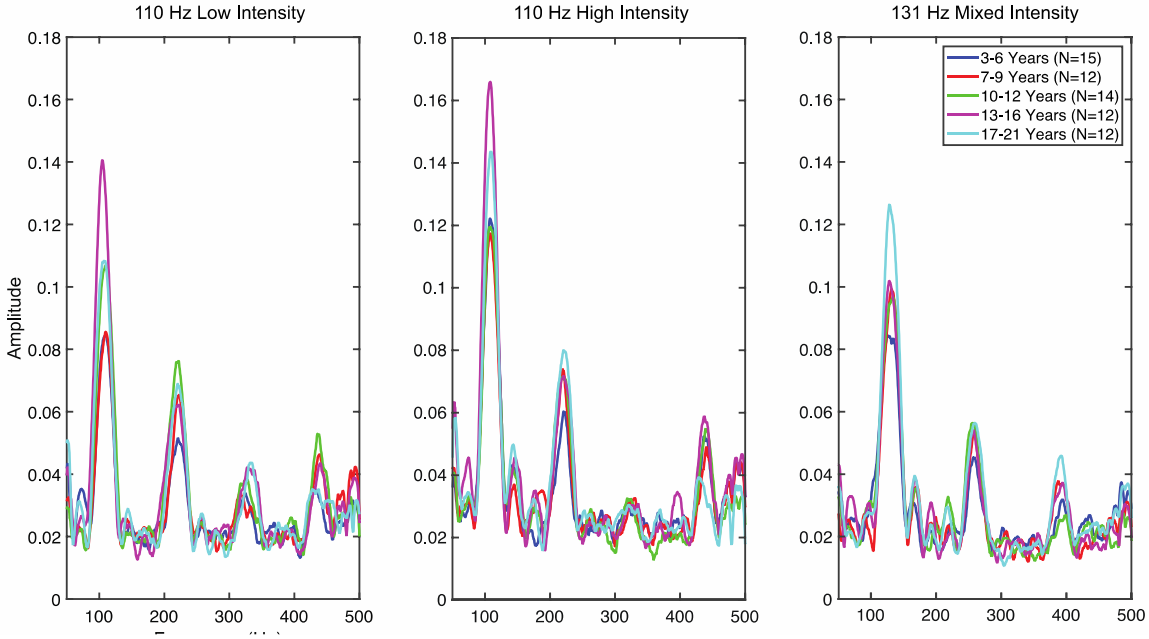


Figure 1.2.B. Subcortical envelope following response: PLV amplitude and PSD energy. PLV amplitude and PSD energy for a 20 Hz average window centered around the fundamental frequency peak. Low intensity (30 dB SPL), high intensity (45 dB SPL), and mixed intensities (25, 35, 40, 50 dB SPL).

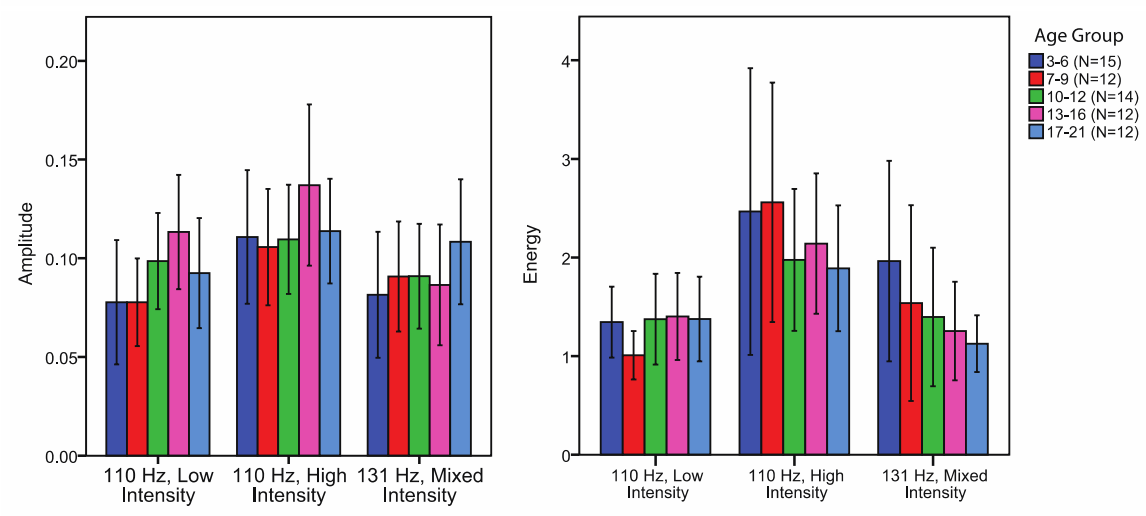
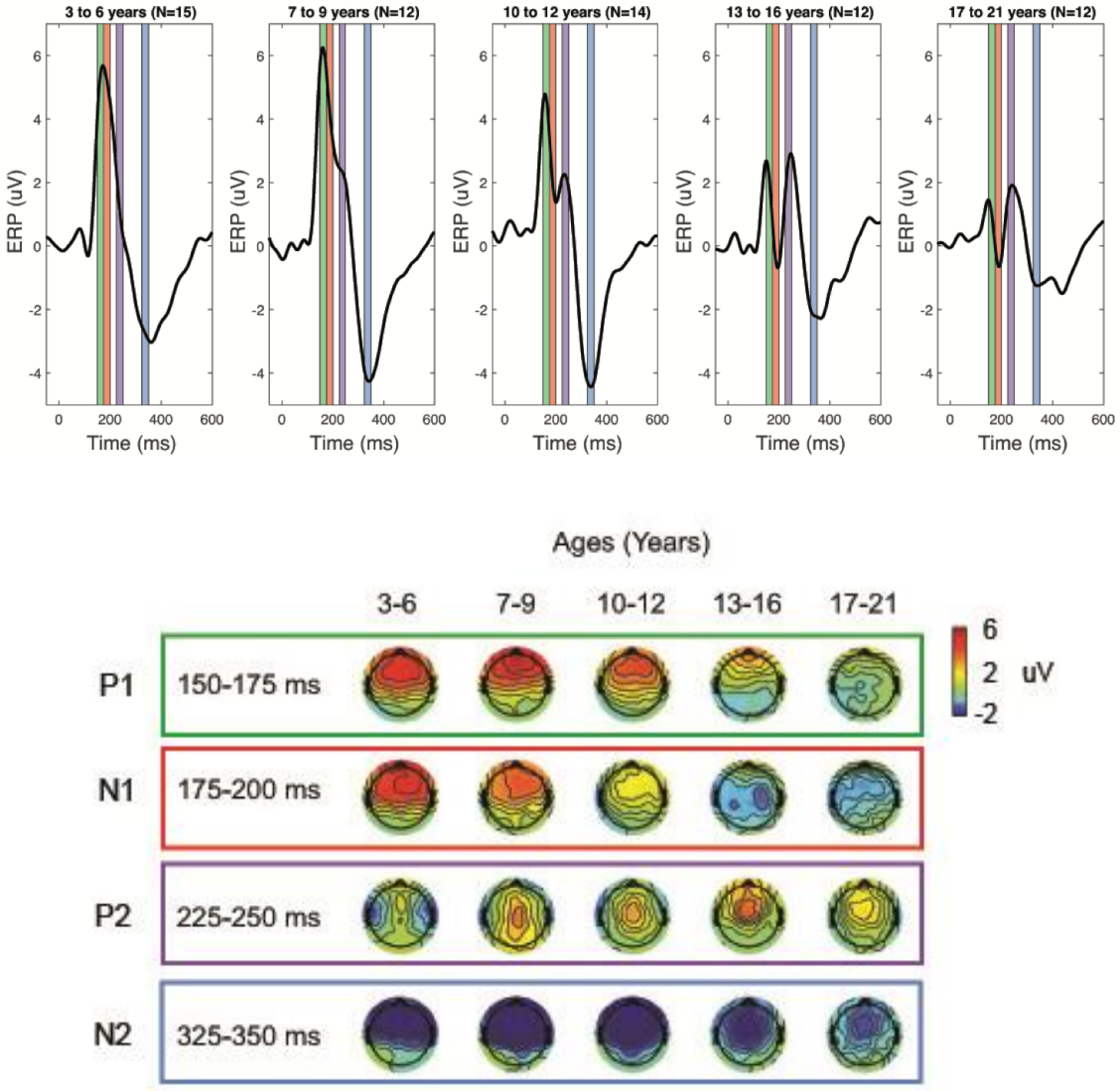


Figure 1.3. Cortical auditory evoked potentials to 110 Hz complex tones. Latency windows of interest are highlighted given average latency of P1 (158 ms), N1 (197 ms), P1 (240 ms), and N2 (348 ms). Top panel shows ERP waveform at channel Fz while bottom panel shows topography of ERP response across pertinent latency windows.



CHAPTER THREE: META-ANALYSIS AND SYSTEMATIC REVIEW OF THE LITERATURE CHARACTERIZING AUDITORY MISMATCH NEGATIVITY IN INDIVIDUALS WITH AUTISM

The following has been published: Schwartz, S., Shinn-Cunningham, B., & Tager-Flusberg, H. (2018). Meta-analysis and systematic review of the literature characterizing auditory mismatch negativity in individuals with autism. *Neuroscience & Biobehavioral Reviews*, *87*, 106-117. https://doi.org/10.1016/j.neubiorev.2018.01.008

"MMN" and "mismatch negativity" are used in place of "mismatch response" and "MMR" within this chapter, but for purposes of this dissertation, can be treated synonymously.

Autism Spectrum Disorder (ASD) is characterized by impairments in social communication and interaction as well as by the presence of repetitive and restricted behaviors or interests, including atypical responses to sensory stimuli like sounds (American Psychiatric Association, 2013). Language impairments, while not core symptoms in ASD, often co-occur (Tager-Flusberg, Paul, & Lord, 2005). Atypical responses to auditory stimuli and difficulty in learning spoken language are linked to disruptions of auditory filtering, acoustic feature discrimination, sound source identification, and auditory working memory (Foss-Feig, Stone, & Wallace, 2012; Näätänen et al., 2012; O'Connor, 2012). Given that these processes are vital components of auditory processing, several researchers have hypothesized that in ASD, there is a common disruption in neural networks that govern basic auditory processing (Bomba &

Pang, 2004; Marco et al., 2011). To pinpoint the underlying bases of atypical auditory processing in brain-based disorders, researchers often turn to measures like electroencephalography (EEG) and magnetoencephalography (MEG). These neuroelectric imaging approaches have the temporal resolution necessary to track neural activity associated with specific auditory events, thereby providing a window into auditory processing not afforded by other noninvasive neural measures[1]. Here, a meta-analysis was undertaken to determine the extent to which neural response that reflect acoustic feature discrimination and auditory working memory in early auditory processing differs in ASD relative to typical development (TD).

We focused on one common approach that can capture such features of early auditory processing: the mismatch negativity (MMN) paradigm (Näätänen et al., 2012; Näätänen, Paavilainen, Rinne, & Alho, 2007). The MMN measures an individual's ability to detect changes in auditory patterns by presenting a regularly occurring, "standard" pattern that is interrupted at random with rare, "deviant" stimuli (Näätänen et al., 1978). Deviant stimuli usually differ perceptually from standards on a single acoustic feature, such as intensity, pitch, or phoneme. Typically, the unexpected, rare sounds elicit neural responses not present when that same sound is expected. The size of those neural responses indexes the degree to which a listener has built up a memory trace of an

[1] For reviews of prior research utilizing neural measures to investigate atypical auditory processing in brain-based disorders like ASD, Specific Language Impairment, Dyslexia, Learning impairment, Schizophrenia, Attention-Deficit/Hyperactivity Disorder, Bipolar Disorder, and Aphasia, see: Aaltonen, Tuomainen, Laine, & Niemi, 1993; Barry, Clarke, & Johnstone, 2003; Bishop, 2007; Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; Erickson, Ruffle, & Gold, 2015; Kraus et al., 1996; Kujala et al. 2013; Näätänen & Kahkonen, 2009; O'Connor, 2012; Umbricht & Krlijes, 2005.

ongoing auditory pattern and detected a deviation from that trace (Kujala & Näätänen, 2010). It has been argued that this neural response is driven by NMDA receptor activity in the bilateral auditory and frontal cortices (Näätänen et al., 2012). MMN components can be well detected on the scalp's frontal-central midline using EEG and can be quantified as a negative component that occurs 100 to 250 ms following a deviant stimulus onset (Haesen et al., 2011). In source space, the mismatch field arises from frontal and supratemporal generators during a similar time window (Novak, Ritter, Vaughan Jr, & Wiznitzer, 1990).

The MMN component itself is calculated from the difference between the response evoked by the same event when it is a standard and when it is a deviant. By directly comparing responses to identical stimuli when they are expected versus when they are deviants, the MMN in a baseline-corrected measure, revealing neural activity driven by hearing an unexpected event. Response latency of the MMN is determined based on the timing of the negative peak in the difference waveform. Response amplitude can be computed by taking the average response in a window centered on this negative peak. However, the analysis window used to determine MMN amplitude and latency varies across studies (e.g., it can be based on each individual subject's waveform, based on the average waveform of each subject group, or based on the average from all participants). Both MMN amplitude and latency metrics signify rapid discrimination that is driven by both bottom-up automatic and top-down attentive processes at early stages of cortical processing (Näätänen et al., 2012; Roberts et al., 2011).

The MMN response can be elicited both during active tasks, where the subject

makes an overt response upon detecting the deviant stimulus, and in settings when the subject listens passively, with no overt response required. As such, the MMN is one of the few established neural measures of auditory processing that does not require a high degree of instruction, overt attention, or active participation from the research participant (Bishop, 2007; Näätänen et al., 2012). This makes the MMN attractive to researchers studying individuals with ASD, whose verbal and cognitive abilities range across a wide spectrum; for paradigms measured in an active setting that require subjects to follow instructions, pay attention to stimuli, or perform a behavioral task, variations in subjects' abilities undoubtedly affect the measured response. To make meaningful cross-group comparisons from experiments that include subjects with and without verbal and cognitive deficits, it is important to use a paradigm for which performance is not significantly influenced by attention or other higher-level cognitive processes.

Many passive MMN experiments have been conducted on the ASD population, but there is no consensus across studies as to whether or not people with ASD exhibit a different MMN response to auditory deviants. Some publications have reported heightened and/or earlier MMN responses to acoustic deviants in ASD, suggesting greater auditory sensitivity to changes in acoustic stimuli (Gomot et al., 2011; Lepistö, Nieminen-von Wendt, von Wendt, Näätänen, & Kujala, 2007). Other publications have reported suppressed and/or delayed MMN responses to acoustic deviants in ASD, indicating a weaker sensitivity (Andersson, Posserud, & Lundervold, 2013; Yu et al., 2015). Still others have reported mixed results, such that some deviant stimuli elicit group differences while others do not (Lepistö et al., 2008, 2005). While several past

reviews have described these conflicting findings (Foss-Feig et al., 2012; Haesen et al., 2011; Kujala et al., 2013; Mcfadden & Rojas, 2013; Näätänen & Kujala, 2011; Orekhova & Stroganova, 2014), none have critically evaluated which factors may account for similarities and discrepancies across studies.

This lack of consensus prompted us to conduct a meta-analysis exploring whether there are methodological or stimulus differences that explain apparent inconsistencies across studies. We compared MMN response amplitude and MMN response latency between individuals with ASD and age-matched TD controls. We compiled the results from all experiments that met our inclusion criteria into a comprehensive statistical framework, treating each experiment or statistic as a single data point in our analysis. Given the complexities of collecting EEG and MEG data from individuals with ASD, sample sizes in individual studies tended to be fairly small and lacked strong power on their own. Our meta-analysis synthesized results across studies, thereby increasing the statistical power when testing for group differences.

We began by analyzing all published experiments that measured group differences between ASD and TD participants using either MMN amplitude or latency in a passive, auditory-based MMN paradigm. We then narrowed our analysis to include only those experiments that controlled for general variation in event-related potential or event-related field (ERP/ERF) responses to different stimulus tokens. Specifically, we only included studies in which the MMN was calculated by comparing responses to identical stimuli presented in two different contexts – one in which they were unexpected deviants and the other in which they were expected standards. Without counterbalancing

stimuli in this way, any difference in signal morphology between the response to deviants and standards might be due to differences in the unrelated neural responses to the specific stimuli presented, such as a loud sound producing a larger ERP/ERF than a soft sound (Duncan et al., 2009; Kujala et al., 2007). We followed up with analyses examining how stimulus characteristics (speech versus nonspeech sounds) impacted group-difference effect size and whether participant characteristics (age and verbal reasoning) influenced the findings.

METHODS

Literature Search and Screening Criteria

Our meta-analysis and systematic review followed PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). We began with a comprehensive literature search to identify publications reporting experiments that measured auditory MMN components in individuals with ASD, using the key terms “MMN,” “MMF”, “mismatch negativity,” “mismatch field,” “oddball,” “autism,” and “ASD” on PubMed, ScienceDirect, and Google Scholar. We used the following inclusion criteria:

(1) The publication had to include an experiment that used a paradigm in which standard stimuli were more prevalent than the interspersed deviant(s).

(2) The publication had to include an experiment that collected data with EEG or MEG.

(3) The publication had to include a passive listening experiment; specifically, participants must have received no instructions to listen and must not have been required

to provide a behavioral response (such as a hand raise or lever press) to detected deviant stimuli. This requirement reduces any influence of top-down modulation of neural responses, allowing for a fair comparison of neural responses from TD listeners and the more heterogeneous ASD sample, which included listeners with cognitive deficits.

Inclusion Criteria for Meta-analysis

Following our initial screening of publications, we established additional criteria for the inclusion of publications in our meta-analysis (**Figure 2.1**). The publication had to include an experiment that reported means, variation of the mean (i.e., standard error or standard deviation of the mean), and sample sizes of either MMN amplitude or latency for both an ASD and a TD comparison group. These descriptive statistics were necessary to calculate effect sizes for the meta-analysis. If any of this information was missing from the publication, we contacted authors of studies published between 2011-2017[2] and invited them to provide us with that information. Experimental statistics that compared participants with ASD to participants with other neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder, receptive developmental language disorder, tuberous sclerosis, dyslexia) were not included. EEG results had to be reported for mid-frontal electrodes (Fz, or if not available, an average of left and right midfrontal channels); we also included MEG results that localized source activity to the superior temporal gyrus (which would appear in mid-frontal electrodes in EEG measurements). To

[2] Individual correspondence with authors was needed in two instances to receive unpublished, additional information.

investigate early, automatic processes of mismatch detection, only statistics from latency windows between 50 and 400 ms were used in the meta-analysis. When statistics were available for specific age groups, we used these data to analyze the influence of age on MMN differences between ASD and TD groups.

Meta-Analysis

We performed all meta-analyses with the 'meta' package in R Version 3.1 (CRAN, 2015; Schwarzer, Carpenter, & Rücker, 2014). Meta-analyses operated on effect sizes, which were derived from the results of each experiment. Effect sizes were calculated based on the magnitude of the difference in MMN amplitude or response latency between ASD and TD participants, taking into account the variance of the difference and the sample sizes of each group. We determined Cohen's d effect size using Hedges' g, the bias-corrected standardized mean difference estimation (SMD) (Cohen, 1988). Positive SMD values reflected a smaller value in the ASD group, while negative SMD values corresponded to a larger value in the ASD group. Pooled deviation was computed based on parameters of standard deviation and sample size; pooled deviation was then used to calculate the 95% confidence intervals for the effect size.

Statistical variability between experiments, referred to as "between-experiment heterogeneity," was assessed first across all experiments, then across experiments that counterbalanced stimuli, and finally separately for speech and nonspeech experiments. To assess between-experiment heterogeneity, we used the Cochran's Q statistic (Cochran, 1954), where a nonsignificant value (above an alpha threshold of 0.05) indicated no

significant variance (Schwarzer et al., 2014). In particular, we used Cochran's Q statistic to determine whether or not the effect size differed within data sets (Q_w) and between data sets (Q_b) (Schwarzer et al., 2015). If there was no significant between-experiment heterogeneity within a single set of data (Q_w), it would suggest that there was a consensus across that set of experiments; similarly, if there was no significant heterogeneity between two sets of data (Q_b) (e.g., data from speech and nonspeech experiments), it would suggest that the sets of results showed similar effects. These methods used DerSimonian and Laird (1986)'s estimator for tau and an inverse variance method for calculations. When heterogeneity between experiments was significant, we computed the effect size using a random effects model; when it was not significant, we computed it with a fixed effects model.

To test for publication bias across reports, we used Egger's weighted linear regression intercept test with significance threshold set to alpha=0.05 (Egger, Davey Smith, Schneider, & Minder, 1997). This allowed us to determine whether what has been published accurately represents all completed research in the field, and, in turn, whether or not the data we were analyzing was inherently biased. For example, a significant publication bias may be suspected if group differences, like reductions in MMN in ASD, were only published in studies with small sample sizes, or null results were only published in studies with large sample sizes.

Subject Characteristics

To investigate the effects of age on MMN group differences, we collected mean

and variance values for each age in years for ASD groups.

In addition, we quantified MMN effect sizes as a function of verbal reasoning ability. Verbal reasoning skills are highly variable in ASD. Across the studies included in this meta-analysis, there was no single measure used to assess verbal reasoning ability. To quantify the role of verbal reasoning on group effect size, we used verbal intelligence quotients (VIQ), when reported. Publications that reported VIQ scores for the ASD group and were included in our analysis of VIQ used the Wechsler Intelligence Scales and the Stanford Binet (WAIS-R, Wechsler, 1981; WISC-III, Wechsler, 1991; WISC-IV, Wechsler, 2003; WPPSI-R, Wechsler, 1990; SB-IV, Thorndike et al., 1986). While not identical, strong positive correlations have been found between Weschler tests (Ross & Morledge, 1967; Shahim, 1992), as well as between the Weschler tests and the Stanford Binet, Fourth Edition (Frandsen & Higginson, 1951), suggesting that the measures capture similar constructs.

RESULTS

Full Meta-Analysis

Our systematic literature review identified a total of 38 publications published between 1980 and 2017 that had at least one experiment that measured EEG or MEG using a passive auditory mismatch negativity paradigm (**Table 2.1.A and Table 2.1.B**). Twenty-two of these publications included experiments that met all our criteria, yielding a total of 67 separate experiments; each of these experiments explored group differences between ASD and TD listeners based on MMN amplitude and/or latency (**Table 2.1.A**).

From these experiments, data from a total of 857 ASD and 831 TD subjects were included in this analysis.

Figure 2.2.A summarizes how the selected 67 experiments characterized deviance detection in different subject groups. We first classified experiments by the type of auditory stimuli used (either natural speech or nonspeech). Speech stimuli included naturally spoken consonants and/or vowels (e.g., “a” and “o” or “ba” and “wa”), or words (e.g., “pie” and “bye”). Nonspeech stimuli included pure tones (i.e., pure sinusoids) or complex tones (i.e., periodic stimuli made up of multiple harmonic components). Often, the frequency content of the complex tones was shaped to mimic the formant structure of a certain vowel, so that they simulated detection of phonemic changes; however, they did not contain the natural spectral dynamics of typical speech so we classified these tones as nonspeech. We further classified experiments by the type of deviant presented. Most commonly, deviants differed in phoneme, pitch (i.e., fundamental frequency), or duration. Less commonly, deviants differed in affective prosody, intensity, rhythm, or spatial location.

From the distribution in **Figure 2.2.A**, it is clear that experiments on children included samples with below-average verbal skills (mean verbal IQ below 80), samples with average or above-average verbal skills (mean verbal IQ above 90), and samples with a mixture of low and average or above-average verbal skills abilities (mean VIQ between 80 and 90). In contrast, studies focused on adolescents and adults included only individuals with average or above-average verbal skills. In addition, nonspeech stimuli were favored in experiments conducted on participants with below-average verbal IQ,

whereas studies on participants with average or above-average verbal IQ included both speech and nonspeech stimuli.

A summary of our meta-analysis across all appropriate experiments in the 22 publications (67 experiments) reporting MMN amplitude and latency appears in **Table 2.2**. There were no overall significant group differences in amplitude or latency. However, effect sizes were not consistent, with significant between-experiment variability. Across the studies from 22 publications, effect sizes for reported amplitude differences formed a Gaussian distribution, indicating that studies selected for publication were representative of all studies conducted on this topic (**Figure 2.3.A**). The available data on latency differences from a total of 17 publications showed evidence of negatively-skewed publication bias; that is, published studies with negative results were over-represented in small-scale studies compared to large-scale studies (**Figure 2.3.B)**.

Deviant-Standard Counterbalanced Experiments

The next stage of our analysis included only those experiments that computed an MMN by taking differences in responses to physically identical stimuli when they were presented as both a deviant and a standard, which resulted in 24 experiments measuring MMN amplitude and 19 experiments measuring MMN latency across 6 publications. A total of 307 ASD and 280 TD subjects were included in the analysis of MMN amplitude and a total of 255 ASD and 231 TD subjects were included in the analysis of MMN latency. Collectively, these experiments included participants between the ages of 6 and 15 and adults over 21; notably, none of these studies focused on adolescents (**Figure**

2.2.B). In addition, the majority of participants in these studies had average or above-average verbal IQs.

A meta-analysis on this data set revealed a standardized mean difference between ASD and TD groups in their MMN amplitude of 0.15 [-0.01-0.32], p=0.07 (**Figure 2.4; Table 2.2**). Although the group difference in MMN response did not reach statistical significance, there was a trend for children and adults with ASD, collectively, to show smaller MMN amplitudes than their TD peers. Tests of heterogeneity confirmed that the experiments measuring MMN amplitude produced consistent results. Just as in the full sample, there was no evidence of publication bias for MMN amplitude (**Figure 2.3.C**). A meta-analysis of latency values revealed that there were no significant group differences; further, there was still considerable within-sample variability and evidence of publication bias (**Figure 2.3.D**). Therefore, we discontinued our analysis of latency differences.

Effects of Stimuli and Subject Characteristics on Amplitude Differences

To explore whether stimulus characteristics influenced our findings on MMN amplitude, we separately analyzed counterbalanced experiments using nonspeech and experiments using speech stimuli (**Figure 2.5; Table 2.2**). For nonspeech stimuli, MMN responses were significantly smaller for individuals with ASD than for TD controls (SMD effect size=0.25, p=0.02). In contrast, there were no significant group differences for experiments investigating responses to speech stimuli (SMD effect size=0.009, p>0.05). However, there was no significant difference between the distribution of effect sizes resulting from speech and nonspeech experiments when the two were directly

compared ($Q_b(1)=1.93$, $p=0.16$).

To examine whether or not the mean age of the ASD participants influenced results, we ran a linear regression in R Version 3.1 (CRAN, 2015; for similar example, see Erickson, Ruffle, & Gold, 2015). Mean age of the ASD group accounted for 25% of the variance in MMN amplitude effect size across experiments ($R^2=0.25$, $F(1,22)=7.28$, $p=0.01$) and age significantly predicted effect size (Beta=-0.03, $p=0.01$). Visual inspection of effect size organized by mean age of the ASD group revealed that the youngest cohorts of ASD subjects had MMN amplitudes that were smaller than TD listeners, while adult cohorts of ASD subjects had MMN amplitudes equal to or larger than those of their TD peers (**Figure 2.4**).

A similar linear regression analysis on the influence of verbal IQ explained only 3% of the effect size variance ($R^2=0.03$, $F(1,19)=0.60$, $p=0.45$) and did not predict effect size values (Beta=-0.004, $p=0.45$). In addition, when verbal IQ was included as a covariate in a linear model that measured the degree to which age predicted effect size, the model accounted for 24.7% of the effect size variance but was not statistically significant ($R^2=0.247$, $F(2,18)=2.95$, $p=0.08$). In this model, mean age still significantly predicted effect size (Beta=-0.03, $p=0.03$). These results suggest that effect size differences across age cannot be explained solely by differences in verbal IQ.

DISCUSSION

Summary

Although a fair number of past publications have investigated the MMN in ASD, individual studies have come to different conclusions. We undertook our meta-analysis to try to resolve these differences. Instead, our analysis revealed several important limitations of these studies. First, the majority of published studies used small sample sizes with fewer than 20 participants per group. This poses problems for efforts to aggregate results with respect to group differences in MMN latency, since our analysis suggests that negative or null effect size results are reported more often in published small studies than in large studies. Furthermore, results from underpowered, small-sample studies are inherently less reliable and noisier than results from larger studies, which limits the power of our meta-analysis. Second, only 24 of the originally identified 67 studies measured MMNs with a rigorous design in which physically identical auditory stimuli were presented as standards and as deviants in different experimental blocks. Third, certain ages and verbal profiles, particularly adolescents and individuals with below-average verbal profiles, were not well represented in the pool of subjects tested. These issues may help explain some of the apparent variability across findings. Once we restricted our meta-analysis to include only appropriately counterbalanced experiments, we found amplitude effect sizes to be more consistent. Within this counterbalanced sample, there was no significant difference between groups in either MMN amplitude or MMN latency. However, there was a trend for ASD subjects to show smaller MMN

amplitudes in response to deviant sounds than their TD peers, a finding warranting further investigation. When we divided our analyses by stimulus type, subjects with ASD had a significantly reduced MMN amplitude response to nonspeech, but not speech, deviants. In addition, younger children with ASD tended to exhibit reduced amplitude responses (i.e., greater effect sizes) while adults tended to show equal or larger amplitude responses than TDs (i.e., lower effect sizes). Moreover, no significant effects could be attributed to differences in verbal reasoning.

Importance of Counterbalanced Experiments

When we considered effect size of group differences across all 67 experiments that met our initial inclusion criteria, no consistent pattern emerged. This was perhaps due to major inconsistencies in MMN measurement; in particular, many of those experiments used stimuli that were not counterbalanced. Differences in the physical nature of standard and deviant stimuli can give rise to different evoked EEG responses, a confound for studies evaluating only the contextual effects of the stimuli. Specifically, the N1 response – which occurs only slightly before the MMN onset – can vary significantly with the acoustic properties of a stimulus (Duncan et al., 2009; Kujala et al., 2007). Different acoustic features in standard and deviant stimuli can contaminate the standard-deviant difference waveform that is computed to quantify the MMN (Kujala et al., 2007). As a result, the "MMN" produced by subtracting these unmatched standard and deviant responses do not solely contain response components that reflect effects of context and detection of an unexpected stimulus.

For example, in this analysis, of the 11 experiments that measured detection of pitch change and did not counterbalance, 8 used deviants that were higher in pitch than their relative standards. In these experiments, the "MMN" might be partially attributable to the fact that the N1 response is larger for high-pitched than low-pitched sounds. Such an effect could be especially significant for those participants with ASD who are particularly sensitive to high pitches (Bonnel et al., 2010, 2003). Similarly, in three of the four experiments that measured duration deviance and did not counterbalance stimuli, the duration of the deviant was shorter than the standard. Under such conditions, the N1 offset to the deviant occurs prior to the N1 offset to the standard due to nonlinear effects in the auditory periphery (Kujala et al., 2007). This difference wave in N1 response could either be misinterpreted as an MMN or obscure the real presence of an MMN (Kujala et al., 2007). Although counterbalancing significantly lengthens the duration of an experiment, we recommend that future experiments compute MMNs by using identical stimuli as "standards" and "deviants" in different blocks. Taking this approach, the MMN will capture stimulus change detection and ensure response components are not due to differences in responses to different sounds.

Variations in Stimulus Features

Prior reports have suggested that group differences between ASD and TDs are specific to either speech or nonspeech stimuli (Fan & Cheng, 2014; Jansson-Verkasalo et al., 2003; Lepistö et al., 2007; Weismüller et al., 2015; Yu et al., 2015). Of the experiments using nonspeech stimuli, the majority employed complex tones, not pure

tones. In our meta-analysis of nonspeech experiments, ASD subjects had smaller MMN responses than TD subjects. These results suggest that complex tone deviants lead to smaller MMN responses in people with ASD. This finding corroborates prior work concluding that individuals with ASD have weak neural and behavioral responses to changes in complex nonspeech stimuli, perhaps due to a weak encoding of spectrally and temporally complex, dynamic information (Samson, Mottron, Jemel, Belin, & Ciocca, 2006). Further, our results support prior work arguing that deficits in nonspeech auditory processing are present in ASD (Foss-Feig et al., 2012). Thus, people with ASD, especially children, may be less efficient in their pre-attentive and automatic processing of auditory regularities in nonspeech stimuli, which is measured by the MMN.

In contrast, our meta-analysis showed no significant MMN group differences in response to speech-based stimuli. Features of early auditory discrimination that arise from deviations in low-level features such as pitch, duration, or intensity deviants should cause similar effects whether the stimuli are nonspeech or speech. However, speech-based stimuli were often used when measuring sensitivity to phonetic deviants, a process which may rely on later stages of cortical processing. Of note, the few studies included in our meta-analysis and systematic review that analyzed results in later latency windows (minimum of window starting at 200 ms) measured speech-elicited neural responses. Processing of speech-feature change may be reflected in later ERP/ERF components like the P3 (Cui, Wang, Liu, & Zhang, 2017; Haesen et al., 2011), rather than relatively early responses like the MMN, which we analyzed. Further investigation comparing late ERP/ERF components in ASD and TD populations should be undertaken to examine

whether later neural processing stages for speech stimuli differ between these populations.

Variations in Subject Characteristics

In addition to our primary meta-analysis, we characterized how group differences in MMN amplitude change across development. This choice was motivated by evidence that the MMN changes over the course of typical developmental and the fact that ASD is a *developmental* disorder (Martin, Shafer, Morr, Kreuzer, & Kurtzberg, 2003; Shafer et al., 2000). We found that age accounted for 25% of MMN amplitude differences. Studies on young children tended to produce the greatest effect sizes, representative of reduced amplitude response in ASD. Studies on adults tended to produce the most negative effect sizes, representative of equal or larger amplitude responses in ASD. However, there were no studies that counterbalanced stimuli and focused on adolescents with ASD. This gap prevented us from fully characterizing age differences in MMN amplitude in ASD compared to TD. Further, the available data was based solely on cross-sectional data. Future studies using a longitudinal approach may uncover whether young children with absent or reduced MMNs develop mature MMN responses with age.

While the conclusions we can make about MMN across age are constrained by limited data, the results of our analysis complement parent-reported data on children with ASD, which suggest that 1) atypical auditory processing in ASD decreases with age (Kern et al., 2006) and 2) sensory modulation symptoms, including abnormal sensitivity to sound, are greatest in middle childhood between the ages of 6 and 9, decreasing

thereafter (Ben-Sasson et al., 2009). The parallels between these reports and our findings point to a potential link between neural response to sounds and an overt sensitivity to sounds that should be explored in future studies.

Given the postulated link between auditory processing and language development in ASD, we also considered the verbal reasoning abilities of subjects across studies (Kujala, 2007). Our findings first and foremost demonstrate that the MMN response in individuals with below-average verbal reasoning abilities is still highly understudied. The set of available data was skewed, with the majority of children between the ages of 6 to 8, as well as adults, displaying average or above-average verbal reasoning and the majority of children between the ages 9 to 12 displaying below-average verbal reasoning. Still, verbal IQ, a measure of verbal reasoning abilities, did not significantly predict individual experiment group differences or account for differences in effect size already predicted by age, which reduces concern that differences in the distribution of verbal reasoning in different age groups biased our findings.

Of the 67 MMN studies identified by our meta-analysis, only 15 included individuals with below-average verbal IQ (standardized mean scores of less than 80), the majority of which were were younger than 12. Researchers need to be aware that there are few studies that include individuals with low verbal ability and work to fill this gap, e.g., using a passive auditory MMN paradigm (Bishop, 2007; Näätänen et al., 2012).

Consideration of Latency

While there was a trend towards significant differences in amplitude between ASD and TD groups, MMN latency did not differ across groups. However, only 19 counterbalanced experiments across 4 publications examined MMN latency, sampling a total of 486 participants (255 ASD and 231 TD). Significant variability within the sample in both full and counterbalanced-only samples were evident. These results were driven considerably by one large study that reported large positive results; all other studies included in this analysis had small effect sizes clustered around zero. Moreover, while significant publication bias was identified, its impact cannot be fully isolated from other findings reflected in the large variability across studies (Peters et al., 2010). Meta-analyses of the MMN in populations with other clinical conditions (e.g., attention deficit hyperactivity disorder, specific language impairment and dyslexia, schizophrenia) have not reported on latency group differences, perhaps because of a similar paucity of such studies (Bishop, 2007; Cheng, Chan, Hsieh, & Chen, 2016; Erickson et al., 2015; Umbricht & Krljesb, 2005). It is also likely that few studies report on latency because it is a relatively unreliable way to quantify noisy ERP/ERF data, especially when there may not be definitive, sharp component peaks (Bishop, 2007; Luck, 2005). These issues with noise become especially relevant when analyzing ERPs/ERFs from young children and individuals with neurodevelopmental disorders. The large, positive findings in the sole study using MEG that we examined begs the question of whether latency differences are more discernable in data sourced to the STG using MEG than data measured from fronto-central scalp channels with EEG. Future refinements in EEG/MEG analysis techniques

are needed to make it possible to calculate latency with greater precision.

Future Directions

While we initially identified a large number of published studies describing the MMN component in ASD, only a handful computed the MMN by comparing standard and deviant responses for acoustically identical stimuli, and even fewer contributed data that could help us identify differences between groups influenced by age or verbal reasoning abilities. Among those that measured the MMN, many had small sample sizes, leading to relatively low statistical power. For future work to identify individuals with ASD who are most susceptible to auditory processing deficits, counterbalanced paradigms need to be administered. These paradigms should be applied to large sets of subjects, from young children through adults, that display a range of severity in their clinical ASD features and language abilities. Based on MMN studies in typically developing adults, there are recommendations for procedures, stimulus design, recording, and analysis techniques that elicit a robust MMN (Duncan et al., 2009; Pakarinen, Takegata, Rinne, Huotilainen, & Näätänen, 2007). Such recommendations should be followed when testing individuals with ASD to produce robust, consistent results that can be compared across studies.

Most research has compared average response magnitudes between ASD and TD. However, we find no major group differences and hypothesize that this is in part due to the heterogeneous nature of ASD. While group-level analysis is important, future research should also consider whether individual differences can be measured reliably in

MMN responses. For instance, researchers can investigate metrics such as the percentage of each group that showed a reliable MMN (Bishop & Hardiman, 2010; Dunn et al., 2008). Subjects in the ASD population who do not demonstrate a reliable MMN response may also tend to share a common phenotypic or clinical feature; this kind of result could allow MMN measures to help identify distinct subgroups within the heterogeneous ASD population.

A few of the studies that we reviewed did look at the relationship between MMN response magnitude and phenotypic characteristics other than verbal reasoning (Andersson et al., 2013; Gomot et al., 2011; Kuhl et al., 2005), but because similar measures were not readily available across studies, we could not combine results in a meaningful way in our meta-analysis. Studies on other brain-based disorders such as schizophrenia have demonstrated associations between MMN amplitude and clinical characteristics such as symptom severity and duration of symptoms (Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; Erickson et al., 2015; Light & Braff, 2005; Umbricht & Krljesb, 2005). Given these successes, it seems promising to investigate relationships between established and commonly used measures of ASD severity (e.g., Autism Diagnostic Observation Schedule Calibrated Severity Score; Gotham, Pickles, & Lord, 2009), language (e.g., Peabody Picture Vocabulary Test, Version 4; Dunn & Dunn, 2007), and MMN in future studies.

Considerable work is necessary to determine whether reduced MMNs in young children translate to poorer outcomes in language or other cognitive domains (Friedrich, Weber, & Friederici, 2004; Leppänen et al., 2002). Still, the MMN is detectable in infants

as young as 8 weeks old (Friederici, Friedrich, & Weber, 2002; Schall, 2015; Shafer, Yu, & Datta, 2011; Trainor et al., 2003) and subject-specific analysis may allow clinicians to use MMN responses to identify children who have atypical cortical processing and who thus might be prone to developing auditory processing deficits.

Conclusions

To our knowledge, our meta-analysis is the first to empirically evaluate the results from a large set of previously published studies reporting MMN responses in ASD. Through this analysis, we found that most studies on this topic were not designed with counterbalanced stimuli and did not produce consistent results. When our analysis was confined to studies that used physically identical stimuli in standard and deviant contexts, we found that there were still no major group differences for MMN amplitude or latency, but that group differences in amplitude became more consistent and changed as a factor of age. Still, these findings were derived from an unrepresentative sample of individuals with ASD and underpowered studies using a small number of participants. Given the heterogeneity of characteristics in ASD and variability we find across studies, studies considering only between-group effects may be overlooking critical information about individual differences in MMN response within the ASD group. These limitations expose major gaps in the current literature.

Table 2.1.A. Summary of 22 publication sources used in meta-analysis. P=Pure tone; C=Complex tone; S=Speech; (SD)* = SD calculated from SD=S.E.M. * √N; NR=Not reported; NR-NWNL=Not reported but indication of not-within normal limits; NR-WNL=Not reported but indication of typical range of scores (within normal limit); Italicized IQs indicate values are Developmental Quotients rather than Intelligence Quotients. Asterisks are placed by the VIQ measures used in our statistical analysis. VIQ or Language Measures: CELF-III=Clinical Evaluation of Language Fundamentals—Third Edition (Semel et al., 1995); EDEI-R=Échelles Différentielles d'Efficiences Intellectuelles—Revised (Perron-Borelli, 1978); PPVT-III=Peabody Picture Vocabulary Test—Third Edition (Dunn & Dunn, 1997); SB-IV=Stanford Binet, Fourth Edition (Thorndike et al., 1986); WAIS-R=Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981); WISC-R=Wechsler Intelligence Scale for Children—Revised (Wechsler, 1974); WISC-III=Wechsler Intelligence Scale for Children—Third Edition (Wechsler, 1991); WISC-IV=Wechsler Intelligence Scale for Children—Fourth Edition (Wechsler, 2003); WPPSI-R=Wechsler Preschool and Primary Intelligence Scales—Revised (Wechsler, 1990).

			n		***Mean (SD or Range)***					
ID	**Source**	**Stimuli**	**TD**	**AUT**	**Age (years)**	**AUT AGE**	**AUT VIQ**	**VIQ Measure**	**MMN Analysis Window (ms)**	**Std-Dev Controlled**
1	Andersson et al. 2013	C	12 (0F)	11 (0F)	~16	16.0 (0.8)	92 (5)	WISC-III	140-220	No
2	Dunn et al. 2008 (passive)	P	34 (14F)	34 (9F)	6-13	9.3 (2)	84 (23)	SB-IV	163-213	Yes
3	Fan et al. 2014	CS	20 (1F)	20 (1F)	18-29	21.5 (3.8)	NR	WAIS-IV	150-250	No
4	Ferri et al. 2003	P	10 (0F)	10 (0F)	6-19	12.3 (4.9)	NR	NR	NR, Approx 109-147	No
5	Gomot et al. 2002	P	15 (3F)	15 (3F)	5-9	6.8 (1.3)	*50 (27*)*	BL-R, EDEI-R	140-230	No
6	Gomot et al. 2011	P	27 (6F)	27 (6F)	5-11	8.3 (1.7)	*43 (14*)*	BL-R, EDEI-R	120-250	No
7	Jansson-Verkasalo et al. 2003	PS	11 (4F)	10 (4F)	7-12	9.1 (1.5)	NR	NR	P: 150-320, S: 200-380	No
8	Jansson-Verkasalo et al. 2005	P	18 (9F)	19 (5F)	7-14	10.6 (0.9)	NR	NR	1: 85-140 2: 140-220	No

9	Korpilahti et al. 2007	S	13 (0F)	14 (0F)	9-13	11.2 (NR)	107 (NR)	WISC-III	150-350	No
10	Kujala et al. 2005	S	8 (4F)	8 (4F)	22-43	33 (NR)	NR	WAIS-R	116-225	No
11	Kujala et al. 2007	C	10 (2F)	8 (2F)	12-42	27 (5.6)	103	NR	100-250	No
12	Kujala et al. 2010	S	13 (2F)	15 (4F)	8-12	10.8 (0.9)	112 (19)	WISC-III	200-320	No
13	Lepistö et al. 2005	CS	15 (2F)	15 (2F)	7-12	9.4 (NR)	59 (40-90)	WISC-III, WPPSI-R	100-400	Yes
14	Lepistö et al. 2006	CS	10 (2F)	10 (2F)	7-10	8.11 (NR)	108 (86-129)	WISC-III	100-400	Yes
15	Lepistö et al. 2007	CS	9 (1F)	9 (2F)	20-41	27 (NR)	104 (90-126)	WAIS-R	100-400	Yes
16	Lepisto et al. 2008 (constant-feature)	S	16 (1F)	10 (1F)	6-11	9.1 (NR)	54 (41-70)	WISC-III	100-400	No
17	Lepistö et al. 2009 (oddball)	P	14 (2F)	16 (3F)	7-10	8.1 (NR)	113 (90-145)	WISC-III	100-300	No
18	Ludlow et al. 2014	S	11 (0F)	11 (0F)	11-16	13.0 (1.1)	101 (10)	NR	NR	No
19	Roberts et al., 2011	P	27 (15F)	51 (2F)	6-15	9.36 (2.11)	Approx. 40-120	CELF-IV	150-350	Yes
20	Seri et al. 1999	P	7 (NR)	7 (NR)	7-10	8.3 (0.69)	NR	NR	130-250	No
21	Weismüller et al. 2015	PS	15 (0F)	18 (0F)	6-15	9.4 (2.4)	NR	WISC-IV	120-300	S: Yes P: No
22	Yu et al. 2015	PCS	1: 16 (3F) 2: 18 (6F)	1: 18 (2F) 2: 16 (1F)	6-13	1: 9.3 (1.8) 2: 9.6 (1.3)	NR	NR	100-250	No

Table 2.1.B. Summarized information of additional 16 publications considered in initial systematic review. P=Pure tone; C=Complex tone; S=Speech; (SD)* = SD calculated from SD=S.E.M. * √N; NR=Not reported; NR-NWNL=Not reported but indication of not-within normal limits. NR-WNL=Not reported but indication of typical range of scores (within normal limit). Italicized IQs indicate values are Developmental Quotients rather than Intelligence Quotients. VIQ or Language Measures: BAS=British Ability Scales (Eliot, 1983); MSEL=Mullen Scales of Early Learning (Mullen, 1984); PPVT=Peabody Picture Vocabulary Test (Dunn et al., 1965); RDLS-2=Reynell Developmental Language Scales—Second Revision (Reynell & Huntley, 1985); VTRG=Test for Reception of Grammar (Bishop, 2005); WISC=Wechsler Intelligence Scale for Children (Wechsler, 1949); WISC-RN=Wechsler Intelligence Scale for Children, Version—Revised, Dutch Version (Van Haasen et al., 1986); WAIS=Wechsler Adult Intelligence Scale (Wechsler, 1955).

			n		***Mean (SD or Range)***					
ID	**Source**	**Stimuli**	**TD**	**AUT**	**Age (years)**	**AUT AGE**	**AUT VIQ**	**VIQ Measure**	**MMN Analysis Window (ms)**	**Std-Dev Controlled**
23	Abdeltawwab et al. 2015	P	30 (12F)	31 (7F)	6-17	11.3 (2.8)	NR-NWNL*	NR	~150-200	No
24	Bruneau et al. 2014	P	NR	NR	6-14	NR	NR	NR	NR	No
25	Ceponiene et al. 2003	PCS	10 (1F)	9 (1F)	6-13	8.9 (2)	NR-NWNL*	RDLS	176-248	No
26	Courchesne et al. 1984 (passive)	S	7 (NR)	7 (NR)	13-21	NR	71 (NR)	PPVT	NR	No
27	Donkers et al. 2013	P	39 (8F)	28 (6F)	4-12	7.5 (2.2)	NR	NR	NR	No
28	Edelson et al. 1999	P	0 (0F)	5 (NR)	4-39	11.6 (NR)	NR	NR	NR	No
29	Kasai et al. 2005	PS	19 (6F)	9 (3F)	15-38	27.2 (7.7)	NR-NWNL*	WAIS-R	100-250	No
30	Kemner et al. 1995 (passive)	S	20 (4F)	20 (4F)	6-13	9.8 (1.5)	80 (19)	WISC-RN	150-325	No
31	Kuhl et al. 2005	S	15 (2F)	29 (3F)	2-5	3.8 (NR)	NR	MSEL	250-400	No

32	Lincoln et al. 1993; 1995 (passive)	P	10 (NR)	10 (NR)	8-14	NR	58 (12)	WISC-R	NR	Yes
33	Niwa et al. 1983 (passive)	P	5 (4F)	4 (0F)	11-22	14.9	NR	WAIS, WISC	NR	No
34	Novick et al. 1980 (passive missing stimulus paradigm)	P	5 (NR)	5 (NR)	Adole-scent	NR	NR	NR	NR	No
35	Oades et al. 1988	P	9 (NR)	7 (NR)	5-18	11.3 (4.0)	NR	BAS	NR	No
36	Oram Cardy et al. 2005	PC	9 (4F)	7 (0F)	8-17	11.9 (3.1)	81 (16)	WISC-3, WAIS-3, CELF-4	80-150	Yes
37	Tecchio et al. 2003	P	10 (2F)	14 (3F)	8-32	16 (9)	NR	NR	100-250	No
38	Whitehouse et al. 2008	CS	15 (0F)	15 (0F)	7-15	10.4 (NR)	94 (70-113)	Verb Test for Rec of Gram	NR	No

Table 2.2. Effect Size and Tests of heterogeneity between experiments comparing MMN amplitude and MMN latency between ASD and TD groups. Results are computed for all experiments in the meta-analysis and experiments that counterbalanced standards and deviants. Positive SMD values correspond to the ASD group's overall reduction in that metric, while negative values represent an increase.

	Test of Heterogeneity						Effect Size		
Sample	**Q**	**df**	**p value**	**T^2**	**H**	**I^2 [95% CI]**	**SMD [95% CI]**	**z-score**	**p value**
Amplitude Measures: All	98.48	63	<0.01	0.09	1.25	36.0 [13-53]	0.071 [-0.06 – 0.20]	1.1	0.27
Amplitude Measures: Counterbalanced	24.07	23	0.40	0.01	1.02	4.4 [0-35]	0.15 [-0.02 – 0.32]	1.78	0.07
Amplitude Measures: Speech	11.27	10	0.34	0.02	1.06	11.2 [0-51]	0.01 [-0.25 – 0.27]	0.07	0.94
Amplitude Measures: Nonspeech	10.87	12	0.54	0.00	1.00	0.0 [0-52]	0.25 [0.03 – 0.46]	2.26	0.02
Latency Measures: All	154.32	49	<0.01	0.36	1.79	68.9 [58-77]	-0.02 [-0.22 – 0.19]	-0.14	0.89
Latency Measures: Counterbalanced	67.03	18	<0.01	0.47	1.93	22.9 [0-56]	0.16 [-0.20 – 0.53]	0.89	0.37

Figure 2.1. Flow chart of selection for meta-analysis. N values represent total number of publications in which experiments were reported. Regions of interest (ROI) are mid-frontal electrodes for EEG studies and bilateral superior temporal gyrus for MEG studies.

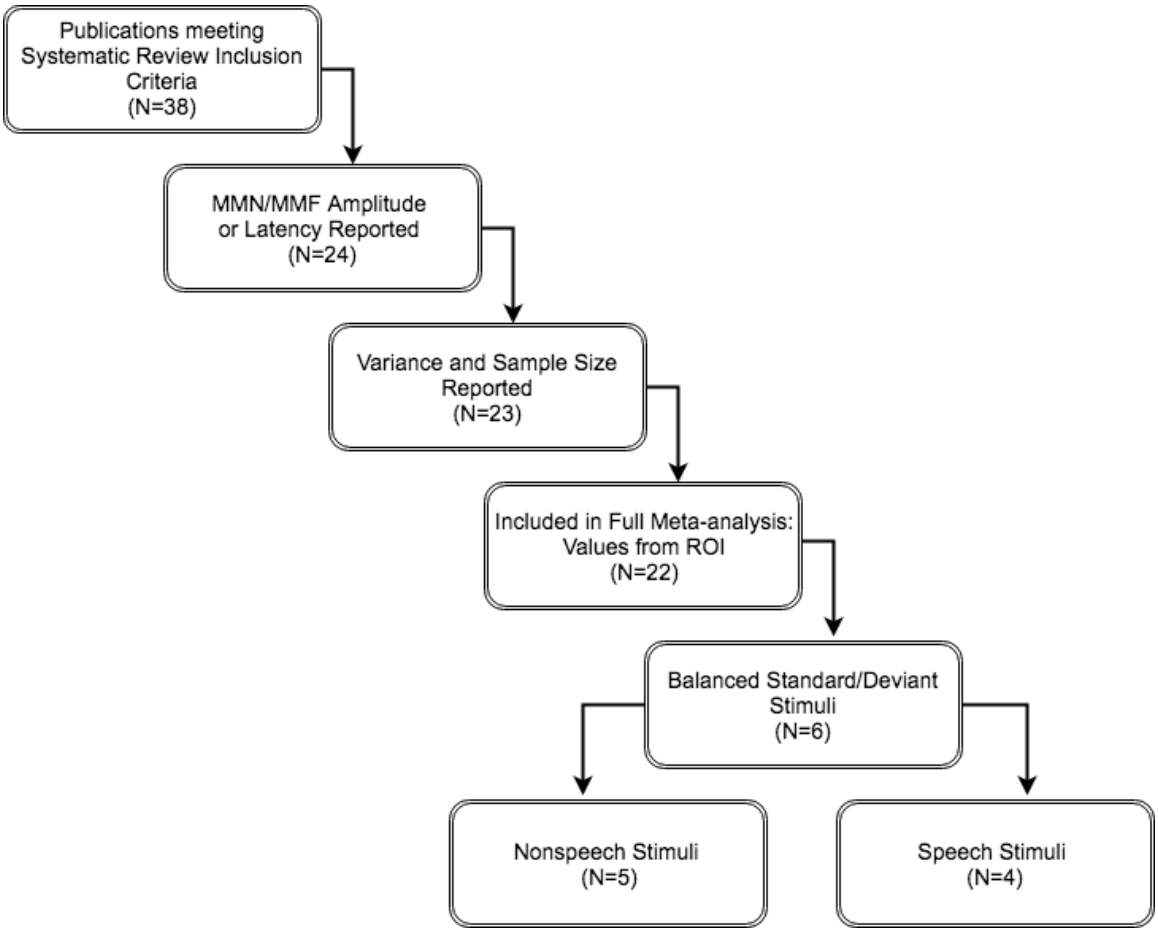


Figure 2.2. Histogram of (A) all 67 experiments included in this meta-analysis and (B) 24 counterbalanced experiments. Experiments are classified by average age and verbal intelligence standard score of ASD participants. Average or above-average verbal intelligence ("Average VIQ") is defined by average standard scores of 90 or above. Below average verbal IQ ("Low VIQ") is defined by average standard scores below 80. Samples that fall between average standard scores of 80 and 90, around the cutoff score for disability (85) are considered as "Combined Low and Average" VIQ. Experiments are also classified based on the auditory feature which is deviating ("Deviant Type") and the nature of the stimuli ("Speech" or "Nonspeech"). The "Other" category includes experiments that deviated stimuli based on "emotional content" (e.g., cheerful, angry, commanding, or sad), gap, or location.

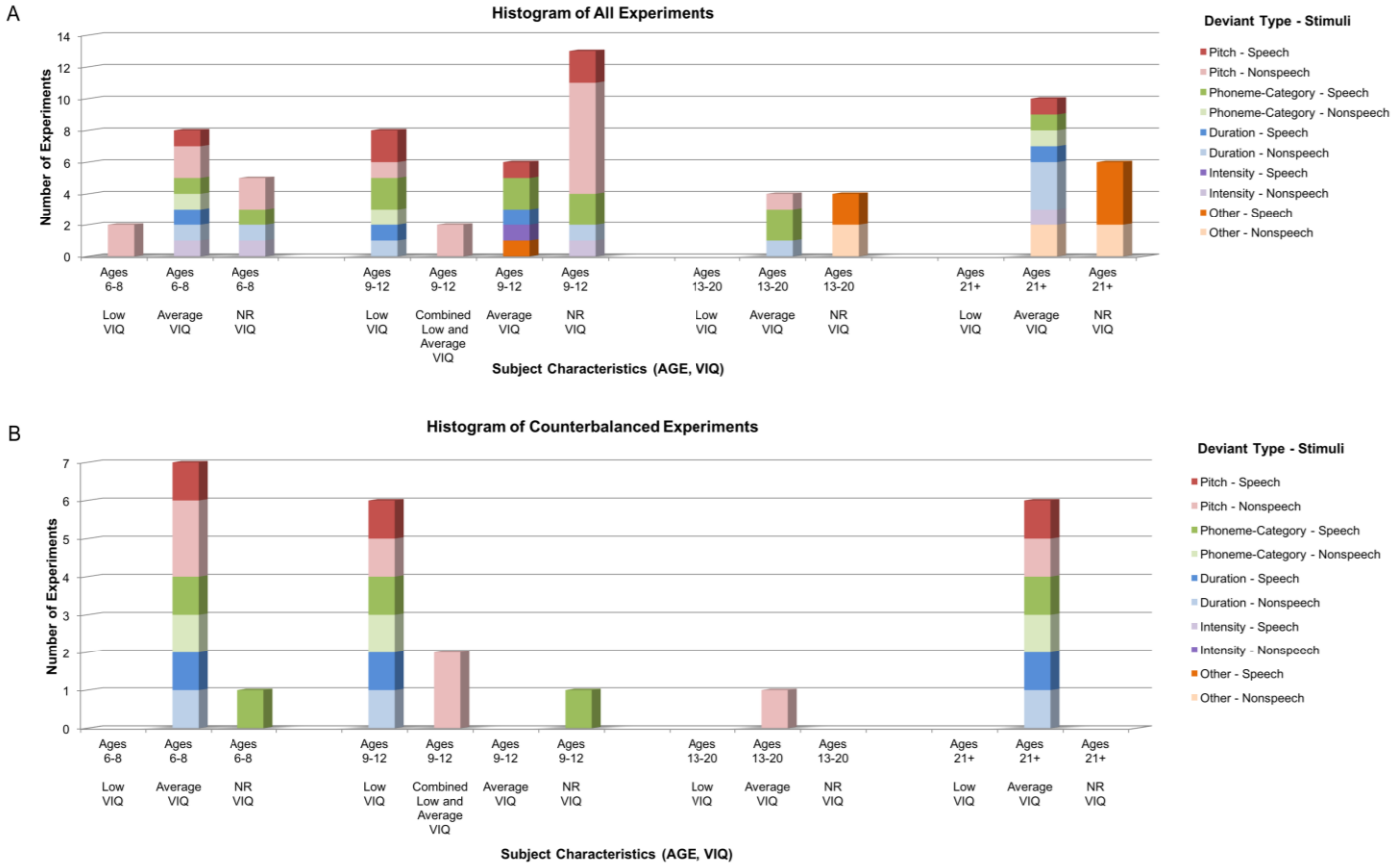


Figure 2.3. No evidence of publication bias based on (A) amplitude and (B) latency effect sizes from full sample, as shown by symmetrical funnel plots. The same was true for (C) counterbalanced amplitude and (D) counterbalanced latency. Egger's regression tests: A. Intercept = -1.23 [95% standard error confidence interval: -2.88– 0.41], t = -1.47, *p*>0.05; B. Intercept: -3.16 [95% standard error confidence interval: -5.90– -0.42], t = -2.26, *p*=0.02. C: Intercept: 0.57 [95% standard error confidence interval: -1.55–2.68], t=0.53, *p*>0.05. D: Intercept: -6.03 [95% standard error confidence interval: -11.29– -0.76], t=-2.24, *p*=0.04

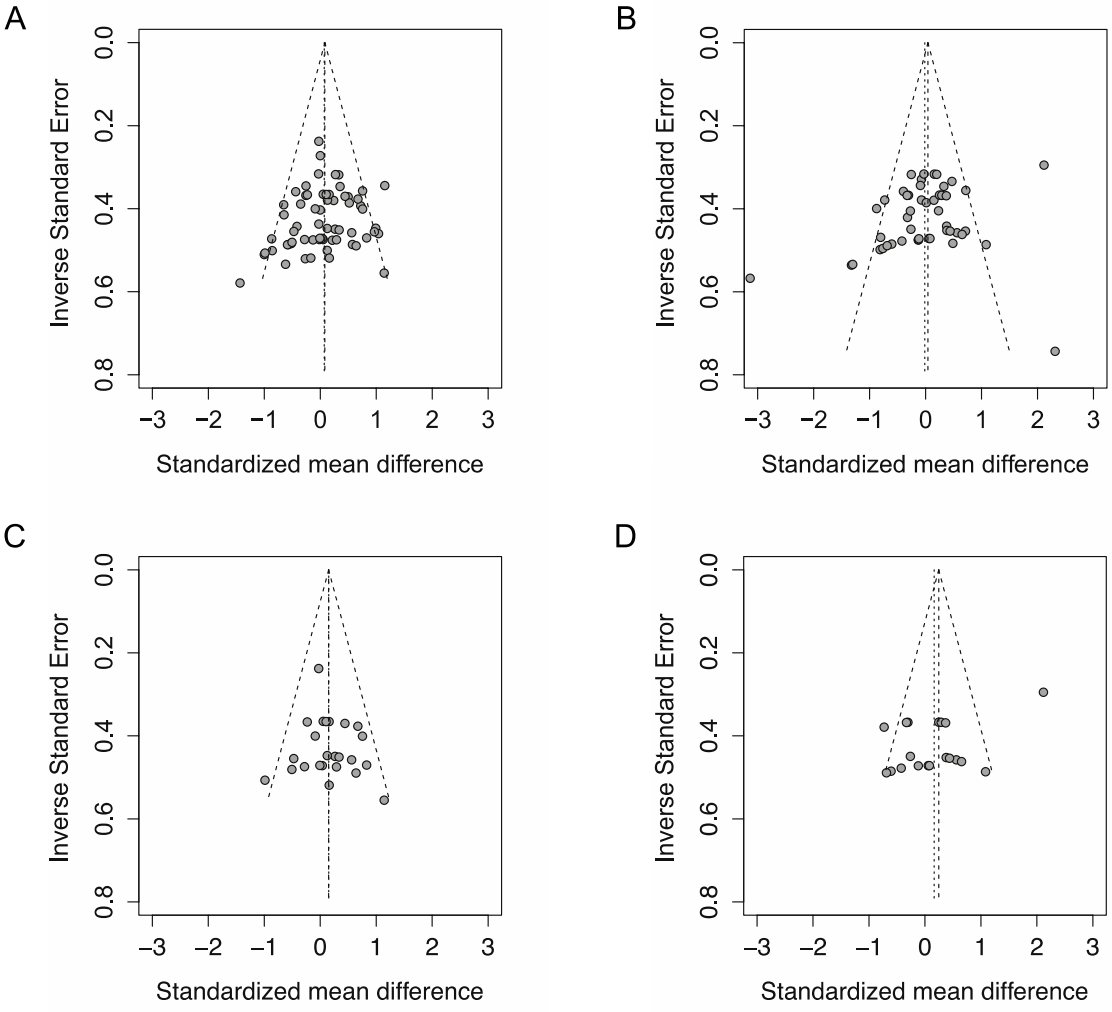


Figure 2.4. Meta-analysis of experiments that counterbalanced deviant and standard stimuli, organized by mean age of the ASD group. Effect size is governed by standardized mean difference value (SMD). Experiment indicated by "Publication Number, as indicated in Table 1: Stimulus type, Deviant Type, (Mean ASD Age)". Stimulus Type: P=Pure Tone, S=Speech, C=Complex Tone.

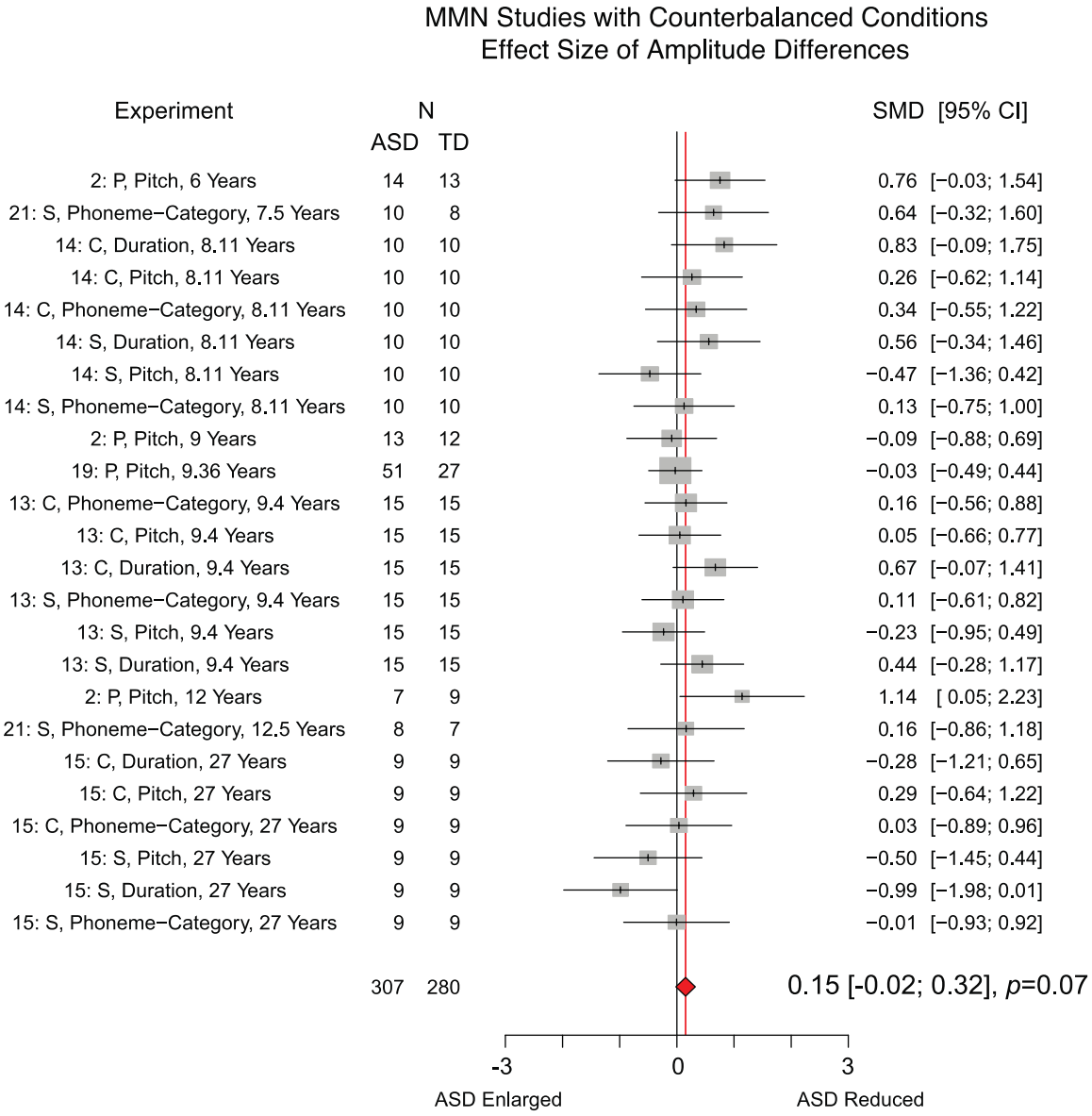
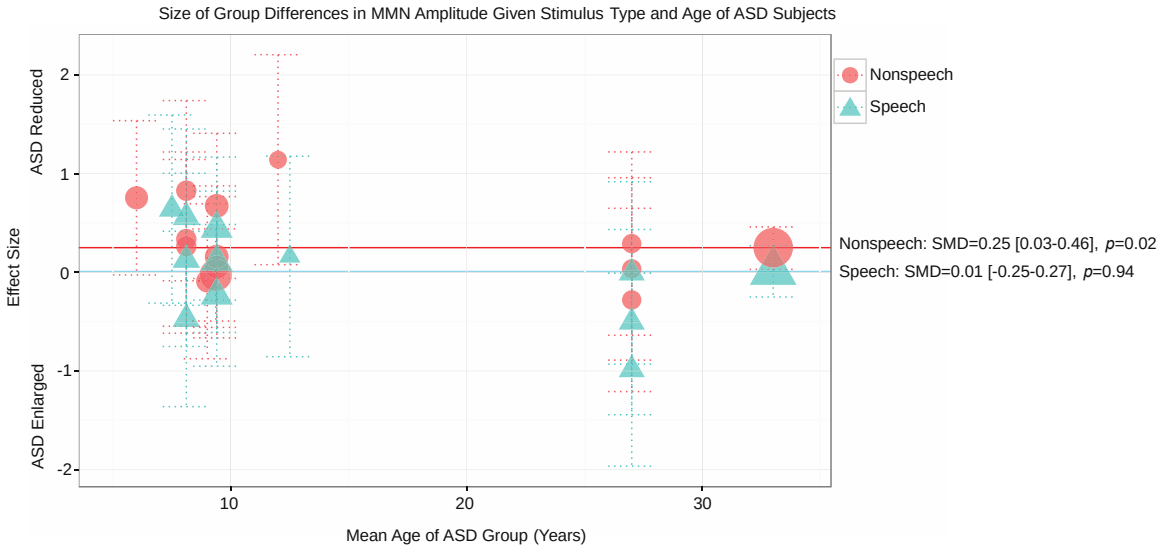


Figure 2.5. Effect size values given mean age of ASD cohort. Data point sizes are weighted based on the experiment's full sample size.



CHAPTER FOUR: ATYPICAL PERCEPTUAL ORGANIZATION OF SOUNDS IN MINIMALLY AND LOW VERBAL ADOLESCENTS WITH AUTISM AS REVEALED BY BEHAVIORAL AND NEURAL MEASURES

Atypical reactions to sensory inputs are a core feature of autism (ASD) that emerge early in life (Ben-Sasson et al., 2009; McCormick, Hepburn, Young, & Rogers, 2016; Rogers, Hepburn, & Wehner, 2003). Sound sensitivity, in particular, is frequently observed (O'Connor, 2012). Many children with ASD adopt habits such as covering their ears, requesting headphones, or humming in settings that are either loud or include multiple speakers (Frith & Baron-Cohen, 1987; O'Neill & Jones, 1997; Pfeiffer et al., 2017); these actions can be described as "atypical auditory behaviors". While most research on this topic has focused on verbally fluent individuals with ASD (ASD-V), atypical auditory behaviors might be particularly pronounced in the subtype of individuals with ASD who are minimally or low verbal (ASD-MLV). Data based on parent report has shown that ASD-MLV individuals exhibit more severe atypical auditory behaviors than ASD-V peers (Patten et al., 2013; Watson et al., 2011) and exhibit more atypical behaviors associated with auditory stimuli than stimuli in other modalities (Harrop, Tu, Landa, Kasier, & Kasari, 2018).

The categorization of ASD-MLV is based on expressive language deficits, but it is receptive language that depends directly upon auditory processing. Therefore, atypical auditory sensitivity may be even more closely associated with receptive language (Groen et al., 2008; Siegal & Blades, 2003). While, by definition, ASD-MLV individuals all

demonstrate poor expressive language, their receptive language skills can vary (Rapin et al., 2009). An intuitive but underexplored hypothesis is that atypical auditory behaviors are more prevalent and severe in those with poor receptive language.

Research on ASD-V children points to a general association between sensory sensitivity to environmental inputs and combined expressive-receptive language skills (Watson et al., 2011). Complicating matters, there is mixed evidence regarding whether atypical auditory behaviors are associated with cognitive impairment (Bishop, Richler, & Lord, 2006; Leekam, Nieto, Libby, Wing, & Gould, 2007; Sanz-Cervera, Pastor-Cerezuela, Fernández-Andrés, & Tárraga-Mínguez, 2015). Given that many ASD-MLV individuals have severe cognitive impairments, research is needed to explain how atypical auditory behaviors vary with receptive language ability after accounting for differences in cognitive ability.

Atypical sensitivities may originate from ineffective perceptual organization of sensory inputs (Donkers et al., 2015). Perceptual organization of auditory inputs is often quantified with neuroimaging techniques like EEG and MEG through the measurement of the mismatch neural response (MMR). The MMR is an indirect index of sensitivity to perceptual sound differences that can be measured in active as well as passive settings, when a person is not attending to the sounds (Näätänen, Simpson, & Loveless, 1982). Because it can be measured passively, the MMR can be used to assess auditory processing in ASD-MLV participants (Matsuzaki et al., 2019; Schwartz et al., 2018). In ASD-V individuals, strength of neural signatures to unexpected sound events (as measured by MMRs) negatively correlates with heightened sensory sensitivity to inputs –

as measured by atypical sensory behaviors and perceived discomfort to sensory inputs (Ludlow et al., 2014; Donkers et al., 2015). In a similar vein, ASD-V individuals who perform poorly on a perceptual task requiring the discrimination of tones based on loudness exhibit more atypical auditory behaviors (Jones et al., 2009). Better performance on frequency and intensity discrimination tasks have also been associated with better verbal reasoning and a combination of restricted patterns of interests (both sensory and topic-specific) (Kargas et al., 2015). Moreover, atypical MMRs correlate with combined expressive-receptive language abilities in ASD-V individuals (Oram Cardy et al., 2008) and combined expressive-receptive communication abilities in ASD-MLV individuals (Matsuzaki et al., 2019). However, the relationship between atypical auditory behaviors, neural indices of perceptual sound organization, and receptive language ability has never been explored in ASD-MLV.

To better understand sound organization in ASD-MLV individuals, we conducted three experiments. In our first experiment, we sought to expand prior work by quantifying the percentage of time that ASD-MLV and ASD-V children and adolescents spent exhibiting atypical auditory behaviors. To test this, we retrospectively coded atypical auditory behaviors from video recordings of the Autism Diagnostic Observation Schedule (ADOS) – a semi-structured assessment of autism severity. Atypical visual behaviors were also measured in an effort to isolate whether any observed findings were auditory-specific or more dependent on domain-general systems of sensory processing. Subsequent experiments focused exclusively on ASD-MLV participants. Our second experiment investigated the extent to which within-group individual differences in

receptive language were related to atypical auditory and visual behaviors. In our third experiment, we measured the relationship between atypical auditory and visual behaviors, receptive language, and sound organization (as measured by strength of neural responses to unexpected, nonspeech sounds).

EXPERIMENT 1

Sample

Participants comprised 83 children and adolescents with ASD who ranged in age from 5 to 21 years (**Table 3.1**). Participants in this study were selected from a larger Autism Center of Excellence research program focused on phenotyping ASD-MLV individuals (Tager-Flusberg et al., 2016). We defined participants as ASD-MLV if they lacked the use of spontaneous functional speech and complex sentences (N=47). All other participants used complex sentences consistently and were defined as verbally fluent (ASD-V, N=36). All participants met criteria for ASD as defined by the Autism Diagnostic Observation Schedule (ADOS), a semi-structured interactive interview designed to measure autism severity through a series of social prompts (Lord et al., 2012). ASD-V participants (children, n=18; adolescents, n=18) and ASD-MLV participants aged 5 to 12 were assessed with the ADOS-2 (Lord et al., 2012). ASD-MLV participants aged 12 to 21 (ASD-MLV, n=23) were assessed with the Adapted ADOS (Bal et al., 2019).

Study Procedures

As a part of a larger research program, participants completed a battery of cognitive, behavioral, and experimental assessments that took place over the course of one to four lab visits. Standardized assessment administration was modified to better ensure that participants understood testing prompts and cooperated with testing (for details, please see Tager-Flusberg et al., 2016).

Nonverbal Intelligence Measure

Nonverbal intelligence (IQ) was measured with the Leiter International Performance Scale, Third Edition (Leiter-3; Roid, Miller, Pomplun, & Koch, 2013) for ASD-MLV participants. This measure is designed to require no expressive language, but testing procedures were modified to help limit the amount of receptive language that was also required (for details, see Tager-Flusberg et al., 2016). Nonverbal IQ was measured with the Kaufman Brief Intelligence, Second Edition, Matrices subtest (KBIT-2; Kaufman, 2004) for ASD-V children and WASI-2 (WASI-2; Wechsler, 2011) for ASD-V adolescents.

Atypical Sensory Behavior Measures

Direct observational measures of atypical auditory and visual behaviors were retrospectively coded from each participant's ADOS assessment video recording. A summary of the operational definitions used in this coding protocol can be found in **Table 3.2**. Researchers coded the onset and offset of atypical behaviors, which were

operationally defined based on domain (auditory or visual). Outcome measures were based on the percent of time spent engaged in atypical behaviors in each domain, relative to the total time of the ADOS. Coding was implemented systematically using The Observer software system (Noldus, 1991). Twenty-one percent of participant videos were independently coded by a second observer to ensure inter-rater coding reliability (κ = 0.81 [0.80-0.83], ρ = 0.99, $p < 0.01$).

Statistical Analyses

Comparisons between the percent of time spent engaged in atypical auditory and visual behaviors by ASD-V and ASD-MLV participants were carried out using rank sum-based multivariate ANCOVAs, while controlling for known group differences in nonverbal IQ ($F(1, 81) = 74.65$, $p < 0.001$, $\eta^2 = 0.48$). Effect sizes were calculated using η^2.

Results

Differences between ASD-MLV and ASD-V groups were most pronounced for the amount of time spent engaged in atypical auditory behaviors during the ADOS (**Figure 3.1; Table 3.3**). ASD-MLV participants showed a higher percentage of time engaged in atypical auditory behaviors than ASD-V participants ($F(2,80) = 33.02$, $p < 0.001$, $\eta_p^2 = 0.45$). In contrast, we found no significant differences in amount of time spent engaged in atypical visual behaviors between groups ($F(2,80) = 3.03$, $p = 0.05$, $\eta_p^2 = 0.07$).

EXPERIMENT 2

Sample

Given the fact that most ASD-V participants did not demonstrate atypical auditory behaviors and consistent with our initial focus on ASD-MLV, only ASD-MLV participants from the sample in Experiment 1 were included in Experiment 2 (N=47).

Receptive Language Measure

Receptive language was assessed for all participants with the Peabody Picture Vocabulary Test – 4 (PPVT-4; Dunn & Dunn, 2007). To better capture individual differences, we based our analyses on raw scores rather than standardized scores (for which many subjects would have a measure floor score of 20). We excluded data for five ASD-MLV individuals for whom we were unable to obtain basal scores (below a raw score of 3).

Statistical Analyses

A hierarchical linear regression model was constructed to determine the degree to which receptive language abilities were accounted for by differences in the time spent engaged in atypical auditory and visual behaviors, after accounting for effects of age and nonverbal IQ. In particular, we conducted a linear regression model with age and nonverbal IQ entered first as dependent variables to predict receptive language abilities. Once accounting for age and nonverbal IQ, atypical visual and auditory behaviors were entered second as dependent variables in a stepwise linear regression model. This model

was performed on ranked values for nonparametric data and unranked values for parametric data. All significance tests were two-sided and conducted at the 5% significance level.

Results

Our model revealed that control variables, age (β = 0.70, *SE* = 0.12) and nonverbal IQ (β = 0.85, *SE* = 0.12), significantly accounted for variance in receptive language abilities ($F(2,40) = 32.10$, $p < 0.001$, Adjusted $R^2 = 0.60$). Ranked atypical auditory behaviors significantly increased this model's accuracy (β= -0.25, *SE*=0.01, $F(3,39) = 25.91$, $p < 0.001$, $\Delta F = 6.19$, $p < 0.05$, Adjusted $R^2 = 0.65$), while ranked atypical visual behaviors did not (**Table 3.4**).

EXPERIMENT 3

Participants

A subset of 18 ASD-MLV adolescent participants were included in this third experiment. Our choice to include only adolescents in this experiment was because we wanted to measure strength of response to deviant sounds with P1-N1 peak-to-peak amplitude, but the N1 is not stable until around the ages of 8-12 (Luck & Kappenman, 2011).

Neural Mismatch Measure

All participants partook in an EEG testing protocol described in Tager-Flusberg et

al. (2016). EEG was collected using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Participants watched a silent movie with subtitles while they heard a stream of tones that were designed to follow a classic one-stream, oddball mismatch response paradigm with intensity deviants. Sounds were presented through two speakers, placed +/-45 degrees in front of the listener. Both standards and deviants were 110 Hz complex tones composed of 10 evenly spaced harmonic frequencies. Intensity deviants were presented at 45 dB SPL relative to 30 dB SPL standard tones. The interstimulus interval was 250 ms with a 0 to 40 ms jitter. Deviants were always proceeded by at least three standards and made up 17% of the trials. Participants were presented with a total of 1000 trials.

Data were referenced online to vertex (Cz), online digitally filtered with a 0.1 Hz highpass filter, and digitized at 1000 Hz (Electrical Geodesics Inc.). After acquisition, data were offline filtered at 1-35 Hz. As is commonly done to quantify MMR (Näätänen et al., 2007), data from the midline frontal channel (Fz) were selected and rereferenced to the average of the left and right mastoids. Data in response deviant 45 dB SPL tones were segmented into 700 ms epochs with a 100 ms pre-stimulus baseline. Trials were rejected if the amplitude of the trial exceeded 100 uV, peak-to-peak. Trials were baseline corrected with respect to the mean of the whole trial. The range of trials accepted and analyzed was 109-170. Strength of MMR was operationalized as the difference in amplitude between the first major positive (P1) and negative (N1) peaks of the obligatory response to the deviant tone. Mean latency of these peaks was identified on the group average and a 30 ms window around those mean latency peaks was used to quantify the

P1 and N1 amplitude for each participant (117 and 181 ms, respectively).

Statistical Analyses

Spearman's Rho was used to conduct nonparametric correlations of atypical auditory and visual behaviors with age, nonverbal IQ, receptive language, number of EEG trials, and MMR amplitude. Significance tests were two-sided and conducted at the 5% significance level.

Results

We found that across participants, neural strength of MMRs significantly correlated with the percentage of time during the ADOS that participants spent engaged in atypical auditory behaviors ($r_s = -0.58$, $p < 0.05$). In addition, receptive language significantly correlated with the percent of time spent engaged in atypical auditory behaviors ($r_s = -0.66$, $p < 0.01$) and amplitude of neural responses ($r_s = 0.49$, $p < 0.05$). There were no significant correlations with age, atypical visual behaviors, or number of EEG trials in relation to the other variables. Unsurprisingly, nonverbal IQ and receptive language were highly correlated ($r_s = 0.75$, $p < 0.001$). Nonverbal IQ was a significant covariate of time spent engaged in atypical auditory behaviors and strength of MMRs as well (**Table 3.5**). Once nonverbal IQ was entered as a covariate in analyses, receptive language no longer significantly correlated with MMR strength ($r_s = 0.42$, $p = 0.10$) or time spent engaged in atypical auditory behaviors ($r_s = -0.39$, $p = 0.12$). However, the correlation between time spent engaged in atypical auditory behaviors and MMR strength

remained significant ($r_s = -0.50$, $p < 0.05$).

DISCUSSION

ASD-MLV children and adolescents were found to engage in significantly more atypical auditory behaviors than ASD-V controls, while in contrast, both groups engaged in a similar degree of atypical visual behaviors. Furthermore, within the ASD-MLV group, receptive language abilities were well-explained by the amount of time spent engaged in atypical auditory behaviors, beyond what was already accounted for by nonverbal IQ and age, and not well-explained by the amount of time engaged in atypical visual behaviors. Consistent with prior research on ASD-V participants, we found that MMRs indexing the organization of nonspeech sounds were weaker in ASD-MLV participants with higher rates of atypical auditory behaviors (Donkers et al., 2015; Ludlow et al., 2014). However, we were unable to detect a relationship between neural response indicative of sound organization and receptive language that was independent of nonverbal IQ.

Results from Experiment 1 support reports that atypical auditory behaviors are more pronounced in ASD-MLV than ASD-V individuals (Patten et al., 2013; Watson et al., 2011). In contrast, the two groups demonstrated similar amounts of atypical visual behaviors, suggesting that ASD-MLV participants display more auditory, but not visual, atypical behaviors relative to ASD-V peers. For this reason, we hypothesize that the heightened atypical auditory behaviors observed in ASD-MLV participants do not originate from disruptions in systems that modulate both audition and vision.

Results from Experiment 2 demonstrate that these atypical auditory behaviors are not uniformly disrupted in all ASD-MLV, but rather, are specifically perturbed in those with receptive language deficits. Findings lend support to the proposition that the brain systems responsible for auditory information processing are more directly relevant to receptive language than expressive language (Groen et al., 2008; Siegal & Blades, 2003). Notably, this relationship remained significant after accounting for nonverbal IQ; this mitigates the concern that the observed relationship is not solely due to a relationship between nonverbal IQ and atypical sensory behaviors (Leekham et al., 2007; Bishop, Richler, & Lord, 2006) or nonverbal IQ and language (Mayes & Calhoun, 2003).

In Experiment 3, we detected a negative correlation between the time that ASD-MLV participants spent engaged in atypical auditory behaviors during the ADOS and a neural component that indirectly measured organization of nonspeech sound inputs. Findings expand prior studies on ASD-V participants that have found an inverse relationship between the strength of MMRs to acoustic feature changes and heightened sensory sensitivities (Donkers et al., 2015; Ludlow et al., 2014). In our experiment, the MMR indirectly captured perception of change related to nonspeech sound intensity. Findings align with prior work showing that the ability to actively discriminate non-speech sounds based on intensity is negatively correlated with heightened auditory sensory behaviors (Jones et al., 2009).

We also hypothesized that individual differences in receptive language ability in the ASD-MLV group would correlate with neural measures of auditory processing, since combined expressive-receptive impairments have been implicated in those with ASD

who exhibit more atypical MMRs (Oram Cardy et al., 2008; Matsuzaki et al., 2019). While we identified a significant relationship between these measures, it was not independent of the variance introduced by nonverbal IQ. In many ways, this is unsurprising. It has been repeatedly demonstrated that nonverbal IQ is highly correlated with receptive language ability (Abbeduto, Furman, & Davies, 1989; Luyster et al., 2008) and can interfere with the ability to detect other effects related to receptive language, especially within small, underpowered samples.

The results from these three experiments lead us to propose that the internal central auditory processing systems responsible for prioritizing important sounds are particularly perturbed in ASD-MLV with major receptive language impairments. In particular, our findings suggest that these individuals are unable to distinguish important from unimportant sounds; as a result, they might inadvertently focus on unimportant aspects of sounds and not effectively disengage from those sounds when more important sounds are presented. Difficulty perceptually organizing sounds in an effective way likely has negative consequences on the ability to process language, which relies on the ability to attend to meaningful units of language like phonetic structure and prosody (Kujala et al., 2007).

The relationship between atypical auditory behaviors and atypical organization of sound inputs raises the possibility that atypical sensory behaviors serve as external compensatory mechanisms to deal with faulty internal brain systems that are typically responsible for regulating that input. For instance, the ability to separate sounds as coming from distinct sources and use that information to suppress irrelevant auditory

information is necessary when it comes to effectively filtering incoming sounds (Bregman, 1990). Without such mechanisms in place, environmental noise could easily become overwhelming, and external behaviors like ear covering and humming would be a logical way to modulate that noise (Alcántara et al., 2004; Lepistö et al., 2009; Russo et al., 2009).

Limitations and Future Directions

One possible limitation of our study was the use of an unstandardized experimental coding protocol to measure atypical auditory and visual sensory behaviors. While inter-rater reliability was established, we cannot be sure that our measure accurately captured atypical behaviors equally across the two sensory domains. Absence of major group differences in atypical visual behaviors could be caused by a lack of sensitivity in our measure to those behaviors. In a similar vein, our measure of atypical auditory behaviors might lack specificity. We could not infer the intentions of the atypical auditory behaviors we observed. For instance, when a person with autism plugged their ears, it might have been to block out noise, but it also might have been to filter sound in a certain way, or even enhance certain characteristics of a sound. It also might have had nothing to do with sound at all – perhaps a participant plugged their ears because of its somatosensory feedback or a participant hummed as an attempt to communicate. Furthermore, we cannot eliminate the possibility ASD-MLV exhibited more atypical auditory behaviors than ASD-V peers because they were administered ADOS modules that potentially presented more opportunities to engage in those atypical

behaviors.

Another limitation of this study is that it was only conducted in children over the age of 5 at a single time point. This limits our ability to establish a causal relationship between auditory processing and the acquisition of expressive or receptive language, because we cannot say whether the observed atypical auditory behaviors were present during the time of language acquisition. Future studies might address this gap by considering how behavioral and neural measures of auditory processing predict future receptive language abilities in ASD-MLV individuals.

The investigation of atypical auditory behaviors is also warranted from a clinical perspective in order to understand the extent to which these behaviors are helpful or harmful. Atypical auditory behaviors may help filter sounds that are distracting or overwhelming, but they may also inadvertently block out important sounds and consequently interfere with a child's ability to hear important sounds.

Conclusions

In summary, our findings demonstrate that while atypical reactivity to sensory input is a core characteristic of ASD, the systems underlying the perceptual organization of auditory inputs might be particularly perturbed in those within the ASD-MLV subtype with severe receptive language impairments. In addition, this research is the first to show evidence of a relationship between heightened occurrence of atypical auditory behaviors and atypical neural indices of sound organization in ASD-MLV individuals. Further research is needed to elucidate how external behaviors might function to peripherally

regulate auditory inputs that have not been adequately organized with internal brain mechanisms.

Table 3.1. Demographics. Language standard score (SS) derived from either PPVT-4 (receptive only) or CELF-4 (core language score). We excluded language scores from 5 MLV subjects who did not acquire basal scores on the PPVT-4. Nonverbal IQ (NVIQ) was derived from Leiter-3 (for ASD-MLV) and WASI-2 or KBIT-2 (for ASD-V). Effect measured by Eta squared. Significance cutoff of $p<0.05$**.**

	Group	**ASD-MLV**	**ASD-V**	**Sig. (*p*)**	η^2
Participants	*N*	47	36		
Age (years)	*Mean (SD)*	11.56 (4.54)	12.32 (4.40)	0.50	0.78
M:F	*Ratio*	37:10	7:29	0.84	
Race				0.07	
	Asian	6	0		
	Black/African American	1	0		
	Caucasian	34	26		
	Native Hawaiian or Other Pacific Islander	1	0		
	Multiple Races	3	8		
	Prefer not to respond	2	2		
Ethnicity				0.82	
	Hispanic	4	4		
	Non-Hispanic	39	30		
	Prefer not to respond	4	2		
ADOS CSS	*Mean (SD)*	7.55 (1.28)	7.66 (1.71)	0.75	
ADOS SA CSS	*Mean (SD)*	7.02 (1.45)	7.17 (2.05)	0.70	
ADOS RRB CSS	*Mean (SD)*	8.45 (1.41)	7.89 (1.88)	0.13	
Nonverbal IQ	*Mean (SD)*	69.79 (19.46)	108.25 (21.21)	<0.001	0.48
Language SS	*Mean (SD)*	38.40 (21.01)	99.06 (24.16)	<0.001	0.65

Table 3.2. Operational definitions of atypical auditory and visual behaviors. Behaviors were assigned to one of eight atypical sensory behavior categories – four associated with the auditory domain and four associated with the visual domain.

Domain	**Atypical Sensory Behaviors**
Auditory	Puts object close to ear or uses object to make noise repetitively, with object near ear; repetitively bangs a noise-making object like a squeaky toy.
	Vocalizations such as humming or high-pitch vocalizations without intent to communicate, not including singing or clear self-talk. Can include humming while cupping ears, humming with hand in front of mouth, humming while other noise is playing.
	Covers ears with palms or inserts fingers into ears, cupping ears.
	Appears distressed facially by the current or expected presentation of a sound or requests that a sound be stopped.
Visual	Stares intently close-up in mirror or moves an object close to his/her eyes.
	Puts hands on either side of gaze to narrow focus of testing environment.
	Repetitively moves finger or object in front of eyes, or moves head down to another level to examine an object from a different perspective.
	Covers eyes with hands or object, turns lights off.

Table 3.3. Group comparisons between ASD-MLV and ASD-V. Multivariate ANCOVA on ranked sum values are reported, controlling for group differences in nonverbal IQ. Effect size quantified by partial Eta^2 from the corrected model.

Domain	**F**	**Sig. (*p*)**	**Effect size ($\eta_p^{2)}$**
Auditory	33.02	<0.001	0.452
Visual	3.03	0.054	0.70

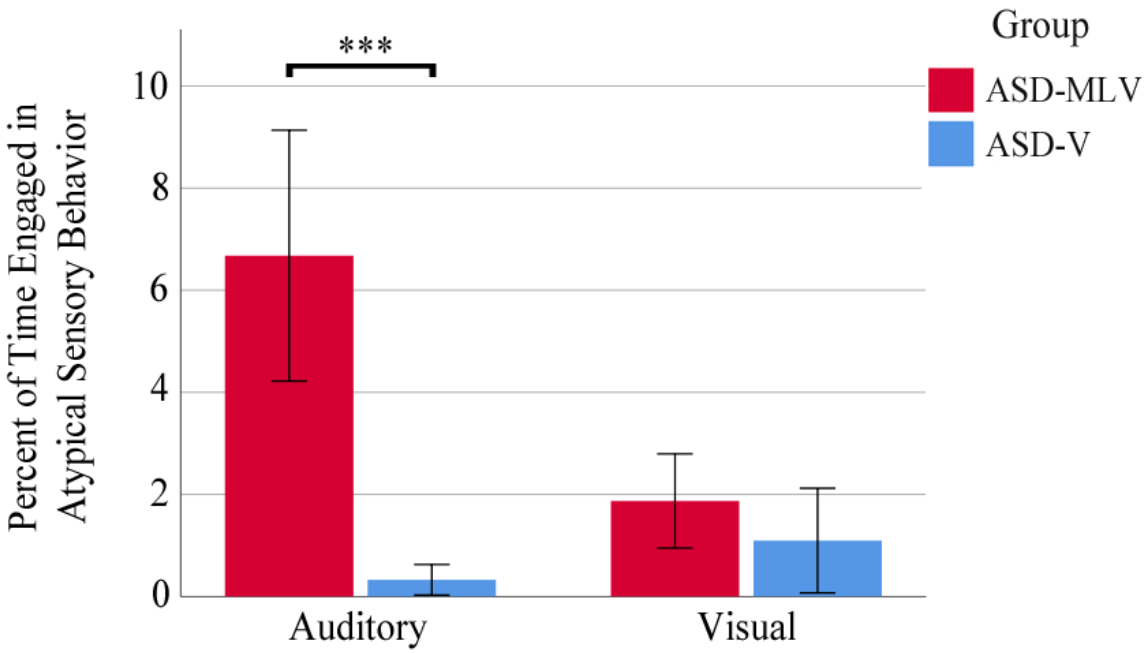
Table 3.4. Hierarchical linear regression model predictors of receptive language. Reports are based on ASD-MLV children and adolescents with valid, above-basal receptive language measures (N=42). *=p<0.05, **p<0.01, ***p<0.001.

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
(Constant)	-123.83	22.29		-77.24	28.67		-62.91	28.88	
Age	5.54	0.90	0.70***	4.65	0.93	0.59***	4.26	0.93	0.54***
NVIQ	1.57	0.21	0.85***	1.37	0.21	0.75***	1.37	0.21	0.75***
Auditory				-0.42	0.17	-0.25*	-0.38	0.17	-0.23*
Visual							-0.26	0.14	-0.18
R^2		0.60			0.65			0.67	
F		32.10			25.91			21.50	
ΔF		<<0.001			<0.05			0.07	

Table 3.5. Nonparametric correlations between atypical behaviors, receptive language, and MMR amplitude in ASD-MLV adolescents. Reports are based on ASD-MLV adolescents (N=18). All correlations with Spearman's rho. *=p<0.05, **p<0.01, ***p<0.001.

	Age	Nonverbal IQ	Receptive Language (PPVT Raw)	Atypical Auditory Behaviors (%)	Atypical Visual Behaviors (%)	Mismatch Response (Amplitude)
Nonverbal IQ	-.316					
Receptive Language (PPVT Raw)	-.189	.748***				
Atypical Auditory Behaviors (%)	-.107	-.573*	-.655**			
Atypical Visual Behaviors (%)	-.246	-.237	-.073	.129		
Mismatch Response (Amplitude)	.023	.469*	.490*	-.578*	-.145	
MMR Trials (N)	-.145	.397	.047	.025	-.283	.066

Figure 3.1. Classification of ASD-MLV (N=47) and ASD-V (N=36) groups by sensory behaviors exhibited. Error bars based on 95% confidence intervals.



CHAPTER FIVE: NEURAL RESPONSE TO ONE'S OWN NAME IS ATYPICAL IN MUTLSPEAKER SETTINGS IN MINIMALLY AND LOW VERBAL ADOLESCENTS WITH AUTISM

Atypical Behavioral Response to One's Own Name in ASD

From a young age, humans use directed speech to guide attention. One's own name (OON) is a particularly salient guide: neurotypical (TD) infants preferentially turn their head to the sound of OON by 4-9 months (Bortfeld, Morgan, Golinkoff, & Rathbun, 2005; Mandel, Jusczyk, & Pisoni, 1995). In contrast, infants who later develop autism (ASD) commonly fail to orient consistently towards speakers using directed, social speech, including OON (Miller et al., 2017; Osterling et al., 2002; Werner, Dawson, Osterling, & Dinno, 2000). This failure to respond to OON is so pronounced that it is one of the first major signs of ASD and is included in all gold-standard diagnostic measures of the disorder (Constantino & Gruber, 2012; Lord et al., 2012; Rutter et al., 2003). Diagnostic testing currently relies on behavioral assessments to identify signs of ASD (including atypical OON), but there is a continuing interest to identify brain-based markers of the disorder.

Typical Neural Responses to One's Own Name

In typical development, preferential neural responses to OON have been detected in children as young as 5 months old (Imafuku, Hakuno, Uchida-Ota, Yamamoto, & Minagawa, 2014; Parise, Friederici, & Striano, 2010; Tateuchi, Itoh, & Nakada, 2015).

These neural responses continue to be detectable throughout the lifespan (Carmody & Lewis, 2006; Key, Jones, & Peters, 2016; Tamura, Mizuba, & Iramina, 2016). Prior electroencephalography (EEG) research has identified strong early neural responses to OON between 100 and 300 ms over frontal scalp regions and strong late responses between 300 and 800 ms over posterior scalp regions, particularly when OON occurs only occasionally and unpredictably (Berlad & Pratt, 1995; Holeckova et al., 2006; Pratt, Berlad, & Lavie, 1999). These robust neural responses can be elicited in both attentive and inattentive, even asleep or comatose, states (Fischer et al., 2008; Perrin et al., 2006). Such responses to OON are consistent with reports that especially salient words or sounds can exogenously "grab" listeners' attention and lead to negative, frontal responses (often characterized as a mismatch response or MMR) and a late, slow parietal positive shift response (LPP) (Folstein & Van Petten, 2008; Näätänen, 1985; Ponton, Eggermont, Kwong, & Don, 2000). Reports also find greater LPPs in TDs when they think about themselves versus other people (i.e., self-other discrimination) (Fan et al., 2013; Gray, Ambady, Lowenthal, & Deldin, 2004; Su et al., 2010). Analogous components have been identified during OON tasks, as well – for the MMR, a positive, parietal response, and for the LPP, a negative, frontal response (Loveless, Simpson, & Näätänen, 1987; Näätänen et al., 1982; Nijhof et al., 2018). Overall, OON MMRs appear to index early, automatic acoustic detection and orientation to OON, while OON LPPs likely reflect later cognitive stages of auditory attention and self-other discrimination (Friedman, Cycowicz, & Gaeta, 2001; Näätänen et al., 1982; Nieuwenhuis, De Geus, & Aston-Jones, 2011). Both responses could be sensitive measures to test whether response to OON is atypical those

with ASD.

Neural Self-Orienting Responses in those with Autism

Past research suggests that verbally fluent individuals with ASD (ASD-V) show typical MMRs but atypical LPPs to OON. In quiet, ASD-V listeners show enhanced MMRs to OON, similar to that of TDs, but reduced OON LPPs (Nijhof et al., 2018). Individuals with ASD-V show similarly reduced LPPs when viewing their written name or face amidst other random names and faces (Cygan, Tacikowski, Ostaszewski, Chojnicka, & Nowicka, 2014; Gunji, Inagaki, Inoue, Takeshima, & Kaga, 2009; Nowicka, Cygan, Tacikowski, & Ostaszewski, 2016). These reports suggest that ASD-V adolescents and adults do not have disordered early detection of OON as a salient stimulus but do show high-order processing deficits pertaining to selective attention and self-other discrimination (Lombardo et al., 2010; Nijhof et al., 2018).

Neural responses to OON has never been measured in individuals who have not developed fluent expressive language (hereon described as minimally or low verbal, or ASD-MLV). However, prior research hints at the possibility of greater impairments in this group. For example, ASD-MLV children demonstrate atypical orienting responses, as demonstrated by atypical MMRs, to speech and nonspeech sounds when compared to ASD-V and TD peers (Matsuzaki et al., 2019; Roberts et al., 2019). It is also plausible that neural responses to OON are related to language ability given that behavioral responses to social bids for attention (like responding to OON) are positively associated with language abilities in ASD (Bottema-Beutel, 2016; Dawson et al., 2004).

Auditory Processing and Selective Attention in Multispeaker Settings

Many individuals with ASD classically present with symptoms related to atypical auditory processing (American Psychiatric Association, 2013; Marco, Hinkley, Hill, & Nagarajan, 2011; Ocak, Eshraghi, Danesh, Mittal, & Eshraghi, 2018). For instance, individuals with ASD often feel overwhelmed in loud, multisource settings (Alcántara et al., 2004; Birch, 2003; Grandin, 1995). Overarousal may be related to overarching disorder-wide problems filtering targets from noise (Haigh, Heeger, Dinstein, Minshew, & Behrmann, 2015; Simmons et al., 2007; Vilidaite, Yu, & Baker, 2017). Selective attention deficits are also pervasive in ASD and at least thirty percent meet criteria for a secondary attention-deficit/hyperactivity diagnosis (Joshi et al., 2013; Plesa Skwerer et al., 2019). Most research on attentional deficits in ASD has been conducted on ASD-V participants, but recent studies suggest that attentional deficits could be more pronounced in ASD-MLV individuals (Lerner et al., 2018; Plesa Skwerer et al., 2019).

Auditory filtering and selective attention deficits have been identified in individuals with ASD through various means. Parent questionnaires like the Short Sensory Profile Auditory Filtering Subscale (SSP; Dunn et al., 1999) reveal that individuals with ASD show more problems filtering out sounds than TD (Tomcheck & Dunn, 2007) or other developmentally delayed, non-ASD peers (McCormick et al., 2016; Rogers, Hepburn, & Wehner, 2003). With psychoacoustic and neuroimaging experiments, researchers have also found that compared to TDs, ASD-V listeners require a larger frequency separation between target and masking signals in order to effectively detect targets (Lepistö et al., 2009; Plaisted, Saksida, Alcántara, & Weisblatt, 2003).

Given reports that individuals with ASD exhibit decreased responsiveness to OON and difficulty processing sounds in complex scenes, we hypothesized that these individuals would show deficits in their neural response to OON in a multispeaker setting. We further hypothesized that a standardized questionnaire like the SSP Auditory Filtering Subscale that captures auditory attention abilities might correlate with these neural measures.

Study Objectives

Our first objective was to test whether ASD-MLV or ASD-V participants showed atypical early, automatic (MMR) and late, higher-level (LPP) neural responses to OON, both in quiet and when heard amidst other speech. Our second objective was to test whether, among those with ASD, the strength of neural response to OON correlated with reported problems with auditory filtering and attention.

METHODS

This study was approved by Boston University's Institutional Review Board and all testing was conducted at Boston University's Center for Autism Research Excellence.

Participants

Participants were between 13-23 years old and spoke English as their primary language. None had any known history of hearing loss, concussion, or traumatic brain injury.

Twenty-eight neurotypical (TD) participants were enrolled as controls to define regions of interest in the EEG portion of our study. Controls came to the lab for one visit and were not assessed with any cognitive measures. None had any diagnosis of intellectual, developmental, or psychiatric disability, nor a sibling with an ASD diagnosis. One control was excluded due to experimenter error.

Fifty ASD participants (28 ASD-V, 22 ASD-MLV) were enrolled in this study and made between one to four visits. Group assignment was based on expressive language (Hus Bal, Katz, Bishop, & Krasileva, 2016). ASD-MLV participants communicated exclusively without complex sentence speech, while ASD-V participants reliably and consistently used complex sentences. Clinical diagnosis was confirmed with the Autism Diagnostic Observation Schedule, Second Edition Modules 3 and 4 (ADOS-2; Lord et al., 2012) for ASD-V participants and Adapted ADOS Modules 1 and 2 (AADOS, Bal et al., 2019) for ASD-MLV participants, administered and scored by an ADOS research-reliable experimenter. Nonverbal intelligence (NVIQ) was measured with the Leiter International Performance Scale, Third Edition (Leiter-3; Roid, Miller, Pomplun, & Koch, 2013). Parent-reported adaptive functioning skills were measured with the Vineland, Third Edition, Comprehensive Parent/Caregiver Form (Sparrow, Cicchetti, & Saulnier, 2016). Auditory filtering ability was measured with parent-report using the Short Sensory Profile – Auditory Filtering Subscale raw score (McIntosh, Miller, Shyu, & Dunn, 1999). This subscale includes six, five-point Likert-scale questions about whether the participant in question has difficulties with selective attention or gets distracted in complex auditory scenes.

The final study sample is described in **Table 4.1**. 27 TD participants had usable data from the EEG study. In the ASD groups, two participants did not complete EEG testing and a third did not have enough usable EEG data to be included, leaving us with 27 ASD-V and 20 ASD-MLV participants. There were no significant group differences in terms of age, gender ratio, race, or ethnicity.

There were also no significant differences in auditory filtering scores between the two ASD groups (**Table 4.2**). However, ASD-MLV participants did have significantly lower NVIQ and adaptive functioning skills.

EEG

Thirty percent of ASD participants went through EEG desensitization procedures as described by Tager-Flusberg and colleagues (2017). Desensitization required between ten minutes in one session to three hours over the course of three sessions to complete.

For the EEG experiment, participants sat in an electrically shielded, sound-attenuated room and watched a self-selected silent, subtitled video that was unrelated to the experiment. They were told not worry about any sounds they heard. Brain signals were recorded with a 128-channel EEG system (EGI Geodesics, sampling rate 1000 Hz). Auditory stimuli were presented binaurally from two loudspeakers, placed +/- 45 degrees in front of participants. At the beginning and middle of the experiment, we confirmed that all channels had scalp impedance levels less than 50 Ohms. Not including setup, desensitization, or breaks, the experiment took a minimum of 35 minutes to complete.

Stimuli: Batches of participant names were pre-recorded by the lead experimenter (a female, American English speaker). Names ranged in length from 440 to 740 ms, with an average of 577 ms (*SD* = 69 ms). A background multispeaker mixture was composed from the overlay of six male English speakers reciting sentences from the American English Matrix Test (HörTech, 2014). Given the purpose of this study, all names were removed from these sentences.

Pre-EEG Recording Protocol: Directly following initial study consent, participants or legal guardians were asked to indicate from a list of names whether any were the name of a "close other" to the participant like a sibling or friend. Any name indicated as special to the participant from the list that was not the participant's own name was not presented as name stimuli.

Paradigm: Each participant heard their own name (OON) and two other participants' names (referred to as SN, or strangers' names) in quiet and multispeaker settings. Names were presented at equal probability, randomly presented in groups of three. The paradigm was designed to elicit a mismatch response in which, presumably, the two other names would be grouped as similar and OON would elicit a unique response. No two names across the three shared the same first phonemic sound. Gender allocation for names was random, but given the nature of the sample, was more commonly male. Names were presented with an interstimulus interval of 1800 ms with 0–200 ms jitter and were presented at 60 dB SPL. When heard in multispeaker settings, names were louder than competing sounds at 8 dB signal to noise ratio – a sound level ratio that is perceptually similar to hearing your name in a crowded restaurant. We

presented 972 trials of the three names across three quiet and three multispeaker setting trial blocks. Quiet and multispeaker setting trial blocks were presented semi-randomly in pairs.

Post-Recording Name Selection: We compared response to OON with responses to one of the two presented SNs. Names selected for analyses occurred once across both OON and SN conditions in 92% of the cases. Participant cancelations prevented us from counterbalancing all participant names across conditions in the remaining cases. Balance across conditions allowed us to better control for any differences in brain responses generated by names with different phonetic structures or lengths and ensured that the primary difference between stimuli was name ownership and familiarity.

Signal Processing: All electrodes on the outer rim of the cap were discarded to avoid potential contamination of muscle artifacts, leaving a remainder of 99 electrodes. Data were filtered between 0.2 and 35 Hz. Trials were segmented into 1200 ms epochs with 100 ms prestimulus baselines. Trials were rejected if any trial exceeded a 200 microvolt peak to peak threshold. Trials were baseline corrected relative to their 100 ms pre-stimulus baselines. Channels were average scalp referenced and subsequently excluded if more than 37% of trials were unusable (equivalent to less than 20 trials per name and condition). Each participant had between 20 and 54 accepted trials for each name in each block, with a total of 69-162 accepted trials for each name in both quiet and multispeaker conditions (**Supplemental Table 4.S1**).

Spatial-Temporal ROI Identification in TD Sample: Spatial and temporal regions of interest (ROIs) were determined based on our reference TD group.

Experimental data were z-score normalized relative to two minutes of raw, baseline state data collected for each participant. Spatial ROIs were selected from fronto-central (5, 6, 12) and parietal-occipital (71, 75, 76) channels based on visual inspection of full scalp topography. To determine temporal ROIs, we relied on nonparametric cluster permutation t-tests as defined by Maris & Oostenveld (2007). Using this method, we compared responses between conditions (OON versus SN) in each spatial ROI across time, from 150 to 750 ms post-stimulus, and determined temporal clusters in which the signals generated from the two conditions significantly differed above a t-test threshold of $p < 0.01$. We then created a distribution of t-value clusters by calculating t-values and resulting significant time clusters in 1000 mock samples of data. These mock samples were created by randomly switching OON and SN trials across participants. Finally, we compared the original t-value cluster data with the distribution of mock data and selected clusters that met a threshold of $\alpha < 0.15$. This allowed us to determine temporal windows of interest along both spatial ROIs.

Statistical Analyses

Between-Group Comparisons: Effect of group (TD, ASD-V, ASD-MLV) on strength of OON and SN responses was evaluated based on mean amplitude (in microvolts) for each spatial-temporal ROI in every trial. Analyses were conducted with full factorial linear mixed effects models of all trials with participant as a random effect. Doing so allowed us to avoid biasing that might be caused due to differences in the number of trials between samples. Statistical significance for linear mixed effects models

were calculated using Likelihood Ratio Tests (Winter, 2013). Significant tests were followed up with post-hoc analyses for main effects and interactions using analyses of variance. All significance thresholds were based on a threshold of $\alpha < 0.05$.

Correlates of Neural Measures: Spearman's rank order correlation was used to test the hypothesized interaction between strength of response to OON (the difference in amplitude between response to OON and SN) and auditory filtering abilities. In addition, we examined the correlation between brain response and other possible covariates (age, NVIQ, and number of usable EEG trials).

RESULTS

Spatial-Temporal ROI Identification in TD Sample

We found no significant temporal windows ROIs when names were presented in quiet settings unless we limited analyses to the first block of trial presentations (See **Supplemental Materials** for further analyses). In multispeaker background settings, ROI clustering analyses identified significant clusters in TDs between 178–332 ms (MMR) and 514–645 ms (LPP). OON response was more negative than SN response along fronto-central channels and more positive than SN response along parietal-occipital channels.

Between-Group Analyses

MMR (178-332 ms): Group significantly affected neural response ($\chi^2(1) = 4.24$, $p < 0.05$) such that the fronto-central MMRs were more negative in the TD than the ASD-MLV group (MD = -0.59 [-0.87 – -0.32] uV, $p<0.0001$), as well as more negative

in the ASD-V than the ASD-MLV group (MD = -0.37 [-0.64 – -0.09] uV, $p < 0.01$) (**Figure 3; Supplemental Table 4.S2**). Name significantly affected neural response ($\chi^2(1) = 17.35$, $p << 0.0001$), such that early fronto-central response to OON was more negative in response to OON compared to SN (MD = -0.39 [-0.63 – -0.14]). The interaction between group and name significantly affected neural response ($\chi^2(1) = 6.58$, $p < 0.05$). TD and ASD-V participants had more negative fronto-central MMRs to OON compared to SN (TD: MD = -0.70 [-1.04 – -0.36] uV, $p < 0.001$; ASD-V: MD = -0.48 [-0.83 – -0.14] uV, $p < 0.01$), while ASD-MLV participants did not show differences in their responses to the names (MD = 0.03 [-0.40 – -0.46], $p = 0.89$).

LPP (514-645 ms): There was no significant effect of name ($\chi^2(1) = 2.58$, $p = 0.11$) nor group ($\chi^2(1) = 1.25$, $p = 0.26$) on neural response (**Figure 4.3**). The interaction between the two terms also did not significantly affect response ($\chi^2(1) = 0.02$, $p = 0.89$).

Behavioral Correlates of Neural Measures

Nonparametric correlations revealed that LPPs correlated with auditory filtering ability ($r_s = 0.43$, $p < 0.001$; **Table 4.3**). We found no statistically significant correlations between LPPs and age, number of trials, or NVIQ. MMRs did not correlate with any of the tested variables.

DISCUSSION

Summary of Objectives and Results

We found that, in multispeaker settings, ASD-MLV participants differed from verbal, age-matched ASD and TD peers in their OON responses. TDs and ASD-Vs had

significantly larger MMRs to OON than SNs, while ASD-MLV participants did not show a significant difference between responses to own and other names. LPPs did not differ significantly between groups, but across ASD participants, LPPs to OON were weaker in those with poorer auditory filtering abilities. These results suggest that early automatic detection of OON as a salient, attention-grabbing stimulus is weaker in ASD-MLV than TD and ASD-V adolescents. Findings also point to an association between the neural processes that discriminate own and other name in multispeaker settings and auditory filtering abilities. The implications of how such findings might guide future investigations on auditory filtering in ASD are discussed below.

Early Salience Detection

Our first major finding was that ASD-MLV participants collectively did not show early, automatic discrimination of OON from SN. With our TD reference sample, we used a data-driven approach to identify a well-known marker of early salience detection (the MMR), generated when participants heard their own name among two other names. The identified spatial and temporal ROIs were in accordance with prior reports of MMRs to OON in neurotypical samples (Berlad & Pratt, 1995; Holeckova et al., 2006). Both ASD and TD verbally fluent groups produced MMRs that suggested they had detected OON as salient compared to the other names heard, while ASD-MLV individuals did not. Findings coincide with prior work describing no significant MMR differences between TD and ASD-V response to own versus other, unknown names (Nijhof et al., 2018). MMR deficits specific to the ASD-MLV group support the hypothesis that those with

language disorders show atypical neural markers that index the discrimination of linguistic and acoustic information (Kujala et al., 2013; Matsuzaki et al., 2019; Schwartz et al., 2018). Deficits might also be indicative of broader difficulties organizing and prioritizing speech inputs (Kujala et al., 2007).

Late Attentional Orienting and Self-Other Discrimination

Our second major finding was that, in those with ASD, LPP neural indices indicative of attentional orienting and self-other discrimination varied with auditory filtering ability. LPP neural signatures detected around 500-650 ms in TDs were consistent with prior reports of own-name EEG response in TD samples (Holeckova et al., 2007; Key et al., 2016). Findings also complement neuroimaging research that has employed techniques with better spatial resolution (e.g., fMRI and PET), in which researchers have consistently identified activation of middle and superior temporal cortex, middle frontal cortex (including the medial prefrontal cortex), and regions within the posterior parietal and anterior occipital cortex (including the posterior cingulate, precuneus, and cuneus) when individuals hear their own name (Carmody & Lewis, 2006; Grossmann, Parise, & Friederici, 2010; Kampe, Frith, & Frith, 2003).

In the multispeaker background condition, we could not detect significant differences in LPPs generated by TD, ASD-V, and ASD-MLV participants. These negative results differ from prior reports of decreased LPPs in ASD-V adolescents, albeit in quiet settings (Nijhof et al., 2018; Nowicka, Cygan, Tacikowski, Ostaszewski, & Kuś, 2016; Tacikowski, Cygan, & Nowicka, 2014). Similarly, our findings conflict with prior

reports of atypical activation along parietal-occipital areas during attentional orienting and self-other discrimination in individuals with ASD (Cui et al., 2017; Eddy, 2016; Kennedy & Courchesne, 2008). Future research is needed to resolve this discrepancy. One possible cause for our inability to detect differences between groups could have been the high variance in later cognitive processing across participants as an effect of multispeaker noise. This hypothesis is supported by our **Supplemental Materials**, in which we find that in comparison to TDs, both ASD-V and ASD-MLV participants have weaker late, prolonged shifts in their response to OON compared to SN.

From an investigation of ASD within-group variability, we found that weaker LPPs to OON were significantly correlated with poorer auditory filtering abilities. The significant association between LPPs to OON and auditory filtering abilities could arise from disorder-wide challenges in selecting relevant from irrelevant information, particularly within the auditory domain (Lepistö et al., 2009; Minshew, Goldstein, & Siegel, 1997). This hypothesis is consistent with frequent anecdotal reports that people with ASD feel overwhelmed in noisy settings (particularly with multiple talkers). It is also supported by psychoacoustic and neuroimaging studies in which individuals with ASD require higher levels of signal-to-noise to adequately identify and encode signal features (Alcántara et al., 2004; Lepistö et al., 2009; Russo et al., 2009). However, more research is needed to determine the extent to which attentiveness to socially relevant stimuli is particularly susceptible to fail in complex scenes in those with ASD.

Limitations and Future Directions

While we sought to obtain more robust signals by presenting more name trials, this approach paradoxically led to weaker average signals in the quiet condition. We suspect that as a result of our decision to triple the number of OON trials that have classically been presented in OON response experiments, participants adapted to hearing OON (See **Supplemental Materials**). However, the adaptation lessened when we presented names within masking signals. Thus, while differences in adaptation prevented us from directly comparing results between quiet and multispeaker noise settings, our approach confirmed that neural adaptation to an increased number of trials can be mitigated by introducing an informational masker (Polich, 2007; Tateuchi, Itoh, & Nakada, 2012).

Our ability to behaviorally characterize our participants was limited to the specific measures we selected based on our initial hypotheses and constraints given our sample. Notably, we relied on one common measure of auditory filtering and selective attention (the SSP Auditory Filtering Subscale) because it can be collected on ASD-MLV participants through parent report. However, if feasible, auditory filtering abilities would be more accurately characterized with direct measures of behavior and psychoacoustic responses. In addition, because TD participants were enrolled exclusively as a normative reference for the neuroimaging experiment, we did not collect behavioral information comparable to that collected on ASD participants. As such, we cannot dismiss that associations between LPPs and auditory filtering abilities may not be unique to ASD samples; future studies should investigate the relationship between response to salient

sounds like OON in multispeaker settings and auditory filtering in non-ASD samples.

By design, the current study was limited to adolescents. However, given that unique response to OON is detectable with neuroimaging techniques in children as young as four months old (Grossmann et al., 2010; Imafuku, Hakuno, Uchida-ota, Yamamoto, & Minagawa, 2014; Parise et al., 2010), one future next step would be to determine whether neural responses to OON could be useful to measure when studying those at risk for ASD. Several studies to date have successfully measured OON neural response in preschoolers with ASD (Carmody et al., 2007; Kellerman, Fan, & Gorman, 2005; Thomas et al., 2019), but more are needed to better understand the links between neural responses and current or future clinical impairments. Given the associations between neural and behavioral response to OON and autism symptomatology, researchers might also consider whether changes in neural response to OON could serve as a useful outcome measure when quantifying success of interventions targeting social orienting in ASD.

Conclusions

This study contributes to the investigation of own and other name discrimination in ASD by identifying neural abnormalities specific to the ASD-MLV subtype. To our knowledge, we are the first to investigate either TD or ASD participants' neural responses when they hear their name in a multispeaker setting. We are also the first to describe how such neural markers relate to characteristics of selective auditory attention in verbal and minimally verbal individuals with ASD. Improved understanding of these

associations may guide future research on deficits in response to OON that commonly accompany ASD.

SUPPLEMENTAL TEXT

In our initial analysis of all quiet condition trials, we did not detect responses to OON that had previously been reported in TD samples (Fan et al., 2013). We conducted post-hoc analyses to address this discrepancy under the suspicion that our inability to replicate prior work may have stemmed from methodological differences. While prior studies presented 30–50 trials of each name, we presented 150 of each. We predicted that stimulus adaptation had masked our ability to observe significant responses to OON. When we limited our analyses to trials from the first block of the quiet condition, we successfully identified two windows of interest. TDs exhibited a late, slow parietal positive shift to OON (LPP; 536-646 ms) (**Supplemental Figure 4.S2**), along with an analogous late, slow frontal negative shift (FN; 590-668 ms), but no early fronto-central response indicative of an MMR.

Next, we conducted full factorial linear mixed models of all trials with participant as a random effect for data collected within this first quiet setting block for the two identified ROIs. Statistical significance for linear mixed effects models were calculated using Likelihood Ratio Tests (Winter, 2013). Significant tests were followed up with post-hoc analyses for main effects and interactions using analyses of variance. All significance thresholds were based on a threshold of $\alpha < 0.05$.

FN (590 – 668 ms): Group did not significantly affect neural response ($\chi^2(1) = 0.15$, $p = 0.70$), nor did name ($\chi^2(1) = 2.45$, $p = 0.12$). The interaction between group and name significantly affected neural response ($\chi^2(1) = 4.23$, $p < 0.05$). TD participants had a more negative late fronto-central response to their own name compared to another name (MD = -0.89 [-1.52 – -0.26] uV, $p < 0.01$) while ASD-V and ASD-MLV participants did not show a difference in neural response between the two names (**Supplemental Figure 4.S3**; ASD-V: MD = 0.04 [-0.60 – 0.69] uV, $p = 0.90$; ASD-MLV: MD = 0.11 [-0.71 – 0.93] uV, $p = 0.79$).

LPP (536 – 646 ms): We found no significant effect of name ($\chi^2(1) = 1.50$, $p = 0.22$) nor group ($\chi^2(1) = 1.27$, $p = 0.26$) on neural response. The interaction between the two terms also did not significantly affect response ($\chi^2(1) = 0.96$, $p = 0.33$).

Results provide evidence for the argument that both ASD-V and ASD-MLV adolescents demonstrate atypical higher-level processing of OON compared to TD controls. This evidence was clear from the FN component that has previously been thought to reflect a familiarity effect evoked by OON (Herzmann & Sommer, 2010; Holeckova et al., 2007). While we were able to identify group differences in FN response, we did not identify its analogous component, the LPP, that has previously been identified between TD and ASD-V groups in quiet (Nijhof et al., 2018). Future work is needed to better understand how these slow late positive and negative shifts evoked by OON differ in TD and ASD samples.

Table 4.1. Comparative demographics of TD and ASD participants included in EEG analyses.

		TD	**ASD-V**	**ASD-MLV**	**Sig. (*p*)**	η^2
Participants	*N*	27	27	20		
Age (years)	*Mean (SD)*	17.81(3.00)	17.21(2.08)	16.81 (2.64)	*NS*	0.03
	Range	13.13–22.21	13.42–20.86	13.15–21.76		
M:F	*Ratio*	16:11	22:5	13:7	*NS*	
Race					*NS*	
	Asian	7	1	*4*		
	Black/African American	3	0	1		
	Caucasian	15	18	13		
	Multiple Races	1	5	1		
	Prefer not to respond	1	3	1		
Ethnicity					*NS*	
	Hispanic	2	1	1		
	Non-Hispanic	25	22	18		
	Prefer not to respond	0	4	1		

Table 4.2. Cognitive-behavioral characteristics of ASD participants included in EEG analyses.

			ASD-V	**ASD-MLV**	**Sig. (*p*)**	**η^2**
Autism Severity	ADOS Calibrated Severity Score	*Mean (SD)*	7.37 (2.32)	8.05 (1.40)	*NS*	0.03
		Range	3–10	5–10		
Nonverbal IQ	Leiter-3 Standard Score	*Mean (SD)*	109.63 (20.83)	54.75 (20.24)	$p<0.001$	0.64
		Range	74–141	30–111		
Adaptive Functioning Level	Vineland-3 Adaptive Behavior Composite Score	*Mean (SD)*	75.41 (10.80)	48.20 (16.08)	$p<0.001$	0.52
		Range	57–102	23–71		
Auditory Filtering Skills	Short Sensory Profile: Auditory Filtering Subscale Raw Score	*Mean (SD)*	16.62 (5.42)	16.95 (4.45)	*NS*	0.001
		Range	10–29	9–28		

Table 4.3. Neural and behavioral correlates. Results are based on MMR and LPP response when names were heard in a multispeaker noise setting. *p<0.05, **<0.01.

	Auditory Filtering Skills	NVIQ	Age	EEG Trials
MMR	-0.21	-0.15	-0.14	-0.02
LPP	.44**	-0.16	0.03	-0.09

Supplemental Table 4.S1. Number of analyzed trials for own and selected other name for each group, organized by experimental blocks.

		Blocks 1 & 2		Blocks 3 & 4		Blocks 5 & 6	
		Quiet #1	Multi-speaker #1	Quiet #2	Multi-speaker #2	Quiet #3	Multi-speaker #3
ASD-MLV	Mean (SD)	81.47 (17.0)	82.84 (17.24)	79.74 (18.21)	79.60 (19.36)	78.90 (16.21)	76.50 (16.80)
	Range	41-108	44-105	45-105	42-106	49-107	55-106
ASD-V	Mean (SD)	92.11 (16.25)	91.67 (13.12)	90.11 (16.95)	91.85 (16.35)	89.93 (14.91)	91.81 (14.90)
	Range	42-108	51-108	49-108	50-108	58-107	61-108
TD	Mean (SD)	97.04 (11.79)	95.07 (10.67)	94.48 (15.64)	98.41 (10.21)	95.00 (12.43)	98.48 (7.87)
	Range	57-107	67-108	54-108	72-108	56-108	81-108
Significance (*p*)		<0.01	0.01	0.02	<0.001	<0.001	<0.001

Supplemental Table 4.S2. Parameter estimates for MMR in multispeaker settings. Post hoc analyses were not conducted for LPP in multispeaker settings.

V1	V2	Mean Difference (V1-V2)	SE	*p*	95% CI	
TD	ASD-V	-0.23	0.12	0.07	-0.47	0.02
	ASD-MLV	-0.59	0.14	<0.0001	-0.87	-0.32
ASD-V	ASD- MLV	-0.37	0.14	<0.01	-0.64	-0.09

V1	V2	Mean Difference (V1-V2)	SE	df	*p*	95% CI	
Own Name	Other Name	-0.39	0.12	74.51	<0.01	-0.63	-0.14

Stimulus	V1	V2	Mean Difference (V1-V2)	SE	p	95% CI	
TD	Own	Other	-0.70	0.17	<0.001	-1.04	-0.36
ASD-V	Own	Other	-0.48	0.18	<0.01	-0.83	-0.14
ASD-MLV	Own	Other	0.03	0.22	0.89	-0.40	0.46

Figure 4.1. Topography of neural response to names presented in multispeaker noise. Results are based on group averages of all trials across all three blocks of name presentations. Responses are plotted for early latency mismatch responses (MMR; 178-332) and late latency parietal positive shift responses (LPP; 514-645 ms). Responses are plotted for response to own name, other name, and differential response of own name relative to other name.

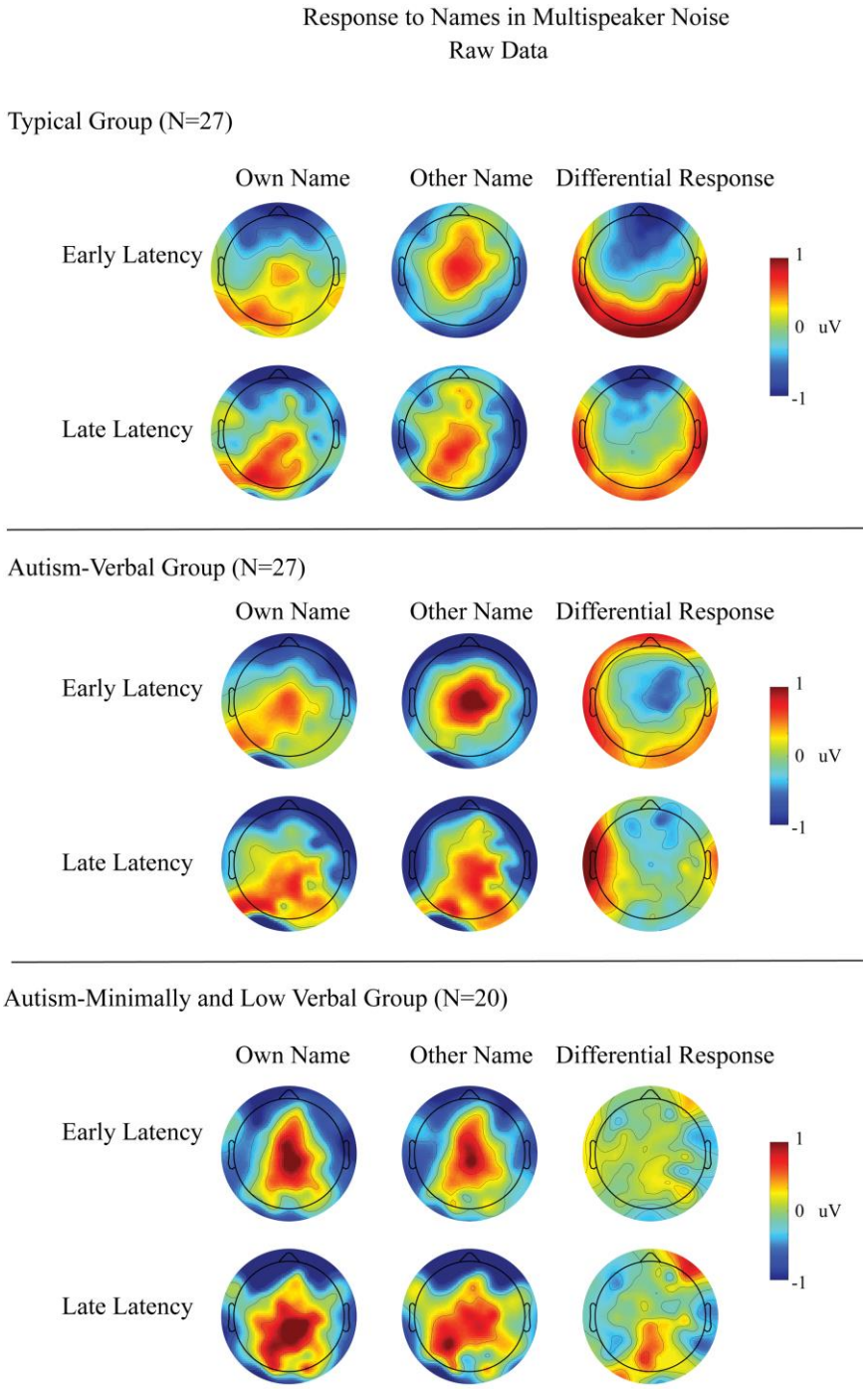


Figure 4.2. Neural response to names presented in multispeaker noise. Results are based on all trials across all three blocks of name presentations. Responses are plotted on the left panel for early fronto-central mismatch responses (MMR; 178-332 ms) and on the right panel for late parietal positive shift responses (LPP; 514-645 ms). Responses to own and other names are plotted in microvolts for TD (N=27, top row), ASD-V (N=27, middle row), and ASD-MLV (N=20, bottom row) subjects.

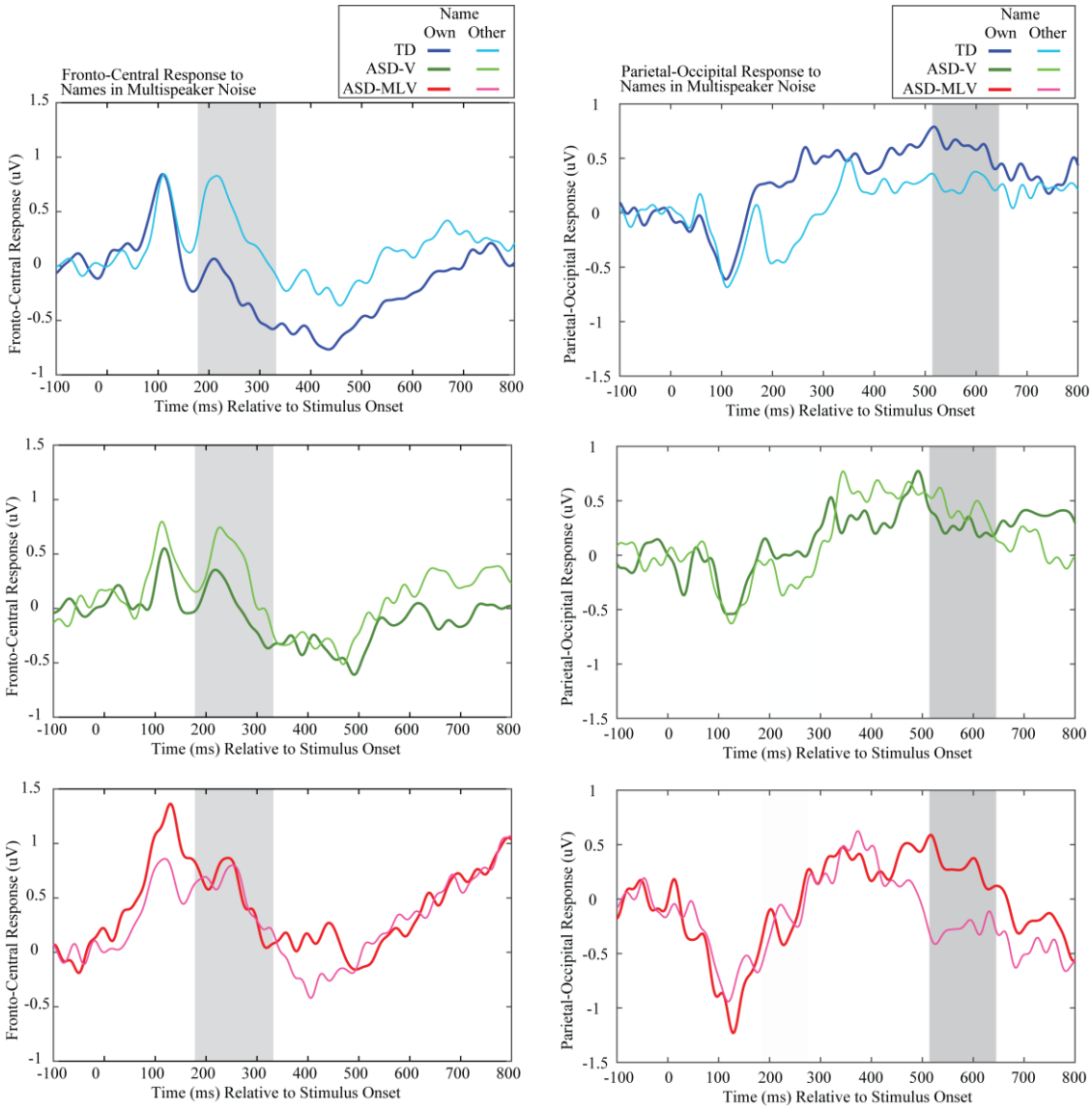


Figure 4.3. Between-group comparison of neural response to names presented in multispeaker noise. Results are based on all trials across all three blocks of name presentations. Responses are plotted for fronto-central early average response (MMR, 178-332 ms) and parietal-occipital late average response (LPP; 514-645 ms). Responses to own and other names are plotted in microvolts for TD (N=27), ASD-V (N=27), and ASD-MLV (N=20) subjects.

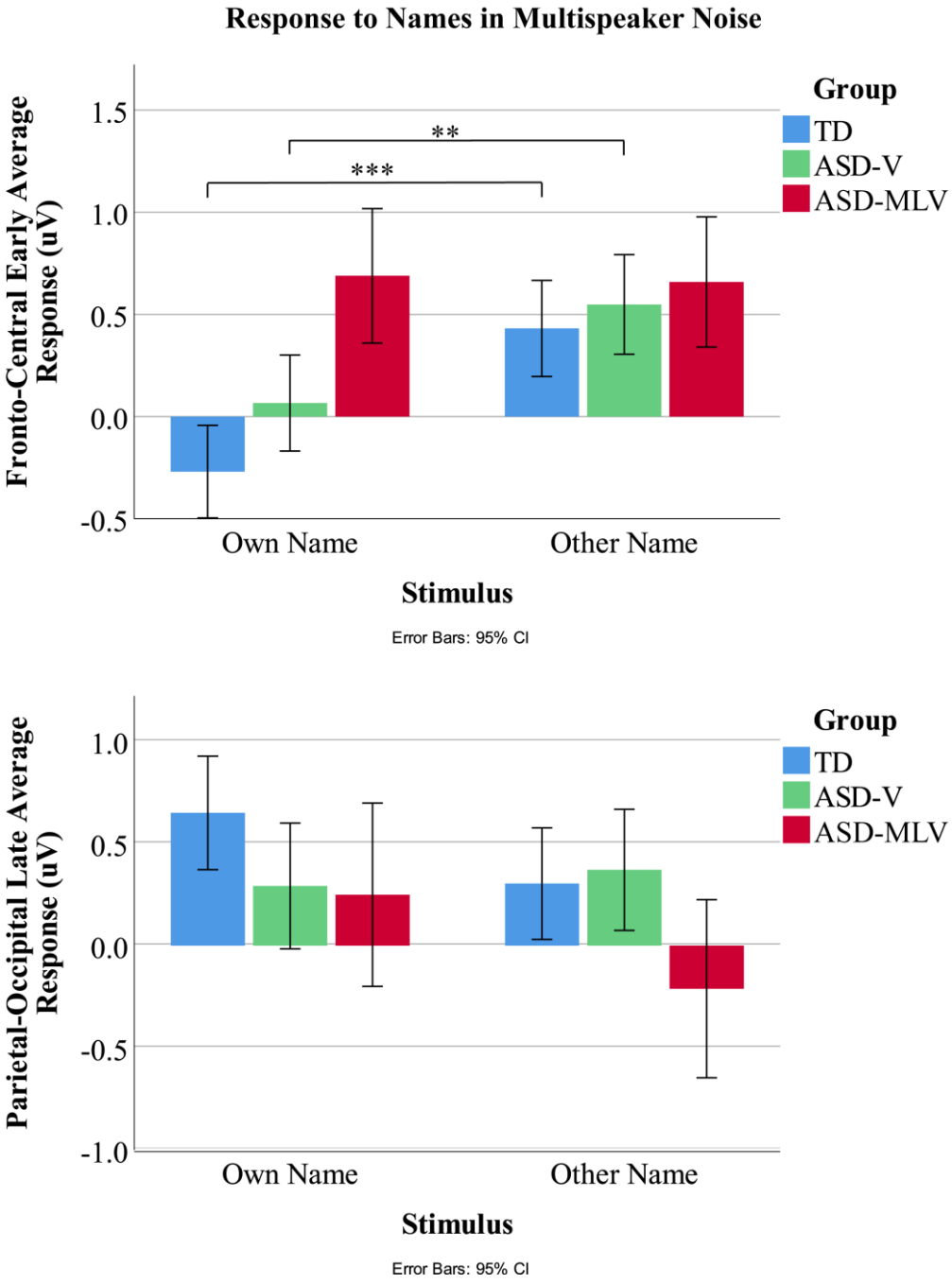
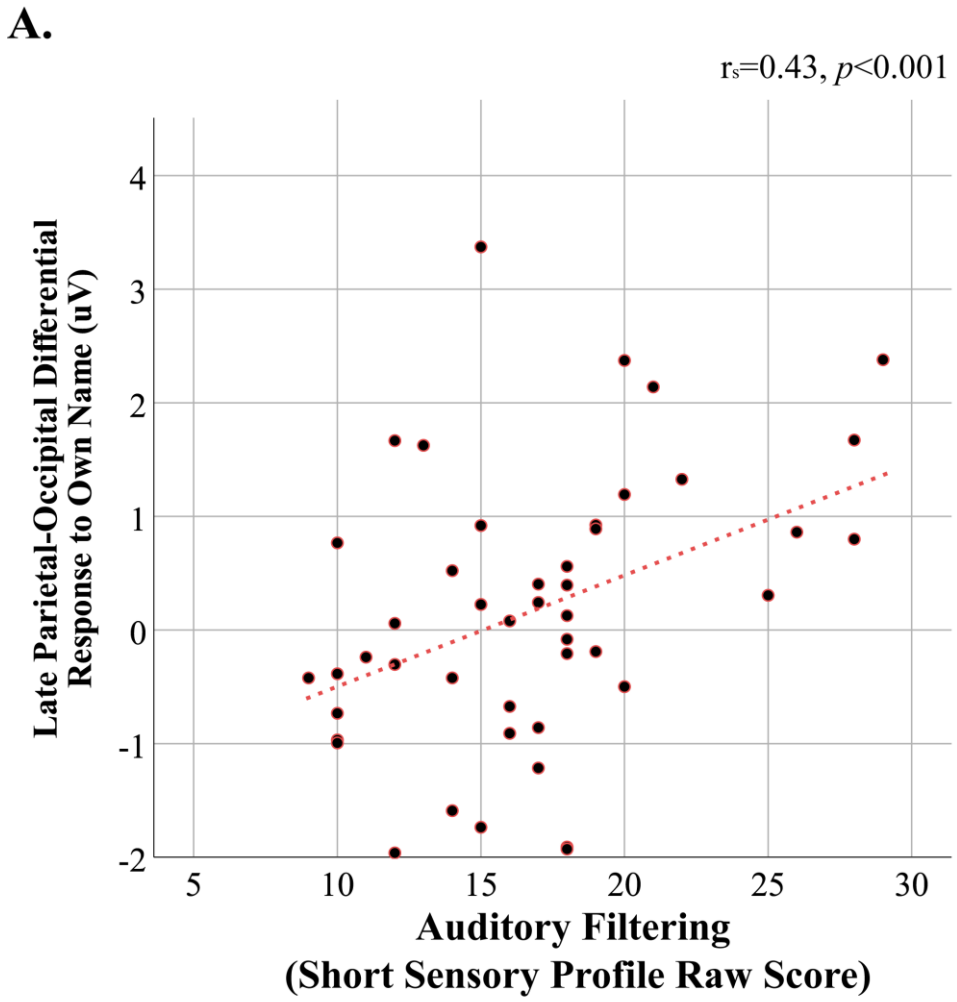
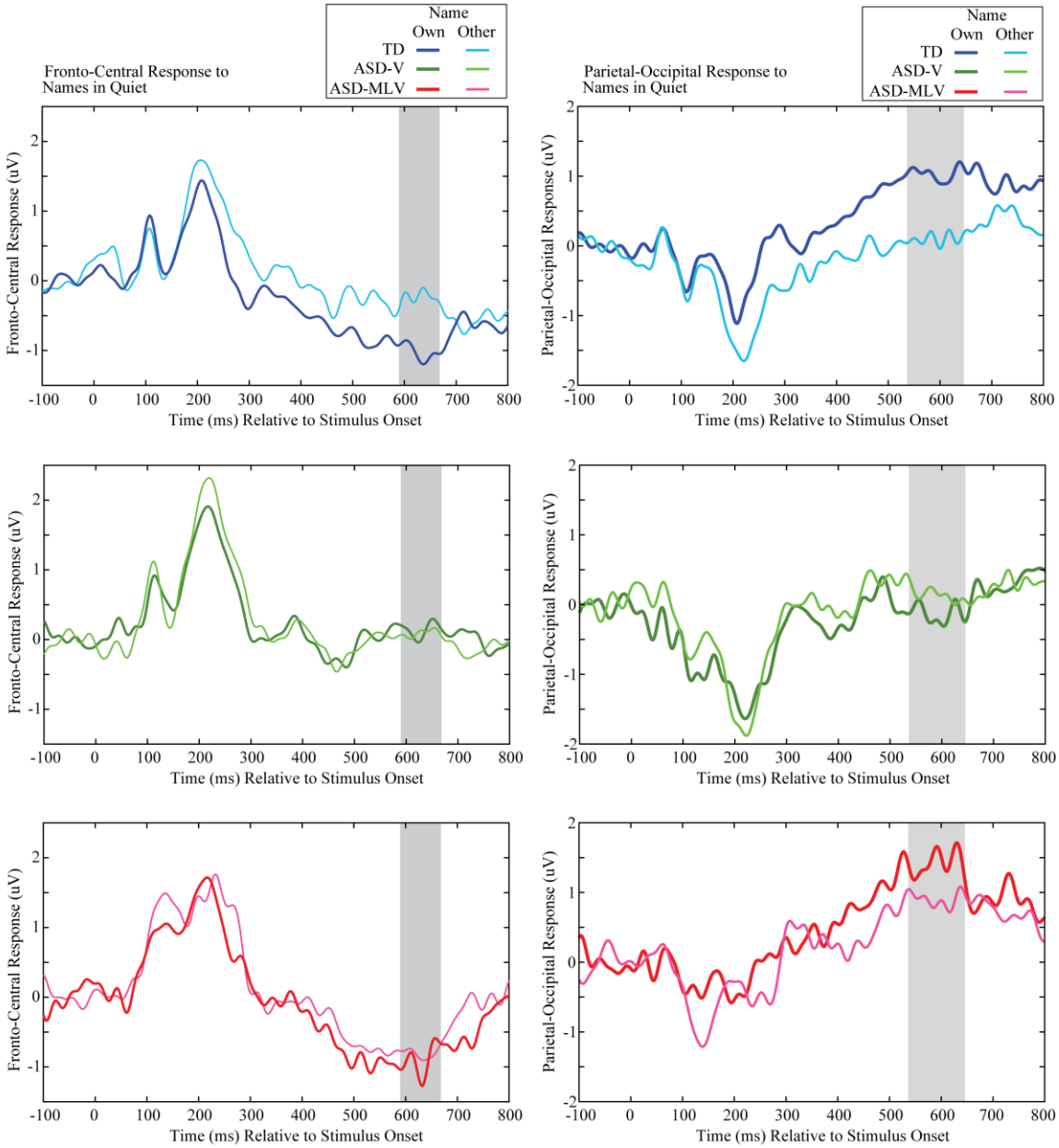


Figure 4.4. Correlates between strength of LPPs to OON and auditory filtering abilities across all ASD participants (N=47).

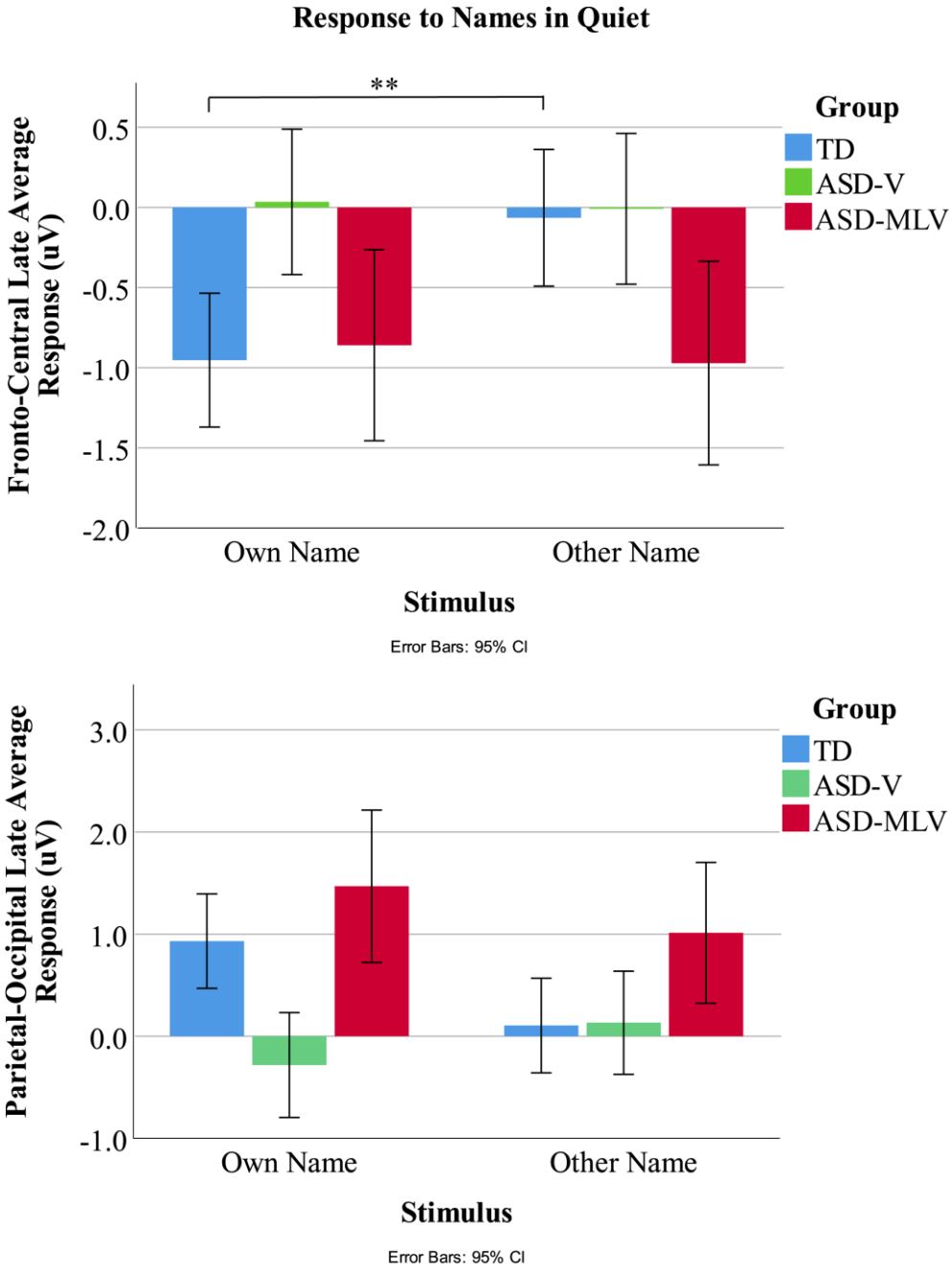


Supplemental Figure 4.S1. Neural response to names presented in multispeaker noise, plotted as baseline-normalized z-scores. Results are based on all trials across all three blocks of name presentations. Responses are plotted on the left panel for early fronto-central mismatch responses (MMR; 178-332 ms) and on the right panel for late parietal positive shift responses (LPP; 514-645 ms). Responses to own and other names are plotted in baseline-normalized z-scores for TD (N=27, top row), ASD-V (N=27, middle row), and ASD-MLV (N=20, bottom row) subjects.

Supplemental Figure 4.S2. Neural response to first block of names presented in a quiet setting. Results are based on trials solely from the first block of name presentations. Responses are plotted on the left panel for late frontal negative shift responses (FN; 536-646 ms) and on the right panel for late parietal positive shift responses (LPP; 590-688 ms). Responses to own and other names are plotted in microvolts for TD (N=27, top row), ASD-V (N=27, middle row), and ASD-MLV (N=20, bottom row) subjects.



Supplemental Figure 4.S3. Between-group comparisons of neural responses to names presented in quiet condition. Results are based on trials solely from the first block of name presentations. Responses are plotted for late frontal negative shift responses (FN; 536-646 ms) and late parietal positive shift responses (LPP; 590-688 ms). Responses to own and other names are plotted in microvolts for TD (N=27), ASD-V (N=27), and ASD-MLV (N=20) subjects.



CHAPTER SIX: GENERAL DISCUSSION

This dissertation investigates central auditory processing in ASD-MLV to determine the extent to which processing differences relate to observed differences in cognitive-language profile and atypical auditory behaviors. The major scientific contribution of this dissertation is its demonstration of the MMR as an effective neural index of atypical central auditory processing in ASD-MLV. In the presented research, we report that ASD-MLV adolescents show atypical MMRs to one's own name, among other names, heard in a multispeaker background. We also report a relationship between MMRs to nonspeech intensity deviants and percent of time spent engaged in atypical auditory behaviors. Using a large cohort of ASD-MLV and control participants, we demonstrate that passive EEG paradigms are sensitive measures of nonspeech and speech processing in ASD-MLV samples.

In this final chapter, I provide a summary of main findings (Summarized in **Table 5.1**) and propose a theoretical framework to explain these findings in the greater context of what is known about ASD (Summarized in **Table 5.2**).

MAIN FINDINGS

The Emergence of Adult-Like Auditory Stream Segregation in Adolescence

In our research on neurotypical children and adolescents (*Chapter 2*), we found that, in a dual-stream setting, we could detect MMRs as indexes of automatic stream segregation in adolescents and adults, but not in pre-adolescent children ages 3 to 12.

These findings significantly influenced how we approached the implementation and analysis of subsequent research. For instance, this guided our research in *Chapter 5*, in which we restricted our study of neural response to OON in a multispeaker setting to adolescents and young adults. The findings from *Chapter 2* shed light on potential obstacles that can emerge when researchers seek to measure automatic neural indices of stream segregation in pre-adolescent children. Future efforts should determine if passive EEG paradigms can be developed to capture pre-adolescent auditory scene analysis. One key hypothesis that emerges from our work is that until the processes underlying automatic stream segregation have matured to an adult-like state, children may need to recruit top-down cognitive processes to aid in stream segregation. This hypothesis could be tested by investigating whether children with attention-based disorders have more difficulty actively segregating sounds in complex settings.

Passive Auditory Mismatch Response Paradigms in ASD-MLV

A major goal in our research has been to develop reliable and robust passive paradigms that can be used to measure auditory-evoked brain activity in ASD-MLV participants. The use of passive paradigms to study auditory processing, particularly in response to speech stimuli, is not well established, but this approach could greatly expand our ability to study the cognitive processes of those who cannot communicate fluently. To date, the absence of passive paradigms has precluded testing of people who cannot complete active tasks, including ASD-MLV participants. In this dissertation, we demonstrate that we can probe early and automatic sensory processes fundamental for

auditory scene analysis and speech processing with passive MMR paradigms in ASD-MLV adolescents.

Furthermore, through our meta-analysis in *Chapter 3*, we identified features of passive MMR experimental designs that have led to inconsistent findings across studies on ASD. Considering these different approaches helped us to refine our own MMR paradigms. For instance, we realized how important it is to control for differences in neural response to different sound tokens (e.g., counterbalanced stimuli). We designed the experiments described in *Chapters 4* and *5* in ways that employed this practice, presenting the same stimuli in different contexts. This work also highlights the importance of considering not only group-level differences but individual differences as well.

Atypical Perceptual Organization of Sounds in ASD-MLV Adolescents as Revealed by Behavioral and Neural Measures

Our findings support the hypothesis that ASD-MLV children and adolescents engage in significantly more atypical auditory behaviors than ASD-V controls (*Chapter 4*; Patten, Ausderau, Watson, & Baranek, 2013; Watson, Patten, Baranek, Poe, & Boyd, 2011). In ASD-MLV individuals, we found that receptive language abilities, as measured by lexical vocabulary, were well-explained by the amount of time spent engaged in atypical auditory behaviors, beyond what was accounted for by nonverbal IQ and age. Our findings that receptive language and atypical auditory behaviors are correlated in ASD-MLV individuals support the conclusions of Foss-Feig and colleagues (2017), who

show a specific relationship between language skills and low-level auditory, but not visual, processing, in ASD-V individuals. Foss-Feig and colleagues acknowledge that while the relationship they found was in children with average to above-average verbal intelligence, they expect the relationship to hold – or even be more pronounced – in those with more severe language deficits. In *Chapter 4*, we showed a correlation between strength of MMRs during the organization of nonspeech sounds and percent of time engaged in atypical auditory, but not visual, behaviors – a finding that expands on previously identified associations between weak auditory MMR and domain-general sensory sensitivities (Donkers et al., 2015; Ludlow et al., 2014) and confirms Foss-Feig and colleague's conclusions, but in a group of individuals with severe language impairments.

Neural Response to Own Name is Atypical in Multispeaker Settings in ASD-MLV Adolescents

When early acoustic detection of OON – arguably one of the most salient speech cues a human can hear – was measured in ASD-MLV, ASD-V, and TD adolescents, we found that ASD-MLV adolescents produced a significantly weaker MMR to OON than the more verbal groups (*Chapter 5*). Findings replicated prior work finding no differences between TD and ASD-V response to OON (Nijhof et al., 2018). We believe our study is the first to note weak OON responses in an ASD-MLV group. The failure of ASD-MLV, but not ASD-V, to produce a typical MMR in response to OON could reflect deficits in how ASD-MLV individuals organize and prioritize salient speech (Kujala et al., 2007;

Matsuzaki et al., 2019).

The interpretation of later cognitive response to OON is less clear. We found evidence that both ASD-V and ASD-MLV adolescents demonstrate atypical higher-level processing of OON compared to TD controls when heard in quiet, as demonstrated by a weaker slow, frontal negative shift. This expands on prior work showing similarly timed differences in a related component along parietal channels in ASD-V adults (Nijhof et al., 2018). However, we did not detect any significant differences between TD, ASD-V, and ASD-MLV participants in late cognitive responses to OON in multispeaker conditions. Nonetheless, detected associations between strength of response to OON (particularly in a multispeaker setting) and auditory filtering abilities within the ASD group bolsters the hypothesis that we can use neural indices to capture individual variability in the ability to select relevant from irrelevant information, particularly within the auditory domain (Lepistö et al., 2009; Minshew et al., 1997).

THEORETICAL FRAMEWORK

This dissertation details perceptual differences in ASD-MLV individuals as evidenced by atypical auditory behaviors and atypical central auditory processing. Individual variability in these characteristics is complicated (as with many aspects of ASD) and must be considered within the greater context of what is known about the disorder. Therefore, much of the theoretical framework described here draws on conclusions that have been made from other research. Consequently, these ideas draw primarily from research restricted to ASD-V individuals as ASD-MLV research is so rare. From the theoretical framework described below, we hypothesize that disruptions in

the central nervous systems responsible for low-level encoding of auditory inputs, which have been demonstrated to exist in ASD generally, are even more severe in ASD-MLV individuals. In parallel, we hypothesize that such deficits manifest strongly when processing complex scenes because they prevent listeners from proper perceptual organization of such scenes. Moreover, we hypothesize that the consequences of these processing deficits cause a cascade of encoding and processing issues throughout the central auditory nervous system.

There are several major findings to support the conclusion that ASD-MLV individuals experience low-level perception-based deficits, with likely origins in limbic structures and sensory systems (Marco et al., 2011). As mentioned, atypical low-level perceptual differences, particularly the ability to discriminate sound features and organize sound mixtures, can be operationalized by measuring neural responses to sound change in single and dual-stream contexts. The conjunction of our research and prior work demonstrate that individuals with ASD can show atypical neural markers in response to sound change in both single and dual-stream paradigms (Lepistö et al., 2009). In our research, we find that ASD-MLV individuals with more atypical auditory behaviors show weaker MMRs to intensity nonspeech deviants and that ASD-MLV individuals show a weaker MMRs to their own name in a multispeaker setting. These findings align with prior work showing more atypical MMRs to speech and nonspeech sounds in ASD-MLV children (Matsuzaki et al., 2019; Roberts et al., 2019). Further work is needed to determine if the genetic abnormalities that underlie the ASD-MLV phenotype impact NMDA receptor activity at excitatory synapses in auditory and frontal cortices (which are

major drivers of MMR neural response and have been proposed to be dysfunctional in ASD) (Lee, Choi, & Kim, 2015).

Symptoms of sensory overload may result from ineffective sensory gating. The impacts of sensory overload are unknown but overstimulation and excessive, unregulated sound inputs could further lead to aberrant development and stabilization of neural connections in the auditory nervous system and greatly impact the neural activity we observe by adolescence (Chang & Merzenich, 2003). Observation of more atypical auditory behaviors than atypical visual behaviors in ASD-MLV individuals suggests that difficulty in organizing sensory inputs may have a greater impact in the auditory domain in ASD-MLV, but more research is needed to test this through direct comparison of auditory and visual MMRs in relation to atypical auditory and visual behaviors.

The finding that MMRs to OON, when heard in noise, are particularly weak in a substantial portion of ASD-MLV individuals could be the result of group differences in perceptual selection and organization of salient information when that information is embedded in a mixture. In particular, individuals might be unequipped to handle the increased demands of information processing and signal extraction that are required in complex scenes. Prior work establishes the theory that selective attention is guided by the organization of information and selective transmission of neural information from one system to another (Houghton & Tipper, 1996). The combination of ineffective sensory gating and attentional regulation, along with known imbalances in excitatory-inhibitory control, are theorized to lead to increased noise in important signals in the brains of those with ASD (Belmonte et al., 2004; Gliga, Jones, Bedford, Charman, & Johnson, 2014;

Rubenstein & Merzenich, 2003). As exhibited from rodent work, ineffective gating along prefrontal and thalamic circuits could be particularly relevant to the auditory filtering deficits observed in ASD (Nakajima, Schmitt, Feng, & Halassa, 2019). Theoretically, if lower-level processing fails to remove this excess noise, information to be transferred to higher-level systems of processing will be degraded (Belmonte et al., 2004; Chang & Merzenich, 2003). This could be extremely detrimental for receptive language processing (Kujala et al., 2013). Furthermore, transfer of unorganized information might be problematic for ASD-MLV by virtue of the severe global cognitive impairments frequently associated with this group; many de novo mutations that lead to decreased inhibitory firing have been identified in those with global, non-ASD specific, cognitive impairments (Bourgeron, 2009; Rubenstein & Merzenich, 2003). As such, the refinement of our findings to ASD-MLV individuals and not all individuals with severe cognitive impairment is worthwhile.

CONCLUSION

In summary, this dissertation details the successful acquisition and analysis of data from 38 ASD-MLV adolescents collected with passive EEG paradigms using the practices described by Tager-Flusberg and colleagues (2017). We demonstrated the feasibility of using the MMR as a sensitive measure of central auditory processing deficits in ASD-MLV. Additional research is needed to determine whether impairments in neural transfer of information at low-level stages of information processing are common in ASD-MLV.

Table 5.1. Summary of Main Results. Constructs include the detection of unpredicted nonspeech complex tones and one's own name (OON). Neural measures include mismatch response (MMR) and late, prolonged positive parietal shift (LPP). Sample includes those who are typically developing (TD), have ASD and are verbally fluent (ASD-V), and have ASD and are minimally or low verbal (ASD-MLV). Ages are documented in years.

Construct	Paradigm	Measure	Sample	Age	Results
Presentation of atypical behaviors related to audition	Video coding of atypical behaviors	Percent of time engaged in atypical auditory behaviors	ASD-V (N=36) & ASD-MLV (N=47)	5-22	ASD-MLVs spent more time engaged in atypical auditory behaviors than ASD-Vs. Percent of time engaged in behaviors was negatively correlated with receptive language in ASD-MLV
Early detection of unpredicted sounds	Single-stream mismatch response	MMR to intensity change	TD (N=65)	3-22	MMR present at all ages
			TD (N=349) & ASD (N=372)	5-43	Some evidence that MMR is weaker in ASD, but further study was needed in ASD-MLV and adolescents, as well as a closer look at individual differences
			ASD (N=18)	10-22	ASD-MLVs who spent more time engaged in atypical auditory behaviors had weaker MMRs to nonspeech intensity deviants
Perceptual segregation of two nonspeech streams	Dual-stream mismatch response to complex tone based on pitch separation	MMR to intensity change	TD (N=65)	3-22	MMR index of stream segregation not adult-like before age 13
Early detection of OON after segregating target speech from multispeaker background	Dual-stream mismatch response to OON compared to two other names	MMR to OON	TD (N=27) & ASD-V (N=27) & ASD-MLV (N=20)	13-22	TD and ASD-V participants show significant MMRs to OON while ASD-MLV participants do not
Late orienting to OON after segregating target speech from multispeaker background		LPP to OON	ASD (N=47)		Weaker LPP in those reported by their parents to exhibit poorer auditory filtering abilities

Table 5.2. Theoretical Framework. Factors are mapped onto clinical observations (A-I). Factor constructs are mapped onto neural correlates of those constructs (1-9). Asterisks indicate evidence collected from ASD-MLV participants.

Individual Variability in ASD Clinical Observations
Might not respond to their own name or other attempts to get their attention[A-I]
Might show distress or trouble functioning in complex auditory scenes with noise or multiple talkers[A, B, C, D, E]
Might regularly cover or plug their ears[A, B, C, D]
Might regularly hums to themselves for purposes that do not appear to be communicative[A, B, C, D]
Might regularly seeks strange sounds that do not produce particularly interesting temporal or spectral patterns[A, B, C, D]
Factors That Impact Individual Variability in Clinical Observations
Low-Level Perception-Based Factors
A. Discrimination of sound features[1, 2, 3, 4, 5]
B. Organization of sound features into auditory objects[1, 2, 3, 4, 5]
High-Level Cognitive Factors
C. Ability to distinguish important from unimportant cues[3, 4, 5, 6, 7]
D. Mental representations about sound meaning (semantic and pragmatic)[1, 6, 7]
E. Poor integration of visual and auditory cues[3, 4, 7]
F. Abstract understanding of self-other distinctions [6, 7]
G. Understanding of joint attention and reference[8]
H. Motivation to engage in social interactions[9]
I. Global cognitive impairments[1-9]
Neural Correlates of Factor Constructs
1. Atypical neural response to sound change (e.g., Schwartz et al., 2020)*
2. Atypical stream segregation (e.g., Lepistö et al., 2009)
3. Atypical neural markers of temporal acuity and integration of sensory inputs (for review, see Baum, Miller, & Wallace, 2019)
4. Atypical synaptic connections between sensory systems (for review, see Marco et al., 2011)
5. Poor signal-to-noise ratio of information in neural signals (e.g., Dinstein et al., 2012)
6. Atypical neural response to one's own name (e.g., Schwartz et al., 2020)*
7. Atypical activity in response to language, audiovisual attention, and self-other differentiation in the superior temporal sulcus and temporoparietal junction (e.g., Deen et al., 2015)
8. Atypical activity during joint attention tasks in dorsal medial prefrontal cortex and superior temporal sulcus, and temporoparietal junction (e.g., Redcay et al., 2012)
9. Atypical activity in response to social interactions and social orienting in reward centers like the orbitofrontal cortex and ventral striatum (e.g., Scott-Van Zeeland et al., 2010)

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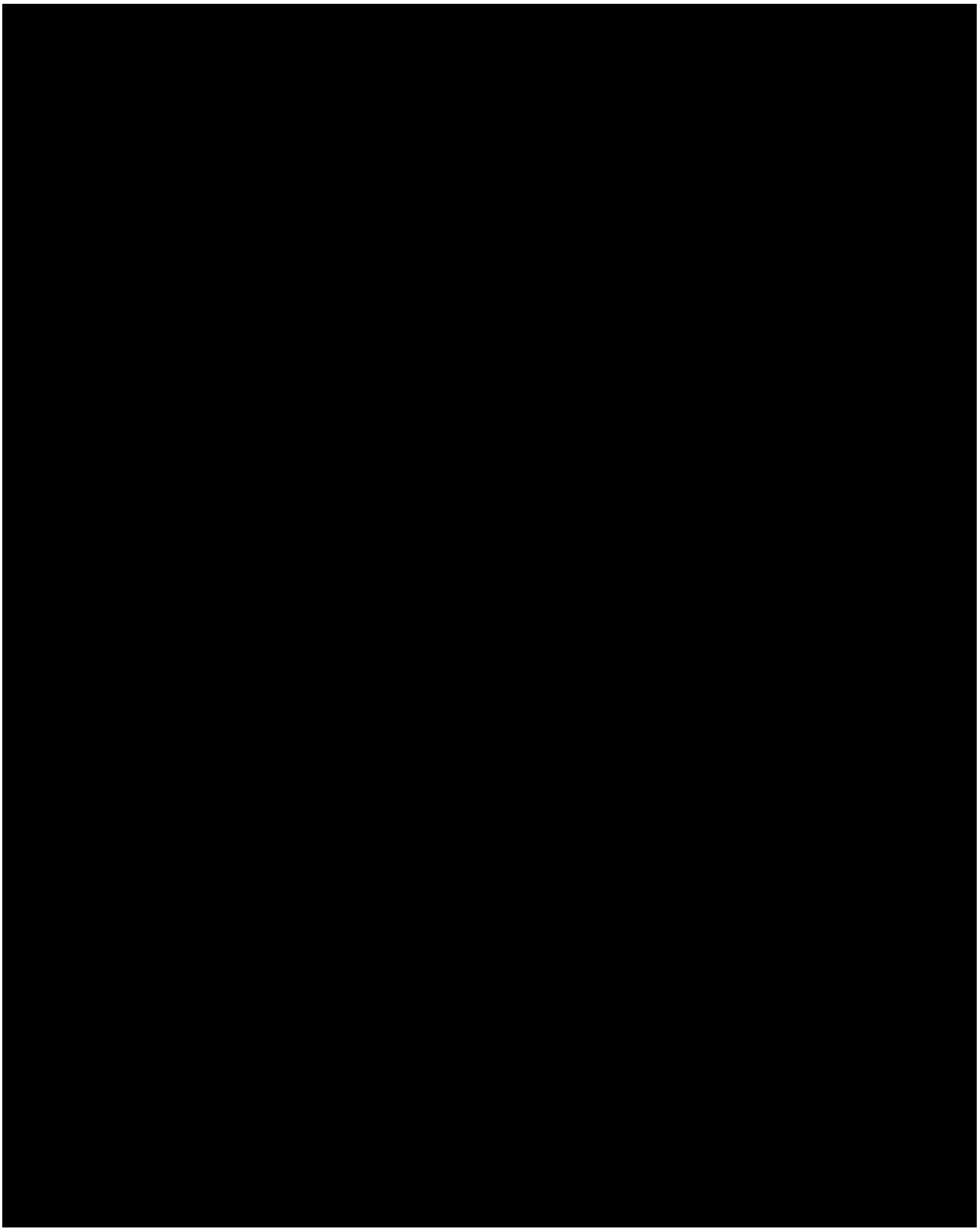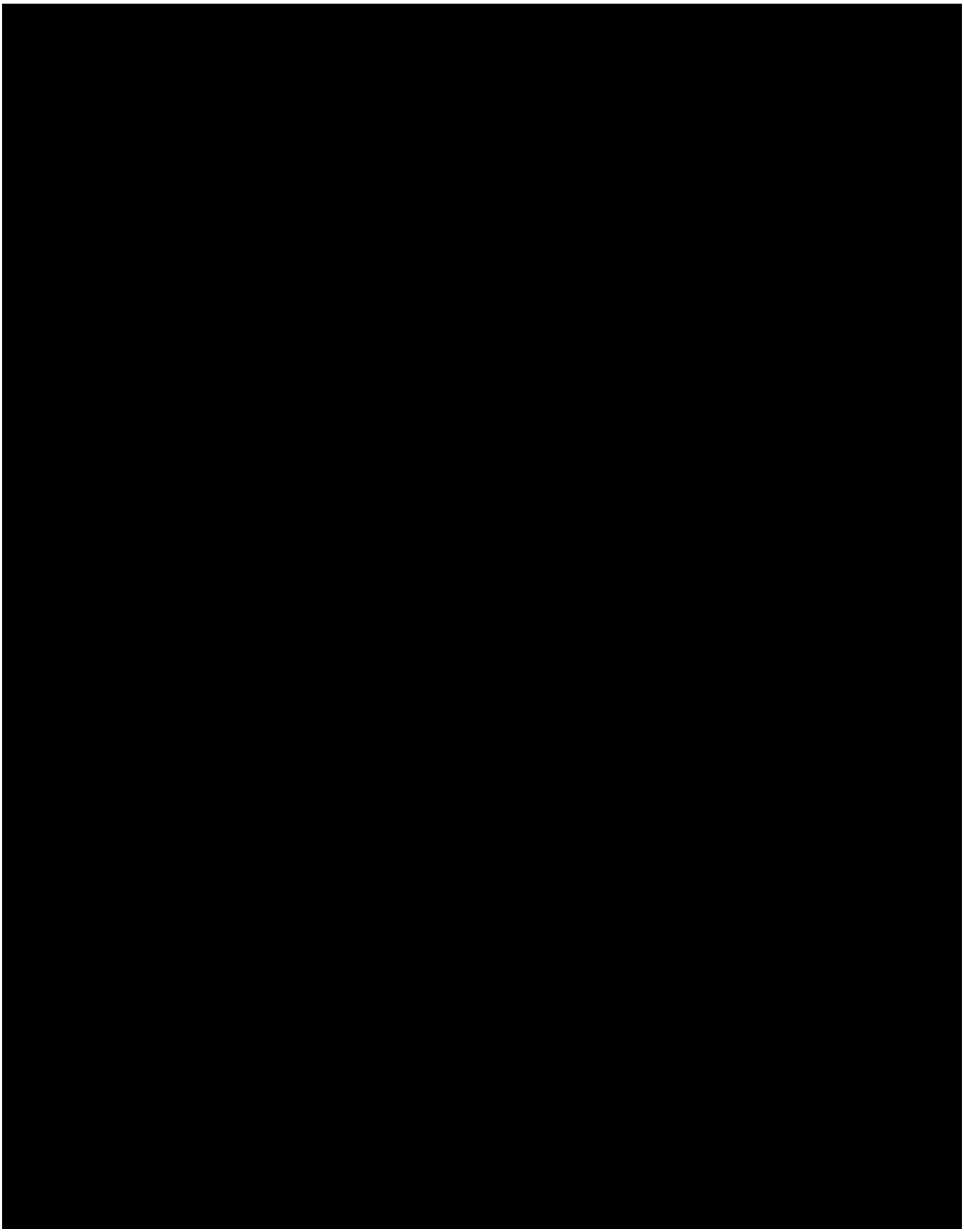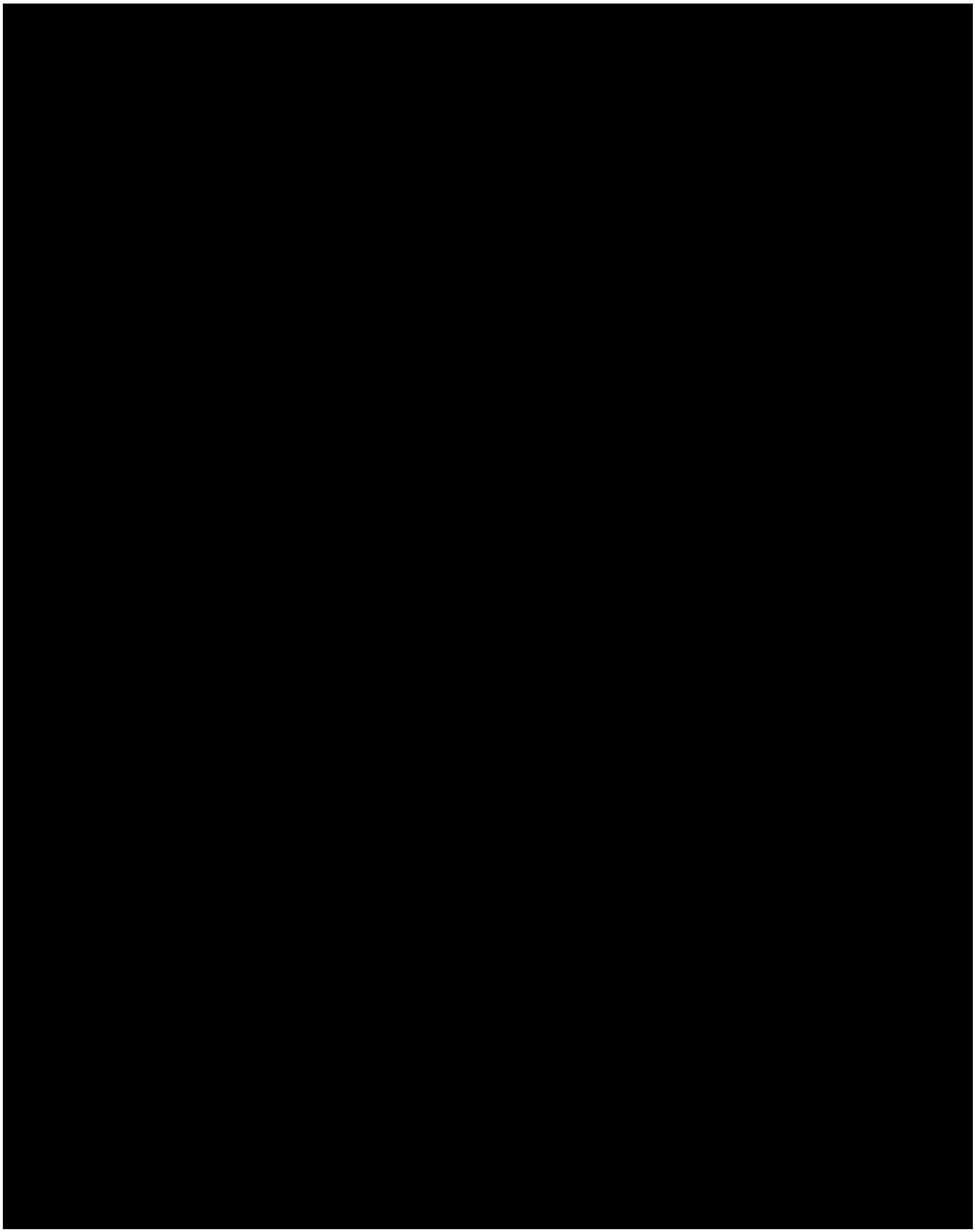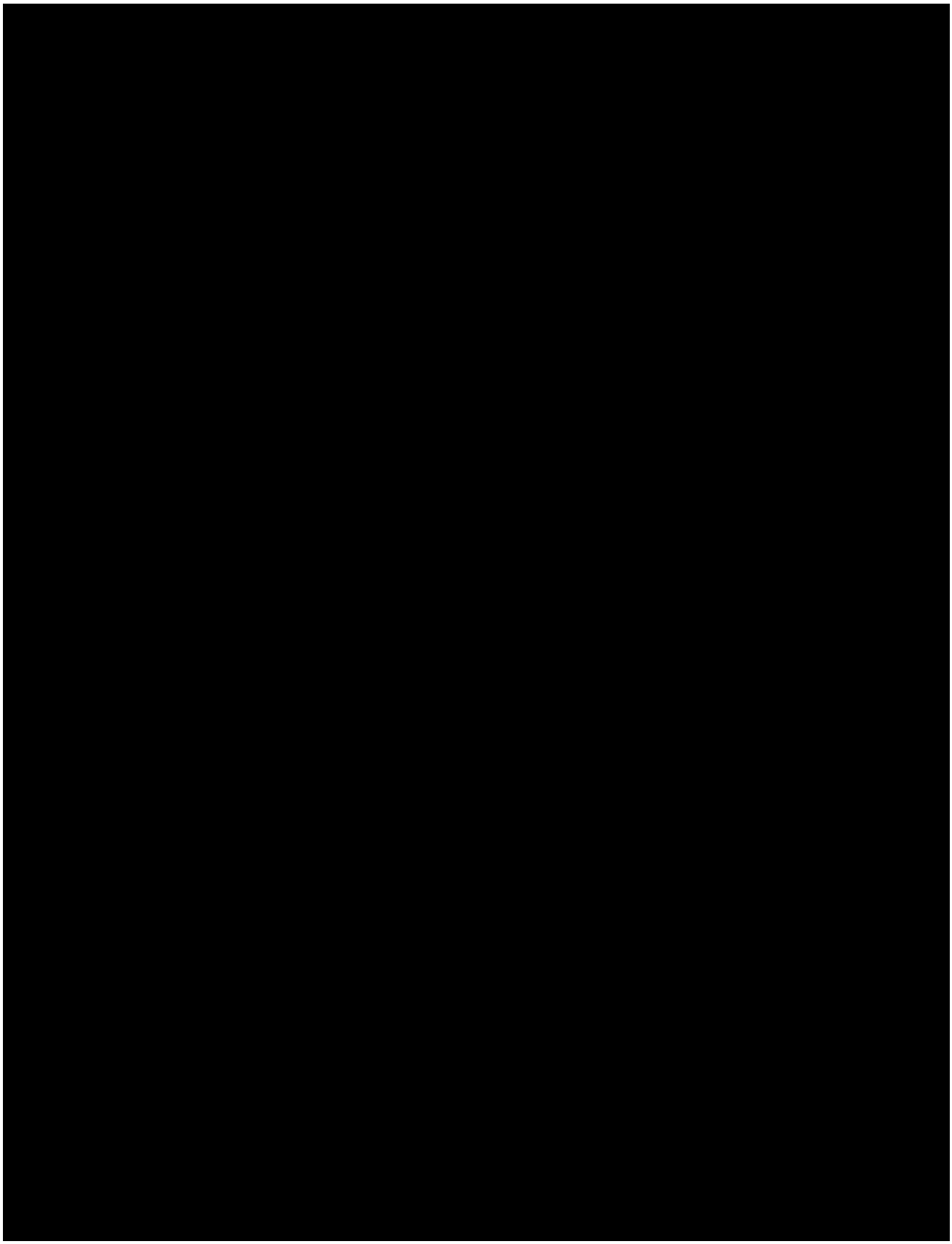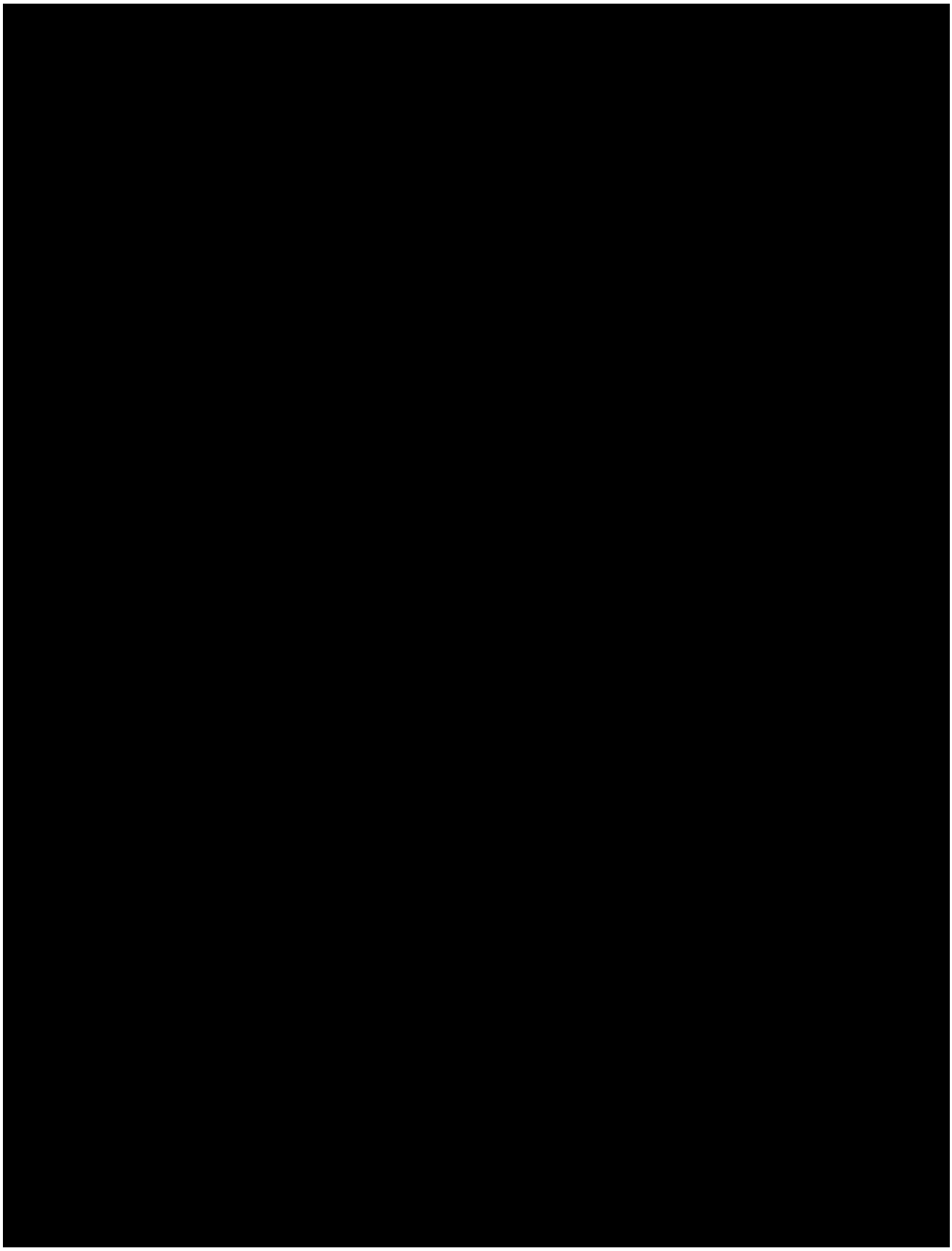
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