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Lisa Tecoulesco
lisa.tecoulesco@uconn.edu

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Auditory Brainstem Response and Language in Typically Developing Children and Children
with Autism Spectrum Disorder

Lisa Tecoulesco

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Auditory Brainstem Response and Language in Typically Developing Children and Children
with Autism Spectrum Disorder

Presented by

Lisa Tecoulesco, B.A.

Major Advisor _____
Letitia R. Naigles

Associate Advisor _____
Erika Skoe

Associate Advisor _____
Marie Coppola

Associate Advisor _____
Deborah Fein

University of Connecticut

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Abstract

Syntactic, semantic, and phonological knowledge are vital aspects of macro level language ability. Prior research has focused on environmental or cortical sources of individual differences in these areas. Subcortical contributions of the auditory brainstem have also been found to contribute to language ability in both typically developing (TD) populations and children with autism spectrum disorder (ASD). This study investigates whether one aspect of auditory brainstem responses (ABRs), response stability, a metric of the variability of instance to instance neural encoding of sound, can predict syntactic, semantic, and phonological performance in TD and ASD school-aged children. This study further investigates the degree to which phonological discrimination serves as a moderator of any relationship found between /da/ stability and syntax and semantics. Results showed that higher /da/ stability was associated with better phonological discrimination and syntactic performance in both TD and ASD children. Furthermore, phonological discrimination was a successful mediator of the relationship between /da/ stability and syntactic performance. This study supports the growing body of literature that stable subcortical neural encoding of sound is important for language development.

Introduction

Language learning is a complex task, and although common stages, strategies, and phenomena (ease and lack of instruction) are readily identifiable, individual outcomes vary as even children with typical verbal skills are not identical in language performance. While the source of at least some of the variation lies in environmental factors, such as the linguistic input children receive, other sources are probably rooted in individual differences in the brain and brain development. Differences in how children's brains process speech, for example, may potentially explain some of the diversity witnessed in individual language abilities. Most investigations in this area have focused on cortical processing, and while assessing cortical structure and function is vital, studying the subcortical processing of speech is also paramount as atypical neural encoding at the earliest stage of processing of speech may impact any later process that depends upon this neural signal. It has been proposed that unstable neural encoding of sound, (i.e., increased variability in the neural response to an auditory stimulus), may cascade into differences in macro level language ability (Hornickel & Kraus, 2013). A great distance exists, however, both theoretically and empirically, between subcortical neural processes and language ability. Intermediary mechanisms therefore, undoubtedly link them, and phonological discrimination is proposed to be one potential link, as phonology (sounds) can be thought of as the 'entry level' to language.

This study is an investigation of the influence of early neural encoding of speech by the brainstem on language performance. This study will examine how stability in the neural encoding of speech at the level of the brainstem relates to language performance at multiple levels (e.g., syntactic, semantic, and phonological). Given the interdependence of various levels

of language, this study also seeks to investigate the nature of these relationships (i.e., if phonology mediates subcortical processing and semantics and/or syntax). These relationships will be examined in both typically developing (TD) children and children with autism spectrum disorder (ASD), who exhibit a wide range of language ability, to see if similar processes are involved in both typical and atypical language development.

I. Individual Differences in Language Development

Individual differences in how children, even typically developing children, acquire language are readily observable across language measures and developmental stages, suggesting that language learning is a heterogeneous enterprise influenced by multiple factors. While language development researchers have long been motivated to understand such individual differences (Bates, 1979; Nelson 1973), initial forays were motivated more by debunking theories of innate language acquisition rather than by identifying and explaining individual learning trajectories (Bavin & Naigles, 2015). In general, while many studies still focus on group level differences between children of different ages or clinical diagnosis and less on individual differences, it is possible to infer variation from their results (e.g., no group of children studied showed 100% ability across all measures). Numerous other studies directly investigate particular factors influencing individual differences in language performance (Frost et al., 2009; Skoe, Brody, & Theodore, 2017). Sources of individual differences in language outcomes are presented here in three broad categories: variability in environmental factors; variability in cortical structure and functioning; and variability in subcortical encoding.

I. 1 Environmental influences on language.

Some sources of difference draw from environmental factors particularly with respect to a critical aspect of semantic development, word learning. Joint attention, that is a child and

caregiver sharing focus on the same object, impacts word learning (Morales et al., 2000; Tomasello & Farrar, 1986) and varies across language learners and situations. In addition, the language input a child receives plays a critical role, and input can also vary across individuals. For example, richer caregiver input (e.g., the use of a more diversified vocabulary and use of more diverse grammatical formations) predicts richer future child language production (Huttenlocher, Waterfall, Vasilyeva, Vevea, & Hedges, 2010). The relative frequency with which children hear verbs from caregivers predicts the order of acquisition of the verbs, and the variety of different syntactic situations children hear verbs in predicts more varied use of a verb on the part of the child (Naigles & Hoff-Ginsberg, 1998). Thus, emerging talkers learn the words they hear the most often earlier, and they also are more flexible in their use of words if they have heard examples of such flexibility (e.g., “He wants the toy” and “He wants to go home” and “He wants me to read the book” are all syntactically different uses of the same verb “want”). The variety and complexity of structures used by caregivers also predict children’s later vocabularies (Hoff & Naigles, 2002). For example, the length and thus complexity of caregiver input significantly predicts children’s utterance length and vocabulary two and a half months later (Hoff & Naigles, 2002). The input children receive, which varies across individuals, is one important source of differences in language outcomes.

I. 2 Cortical contributions to language.

Individual differences in language performance in TD individuals have also been found to relate to variability in their brain anatomy and functioning. In studies looking at language development in TD children, multiple methods are routinely utilized to investigate both structural and functional neural correlates of language processing (for an overview see Friederici and Skeide, 2016). Multiple cortical indices of language abilities have been found for TD

individuals (for an overview see Golestani, 2014). For example, individual differences in vocabulary ability were associated with relative gray matter density in both right and left posterior supramarginal gyri in 34 TD adolescents between the ages of 12 and 16 (Lee et al., 2007). Individual differences in white matter tracts have also been found to predict syntactic performance. For example, structural integrity of tracts arising from the left pars opercularis and the left pars triangularis, two subregions of Broca's area, were positively associated with performance on tasks involving learning an artificial grammar in TD adults (Floel et al., 2009).

Studies involving typically developing control groups and groups of subjects with developmental disorders which include language differences (e.g., specific language impairment, autism spectrum disorder, dyslexia, Down Syndrome) have also provided important information about brain and language correlates. Comparing brain structure and activation between TD children and children from a particular diagnostic group allows inferences to be made about the mechanisms typically involved in language learning and processing. For example, atypical white matter tracts in ventral and dorsal tracts have been found in children with specific language impairment (SLI; Vydrova et al., 2015) and children with autism spectrum disorder (ASD) with less developed white matter tracts have been found to have lower language scores (Naigles et al., 2017). Functional differences have also been found, including less activation in language areas in children with Down Syndrome (Jacola et al., 2014). Reading difficulties have also been associated with differences in event-related potentials (ERP) to linguistic stimuli (Molfese, 2000; Lovio, Naatanen, & Kujala, 2010), structural grey matter differences, (Richlan, Kronbichler, & Wimmer, 2012) as well as hypoactivation (Norton, Beach, and Gabrieli, 2015) and reduced functional connectivity (Pugh et al., 2000) in language processing areas of the brain. Sources of individual difference in language performance have thus been found in cortical regions of the

brain for children whose language development is typical and for those whose language development is atypical.

I. 3 Subcortical contributions to language.

While most studies to date have focused on cortical indices of language ability, a growing body of literature is finding evidence that differences in language ability may be due to disruptions at an earlier stage of auditory processing, namely the level of the auditory brainstem (i.e., subcortical regions). Differences in auditory brainstem responses (ABRs) have been found to be related to language differences in reading (Banai et al., 2009; Hornickel and Kraus, 2013; Neef et al., 2017; Neef, Shaadt, & Freiderici, 2017) and expressive and receptive language (Russo et al., 2009). Subcortical processing has been examined in populations with atypical language development, including specific language impairment (SLI; Basu, & Weber-Fox, 2010; Gabr & Darwish, 2016), and autism spectrum disorder (ASD; Russo et al., 2009; Otto-Meyer et al., 2017; Russo et al., 2008; Miron et al., 2018).

There is evidence that timing and precision of encoding at the level of the brainstem affects language ability. In very general terms, shorter latencies for speech in childhood are associated with better language. For example, in a study of 63 children aged 7-15 years, with a wide range of academic ability, but all with IQs over 80, Banai and colleagues (2009) found that timing differences in waveforms to speech evoked ABRs related to reading, spelling and phonological performance. Shorter response latency was found to be indicative of better performance and delayed timing with poorer performance (Banai et al., 2009). In another study involving 11-13-year-old adolescents, Neef and colleagues (2017) reported that more precise encoding of stop consonants at the level of the brainstem was predictive of literacy (a composite of reading and spelling performance). Four to 11-year-old children with SLI have been found to

have longer wave III and V latencies at faster stimulus rates (those over 30 Hz) (Basu, Krishnan, & Weber-Fox, 2010). Children with SLI (3-7 years old) also displayed delayed latencies and reduced amplitudes to all characteristic components of the response waveform to the speech syllable /da/ (Gabr & Darwish, 2016).

There are multiple reasons to further examine subcortical processing in addition to cortical processing to explain language variability. For example, compared to cortical ERPs, ABRs are less influenced by attentional processes, the neural generators (i.e., the neurons, or groups of neurons, that fire in response to stimuli) are more clearly delimited, and ABRs have even finer-grained temporal resolution of rapid auditory stimuli (Skoe & Kraus, 2010). The sampling rate of ABR is much higher than that of mid or late latency EEG, and thus ABRs can capture electrical activity in milliseconds. The latter is especially important given the temporally dynamic nature of speech. There is also tremendous fidelity to stimulus features in brainstem representations, allowing direct connections to be made between individual aspects of the stimulus and the neural response that is not found in cortical encoding (Russo et al., 2009). Furthermore, in order to fully understand how the brain is processing speech, it is vital to begin at the temporal beginning of said processing and follow the processing through all stages of neural processing. The absolute beginning occurs when speech sounds are transformed to neural code in the auditory brainstem. This is important from two, equally important, perspectives. From the sensory point of view, speech has to be processed by the brainstem in order to go on to cortical areas of language processing (e.g., auditory cortex, Hershler's gyrus). From the psychological point of view, this initial encoding enables statistical learning, which is the ability to abstract patterns from ambient input, in this case regularities in the sound structure of

linguistic input (Saffran & Thiessen, 2007) which is important for oral language acquisition. The latter will be discussed in depth in later section.

II. Auditory Brainstem Response in Depth

Atypicalities at the level of the auditory brainstem may thus be an important factor influencing atypical language development. How the auditory brainstem processes sound stimuli can be revealed through ABRs. ABRs are far field electrophysiological responses, so-called because they are collected using electrodes on the scalp but produced deep within the brainstem. They are routinely employed to assay the integrity of the central and peripheral auditory systems in clinical and research settings. ABRs are the result of electrical potentials generated by the synchronous activity of neurons within the auditory nerve, cochlear nucleus, superior olivary complex, lateral lemniscus and inferior colliculus (Hall, 2006; Hood 1998).

II. 1 Latency of ABRs.

Interpretation of the ABR most commonly focuses upon peak latencies, interpeak latencies, peak amplitudes, and waveform morphology, all of which are analyzed within the time domain. Extensive research has established a body of age and gender norms and given the extremely short timeframe and voltage, even the smallest divergence from these norms can be meaningful (Skoe, Krizman, Anderson, & Kraus, 2013). The most common stimulus used to elicit ABRs is a click, a rectangular, broadband pulse with constricted rise and fall times, and a duration of less than 20 milliseconds. Clicks, and pure tone bursts, however lack the acoustical complexity of speech. Responses to complex sounds, for example a speech sound /da/, which incorporate both transient and sustained elements, cannot be completely predicted by responses to simpler clicks or tone bursts (Song et al., 2006). When ABRs are recorded to speech (or other

spectrotemporally-complex sounds) fidelity to the stimulus is high (Skoe & Kraus, 2010; Johnson, Nicol, & Kraus, 2005). Figure 1 shows a /da/ stimulus and typical response waveform.

II. 2. Stability of ABR responses, a new and potentially revealing measure.

ABRs to speech stimuli are primarily analyzed for three factors: the specificity of the neural response (Neef, Shaadt, & Friederici, 2017); the timing of waveform elements (Banai et al., 2009); and the stability of the neural response (Hornickel & Kraus, 2013). The last has influenced the Auditory Stability Hypothesis, which holds that if neural processing is not coherent from one instance of a sound to the next, this interferes with the ability to form a stable representation of the auditory world, which in turn negatively affects higher-level functions that depend on that signal, such as language (Tecuolesco, Skoe, & Naigles, 2017; Hornickel and Kraus, 2013; Skoe, Krizman and Kraus, 2013). According to this hypothesis, stable neural responses to speech sounds facilitate language development, and low stability may negatively impact language learning trajectories. In other words, if sounds, or words are not consistently encoded then “fuzzy” representations might ensue. A fuzzy representation can be thought of as analogous to what a person hears when listening in a noisy environment or across a poor telephone connection. In these cases, due to fuzzy representations of even commonly heard words, it is frequently necessary to ask for repetitions of these poorly discernable words to understand what was said; ‘fuzzy’ representations are not clear enough to be understood properly. This lack of definition would slow down the language learning process, possibly at multiple levels (syntactic, semantic, and phonological).

Response stability is thus proposed to be a metric of variability in individuals’ ABRs to the same auditory stimulus (e.g., /da/), revealing the consistency of an individual’s auditory system in responding to a given stimulus (Skoe and Kraus, 2010). Response stability is

calculated by correlating averages of subsets of ABR waveforms to a given repeated stimulus. For example two sets of 3000 responses to /da/ are collected and averaged. A linear correlation is then calculated for the two averaged waveforms to determine similarity. Responses with high stability (i.e., have correlation values approaching 1) show similar waveform morphology across repeated trials within a test session, suggesting that the auditory system is stable in its response to a given stimulus. On the other hand, responses with low stability (i.e., correlation values approaching 0) are characterized by greater test-retest variability, suggesting the same sound stimulus is engendering different neural responses (Skoe & Kraus, 2010). Figure 2 depicts two sets of waveforms, one from a child with high response stability to /da/ and one set of waveforms from a child with low response stability

A growing number of findings have reported associations between ABR stability and language in school age children. For example, Russo and colleagues (2009) examined 38 children between the ages of seven and thirteen years, 21 with ASD and 18 TD, all of whom had typical responses to click stimuli. Russo et al. examined neural responses to the speech syllable /da/ in both high noise and low noise conditions. When they compared averaged response waves for each group in each condition to the stimulus waveform, they found the ASD group to have less fidelity to the stimulus in both conditions than the TD group. In this case, the responses were compared to the stimulus waveform; however, more faithful responses to the stimulus can be taken to indicate better stability. Russo and colleagues also found that the TD group's responses in quiet and noise were more similar than those of the ASD group, indicating that the ASD group was more affected by noise. With respect to language, they reported that more similar responses to /da/ compared across noise conditions (greater stability over conditions) was related to core and receptive language ability in TD children and children with ASD. In other

words, children with more similar neural responses to /da/ in both conditions, indicating better speech in noise processing, performed better on language assessments. However, no visualization of the correlation (e.g., scatterplot) between /da/ stability and language measures was provided, so it is difficult to determine the precise nature of the relationship and whether it was driven by outliers.

There is evidence that children with reading difficulties also show less stable responses to speech sounds (Hornickel and Kraus, 2013). Hornickel and Kraus (2013) measured reading ability in a group of 100 school-aged children, all with normal hearing and no learning problems. They divided the children into three groups (good, average, and poor) based on performance on a reading battery. ABRs to the speech sounds /ga/ and /ba/ were then collected. When they compared the responses of good and poor readers, they found that the children with poorer reading skills had less stable neural responses to speech sounds than peers who were good readers. When averages of subsets of responses containing the formant transition were compared, children in the better reading group had significantly more stable responses to these speech sounds than the poor readers.

Similar results have been found in languages other than English. Neef and colleagues (2017) examined the stability of responses to a 170ms /da/ in a group of 159 German speaking children aged 4-13 who had normal click ABRs, in a study of dyslexia risk genes, KIAA0319 and DCDC2. After controlling for age, gender, family risk, and IQ, they found that children with greater numbers of risk alleles of KIAA0319 showed less stability in their neural responses, and children with fewer risk alleles had greater stability. However, with respect to DCDC2, they found the opposite pattern where children with more risk alleles had greater stability although

this only trended towards significance. The precise relationship with language performance was not reported.

Finally, response stability across multiple stimuli has also been investigated. Otto-Meyer and colleagues (2017) also investigated neural stability in a group of 12 children with ASD and 12 TD children who were a subset of the children who participated in Russo et al. (2009). The average age of participants was 10.7 years and the two groups were matched on verbal and nonverbal IQ, with all members of both groups having scores over 80. They compared stability of ABR responses to four stimuli, a click, /d/, rising /ya/ and falling /ya/. Although no gross differences in overall waveform morphology were found between the groups, the overall stability of responses was consistently and significantly greater for the TD group for all four stimuli. Means for the TD group (reported in r values) ranged from .405 to .886 while means for the ASD groups ranged from .327 to .792 (Otto-Meyer et al., 2017). Interestingly, no comparisons to actual language measures were included. Thus, while group level differences were confirmed, the impact at the individual difference level is unknown.

In sum, current research has found intriguing indications that stability varies between ASD and TD groups, and stability may explain some degree of language variability across different groups. However, detailed investigations into the relationship between language and ABR stability have not been performed.

II. 3 /Da/ stability and early language, pilot work.

While relationships between concurrent language and /da/ stability remain unexamined, links to prior language ability have been found in pilot work for this study. ABRs to /da/ were collected from both TD school aged children and school aged children with ASD and response stability was compared with the children's spontaneous speech found in samples collected when

they were preschoolers. Children, who as preschoolers had produced a higher proportion of nouns and plural nouns as well as more progressive morphemes and auxiliaries with their verbs, had more stable neural responses to /da/ several years later (Jones et al., 2017; Meagher et al., 2017).

Relationships between /da/ stability and early language comprehension (intermodal preferential looking, IPL) measures have also been found (Stevens, 2018). During an IPL task, children view side-by-side videos of objects, actions, and events and hear an audio track that matches only one of the videos. Looking more quickly to the matching video, and/or looking longer at the matching video, indicate the child understands what they hear (Piotroski & Naigles, 2012). This is a suitable means of investigating linguistic comprehension in children as young as 12 months, as well as children with ASD, as it lacks strong social demands and does not require specific productions. A positive correlation was found between da/ stability and longer looking times of the children to the matching video, indicating an understanding that verbs in transitive frames refer to causative actions (i.e., syntactic bootstrapping, Naigles, Kelty, Jaffery, & Fein, 2011).

While /da/ stability relating to language use from several years earlier is of interest, it must be noted that the time differential is somewhat problematic for interpretation. Given the development of both the auditory system and language ability over childhood, relationships with concurrent language samples need to be examined.

III. Individual Differences in Atypical Language Development

Studies investigating sources of individual difference in language ability frequently include both TD and atypically developing populations. But how do atypical and typical developmental trajectories relate? Tomblin (2015) has argued that one way to theorize about

atypical development (referring specifically to children with SLI) is to see them as representing one end of the developmental spectrum. In this view atypical language development is often delayed with respect to typical trajectories but does not represent a fundamentally distinct mode of language acquisition. Thus, sources of language variation in atypically developing children would also likely cause individual differences in TD children (Tomblin, 2015) although possibly to a less evident degree. And in fact, the same environmental sources of language variability found in TD children have been found to affect atypical groups (Tomblin, 2015). Under this view, variation in language performance due to differences in subcortical processing should be observable in both typical and atypical development, for example in TD children and children with autism spectrum disorder.

III. 1 Autism Spectrum Disorder.

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental condition that is diagnosed based on the presence of social, communication, and behavioral differences (American Psychiatric Association, 2013). Although language impairment itself is not a diagnostic criterion, it remains in the DSM-5 as a specifier given the considerable variability with respect to language that exists within the ASD population. Some children with ASD have language development similar to that of typically developing peers and others show little or no language development (Tager-Flusberg, et al., 2005). Grammatical abilities can be in the typical range for some children with ASD (Kjelgaard & Tager-Flusberg, 2001; Tek, Mesite, Fein, & Naigles, 2014) while others have established difficulties (Eigsti et al., 2007; Tager-Flusber & Joseph, 2003). Many who do develop language experience early delays in language acquisition (Tek, et al., 2014).

In addition to differences in language ability, differences in brainstem anatomy have been found between individuals with ASD compared to TD peers. Fewer neurons in the brainstem in children with ASD have been reported (Courchesne, 1997) as well as atypicalities in the superior olivary complex (Kulesza, Lukose, and Stevens, 2011; Lukose, Beebe, and Kulesza Jr., 2015). These differences may be present before outwards signs of ASD are evident, (Miron et al., 2016; Cohen et al., 2013; Geva et al., 2013). Studies of adolescents or populations of more varied ages, have reported mixed results regarding ABR latencies, with some finding differences between ASD and control populations and others not (Russo, Nicol, Trommer, Zecker, & Kraus, 2009; Tharpe, Bess, Sladen, Schissel, Couch, & Schery, 2006; Courchesne, Courchesne, Hicks, & Lincoln, 1985; Russo, Skoe, Trommer, Nicol, Zecker, Bradlow, & Kraus, 2008; Rumsey, Grimes, Pikus, Duara, & Ismond, 1984).

The lack of group effects in some studies may be due to including individuals of diverse ages, language levels, otological factors, and diagnostic severity in the sample. There is also the possibility that the click stimulus itself is not representative of more subtle features, and thus responses to it are not sensitive to auditory brainstem atypicalities that are present (Song, Banai, and Kraus, 2008; Russo et al., 2009). For example, Russo and colleagues (2009) found that ASD and control groups (7-13 years old) did not differ with respect to their latencies on click-evoked ABRs but did differ on their latencies on speech-evoked ABRs.

Additional comparisons of ABR responses in ASD and TD control groups are clearly needed, as well as inclusion of analysis of more ABR measures than just latencies, and more stimuli than just clicks. This is one purpose of the current study. Furthermore, in depth investigations of language ability and ABR relationships have not yet been done with ASD populations. This is the second purpose of the current study. The third purpose of the current

study is to further explore just how an ABR-language relationship might develop; the next sections provide one proposal for this connection.

IV Phonology as Potential Mediator

The previous sections have argued that ABR in both TD and ASD populations relates to language ability. However, finding that /da/ stability is able to predict concurrent semantic and syntactical performance would not yet explain how ABR stability translates to lexical and grammatical variability. There exists a gap between subcortical processing and language that must be explained, because a sound that has been processed by the brainstem is not yet a word, nor has it been integrated into a language system. A large distance thus remains between subcortical processing of speech sounds and macrolevel language ability.

Phonology may be one of several factors that connect sensory processing and semantic and syntactic performance. Phonology is the systematic organization of units of production of a language; specifically, it includes the individual speech sounds in an oral language and the ability to manipulate them (Liberman, Shankweiler, & Liberman, 1989). Over development, representations of individual sounds are built up that facilitate speech perception, word learning, grammatical knowledge, and reading. If phonology is a mediator it should connect to both the auditory encoding and semantics and syntax; that is, more robust auditory processing should lead to more robust phonological representations of speech sounds which in turn facilitate semantic and syntactic development.

IV. 1 How phonological representations facilitate language development.

Much of the language learning process, from the earliest point depends on auditory processing of the speech signal. To take one example, speech streams are continuous, and an infant learner must somehow locate where one word, or morpheme, stops and the next begins

(i.e., segmentation). One proposed mechanism that supports early segmentation of the speech stream is statistical learning. In the most general terms, statistical learning involves attending to regularities in the environment (Saffran & Thiessen, 2007). The finding, following, and holding in memory of relationships between individual elements in a steady stream of input is the basis of statistical learning. By seven months, infants have been shown capable of this process (Jusczyk & Aslin, 1995). Difficulties in statistical learning have been reported to affect language outcomes (Newman, Ratner, Jusczyk, Jusczyk, & Dow, 2006).

In order to segment the speech stream for statistical learning, speech sounds need to be categorized. This is no small feat, as speech sounds vary along a continuum of small changes in sounds and categorization requires hearing discrete classes of sounds (Lieberman et al., 1967; Pisoni & Luce, 1987). Thus, a representation of a sound category is needed, and judgements made on whether an individual sound fall in that category or not as actual instances are too varied and often ambiguous. While the brainstem itself has been reported to faithfully encode the speech input (Bidelman, Moreno, & Alain, 2013; Johnson; Skoe & Kraus, 2010), categorization judgements are made cortically (Bidelman, Moreno, & Alain, 2013). However, the quality of the neural encoding by the brainstem has been reported to relate to adult categorization in that more robust neural encoding leads to better categorization (Bidelman, Weiss, Moreno, & Alain, 2014; Weiss & Bidelman, 2015). More robust neural responses at the level of the brainstem can be inferred to facilitate the formation of phonological representations that in turn facilitate semantic and syntactic development.

Without accurate auditory processing at the level of the brainstem, then, statistical learning may be impacted. When neural response stability is low, ‘fuzzy’ representations of sounds may ensue. To borrow a more readily accessible example from the visual realm, the

process of learning to distinguish speech sounds when neural response stability is low, would be similar to learning to distinguish colors in very dim light. In very dim light all colors tend to merge into various strengths of grey and tan due to the cones needing light to function making them much harder to classify. Bidelman and colleagues (2011) have found that more robust neural encoding of frequency following responses (FFRs) relates to better discriminatory ability. The FFR is a response to periodic or quasi-periodic stimuli and is due to phase-locking of neurons in the inferior colliculus. They found that more faithful encoding of stimuli predicted better pitch discrimination performance. While this effect was seen in trained musicians, indicating that musical training can affect neural encoding, it nonetheless provides evidence that better discrimination rests on a better quality, more precise, signal.

A fuzzy representation of speech sounds could impact higher order language acquisition in a number of ways. On the semantic side this would influence word learning, as learning the probabilistic co-occurrence of speech sounds that make up words would likely take much more exposure. Poor phonological abilities may cause bottlenecks in language processing by increasing the processing load (Crain, 1989). Fuzzy representations may reduce the automaticity of speech processing, and when phonological process is not automatic, more resources need to be allocated to that leaving less for syntactic processing. Language-specific phonology is acquired in TD children by the end of preschool age and phonological difficulties have been shown to impact word learning in the preschool years. For example, children with poor phonological skills have smaller vocabularies compared to peers with strong phonological skills (Edwards, Fox, & Rogers, 2002; Felsenfeld, Broen, & McGue, 1992). Preschoolers with phonological delays also do not learn novel words as readily as TD peers when the new words are

phonologically similar to many other words the child already knows (Storkel, 2004; Storkel, Maekawa, & Hoover, 2010).

On the syntactic side, phonology aids in segmenting grammatical words and morphemes as well. Functors (e.g., words like ‘a’ and ‘the’) are high frequency words that routinely come before nouns. If encoding of these words is not stable, it may affect the ability to structurally frame nouns. Learners must learn to parse “an apple” or “an alligator” as opposed to “uh napple” or “uh nalligator” or “a banana” or “a kitten” and not “ab anana” and “ak itten.” Other elements such as aspect (e.g., “ed” or “ing” endings that are short sounds that change the understanding of a verb) or axillary verbs, and plural endings must also be distinguished. These morphemes can support language development as they can be used as frames which support meaning.

IV. 2 Neighborhood density a further component of phonological representations.

As individual speech sounds are combined to make words, one property words have based on the speech sounds from which they are composed is neighborhood density. Neighborhood density reflects the number of words that are phonologically similar to a given word, varying only by a single phoneme through addition (e.g., ‘lip’ to ‘slip’), substitution (e.g., ‘sat’ to ‘sap’, or deletion (e.g., ‘clump’ to ‘lump’) (Luce & Pisoni, 1998). A word is said to be in a dense neighborhood if there are many words similar in sound, while a sparse neighborhood refers to words with few similar sound neighbors. For example, the word ‘cat’ resides in a high-density neighborhood of 40 words, including ‘can’, ‘cap’, ‘bat’ ‘kit’ and ‘kite’ while the word ‘fish’ is from a low-density neighborhood of nine words including ‘dish’, ‘fig’, and ‘Phil’. In adults, words from dense neighborhoods are recognized more slowly (Luce and Pisoni, 1998). The most common explanation offered is lexical or phonological competition; that is as more

candidate words are activated, the process of recognizing the target word becomes more difficult (McClelland & Elman, 1986). On the other hand, words from dense neighborhoods have an advantage in speech as they are produced more quickly due to speech production being aided by multiple activation (Vitevitch, 2002). Thus, individuals would be slower to recognize ‘cat’ than ‘fish’, but faster to say ‘fish’ than ‘cat’. This high neighborhood density advantage in production and disadvantage in recognition has also been observed in children who repeat and recognize real words from high density neighborhoods more slowly than those from low and also require hearing more of the word from high density neighborhoods to identify it (Metsala, 1997). TD children also name real words from high density neighborhoods more accurately and more quickly than those from low density neighborhoods (German & Newman, 2004). However, when nonwords are used, the results are somewhat different. Adults are faster to say nonwords with high phonotactic probability (a proxy for neighborhood density) than nonwords with low phonotactic probability (Vitevitch & Luce, 1999).

As children increase their lexical knowledge, new words connect to similar sounding words already present in the mental lexicon. Children may first hold holistic representations of words, and then as more words are added, representations become more exact (Metsala & Walley, 1998; Charles-Luce & Luce, 1990). With fewer words, the words are more distinct from each other and may require less detailed phonological information to distinguish them. Words falling into high density neighborhoods would need to have more explicit representations. The formation of these representations requires accurate auditory processing and neural encoding. Lack of stability in neural responses may lead to fuzzy encoding, and thus poorly defined representations. In adults better ABR stability has been associated with faster word recognition (Johns, Myers, Skoe, & Magnuson, 2017). Similar to manner in which less distinct

representations are formed for words from low density neighborhoods, if poor auditory stability leads to a fuzzy encoding of even high-density words, then a high neighborhood density advantage would be lost.

V Current Project

In sum, there are three gaps in the literature that this project aims to fill; all focus on addressing how language variability relates to the stability of neural encoding of sound in the brainstem. First, while numerous studies have reported cortical differences between ASD and control groups, results comparing subcortical differences are mixed. Possibly this is because ABR measures have focused on latency. The current study also includes stability of ABRs to speech sounds. Second, while some studies have reported relationships between stability and language, these have only included general language measures rather than scrutinizing effects on syntax, semantics, and phonology separately. Third, finding links between ABR and specific language components does not yet reveal the directionality of these relationships. By hypotheses it is phonology that connects ABR and words/sentences, not the other way around.

Although ABR responses, including stability, have been found to predict language ability (Russo et al., 2009; Hornickel & Kraus, 2010); Skoe, Brady, & Theodore, 2017), a comparison of ABR response stability and concurrent language ability at multiple levels (syntax, semantics, phonology) has not been undertaken. Thus, how ABR response stability relates to individual differences in syntactic, semantic, and phonological processes remains unknown. The current study will investigate the relationship between subcortical processing of speech and concurrent language ability in school age children, both TD and those with ASD to attempt to fill this gap. Specifically, the relationship between stability of neural responses to /da/, a complex speech sound, and concurrent syntactic, semantic, and phonological abilities will be examined. The

study will also look at the intersection of these relationships to see whether the ability to discriminate between sounds mediates early sensory processing and higher order semantics and syntax. Following the Auditory Stability Hypothesis, it is hypothesized that children with more stable neural encoding of speech sounds will have better phonological discrimination skills, as well as stronger semantic and syntactic abilities. This study is also investigating the degree to which phonological discrimination links sensory processing and semantic and syntactic performance. Following Tomblin (2015) it is hypothesized that the relationships between /da/ stability and language performance will be fundamentally similar in both TD and ASD children, although more variability in the ASD group is expected.

ABRs and language measures will be collected from both children with ASD and TD children. First group level differences in several ABR measures will be examined. Then individual differences in each group individually and the whole group together will be examined. If language depends on the stability of early subcortical neural responses, then children with more stable responses to /da/ should have more advanced language abilities and better phonological discrimination. If the underlying mechanism is the same, this should be seen in both groups, although increased variability is expected in the ASD group.

Methods

Participants

Thirteen children with ASD and fourteen TD children participated in the current study, which was part of an ongoing longitudinal investigation of early language development in autism (Naigles & Fein, 2017). All participants were monolingual English speakers. Inclusionary criteria for the current study consisted of a three part hearing screening. All participants had to pass a 20dB HL pure tone audiometric peripheral hearing test at 500, 1000, 2000, 4000, and

8000Hz. They had to have normal outer and middle ear function as confirmed by otoscopy. They also had to have normal outer hair cell function as confirmed by distortion product otoacoustic emissions.

The children with ASD were originally recruited through various service providers in the Northeastern U.S. and all had a diagnosis of autism prior to being contacted for the original study. The Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord, Rutter, DiLavore, & Risi, 2002) was used to confirm the diagnosis at the initial and subsequent visits. The TD children were originally recruited from the local area via birth announcements and word of mouth. At the beginning of the longitudinal study, the TD and ASD groups were matched on language level, resulting in the ASD group being chronologically older than the TD group. The children's ages, ADOS scores, vocabulary, and cognitive scores at the initial visit are found in Table 1.

At the time of the current study, because only a subset of the original participants is included, the groups were not statistically different with regard to age; the distributions of the two groups, as noted by the larger standard deviation in the ASD group, differed. Figure 3 depicts the age distributions of both the TD and ASD groups. The TD and ASD groups are no longer matched on language performance; considerable variability, however, can be observed within the ASD group and variability is present in the TD group as well. When raw scores were compared in order to see if a difference in actual language performance without recourse to age-level expectations emerged, no significant group differences are found on any of the subtests. Standard Scores, scores calibrated weighting participant age, were also compared given the wide age range represented in the sample (7 to 17 years), and these reveal significant group differences for all of the four subtests. Group level differences emerged for only one subtest of

the nonverbal cognitive tests given. Participants' concurrent ages, language, nonverbal IQ, and ADOS-2 scores (Lord et al., 2012) scores can be found in Table 2.

Four children (one with ASD) participated in the ABR portion of the study but did not complete the phonological discrimination tasks or language assessments. Two children (one with ASD) did not participate in the ADOS-2 due to time constraints.

Materials

Standardized measures.

Differential Ability Scales (DAS; Elliot, 2007). The DAS was administered to gauge children's general level of nonverbal cognitive functioning. Three subtests were administered: Matrices, Recall of Digits, and Pattern Construction.

Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012). The ADOS was administered to verify the current level of autism characteristics. Module 3 was administered to all children. Two children (one TD, one ASD) did not receive the ADOS-2 due to time constraints.

Clinical Evaluation of Language Fundamentals, Fifth Edition (CELF-5; Wiig, Semel & Secord, 2013). The CELF-5 was administered to assess current language ability. Four subtests were given (Word Classes, Repeating Sentences, Formulating Sentences, and Following Directions) covering both semantic and syntactic abilities. Word Classes evaluates the ability to use semantic class features to understand the relationship between words. Formulated Sentences evaluates the formation of syntactically correct spoken sentences that increase in both length and complexity. Recalling Sentences is a measure of how well individual spoken sentences can be repeated exactly as they increase in length and complexity. This indexes short-term memory as well as syntactic and semantic competence. Following Directions measures the ability to

interpret spoken directions that increase in complexity and length and is reflective of short-term memory capacity. Recalling Sentences and Following Directions were not included in analysis for two reasons; the auditory demands of these subtests could be a confound; and they also test working memory which is not specifically investigated in the current study.

Electrophysiological measures.

ABRs were recorded to two stimuli: a 100-microsecond click stimulus (31.1/sec) and a 40-millisecond (ms) synthesized speech stimulus /da/ (10.9/sec). The collection parameters of Banai et al. (2009) and Krizman, Slater, Skoe, Marian & Kraus (2015) were followed to facilitate comparisons. Three Ag/AgCl plated electrodes were placed on the head using a vertical, ipsilateral montage (Cz, right ear, forehead). To achieve a low-impedance recording (<5kOhms), electrode sites were cleansed with a gentle scrub and adhered using conductive paste. Stimuli were presented in separate blocks at 80 dB SPL into the right ear through an insert earphone (ER-3A, Etymotic Research, Inc). The click was presented at least 3000 times while the /da/ was presented at least 6000 times. The Navigator Pro AEP system (Natus Medical, Inc.), a portable laptop ERP system, controlled both stimulus delivery and ERP averaging. ABRs were bandpass filtered online from 100 to 2000 Hz, with a recording window that began 15 ms prior to the stimulus onset and extended to 58 ms post stimulus onset for /da/. For the click stimulus, the averaging window extended from 0-10 ms. Trials exceeding $\pm 23.8 \mu\text{Volts}$ (muscle artifacts) were automatically excluded from the average. For each block, the recording terminated when the average reached 3000 artifact-free trials, 1500 per polarity.

There are four specific variables of interest at the group level; latency of wave V for clicks; latency of wave V /da/; click stability; and /da/ stability. For investigating individual

differences, raw /da/ stability scores were transformed under Fisher transformations in order to stabilize the variance. The Z-scores were used in analysis.

Phonological discrimination task.

The novel word discrimination task was presented using PsychoPy (Pierce, 2007). Participants, seated opposite a laptop with a large button box holding one red and one green ‘big mac’ switch, heard pairs of novel words presented through headphones. Children were asked to press the green button if they considered the two novel words to be identical and a red button if they determined them to be different words. The computer screen showed pictures of a green circles with “same” over it and a red circle with “different” over it. Reaction times and accuracy were recorded by the computer.

Procedure.

A training phase was conducted immediately prior to testing. During the training phase, the children did not wear the headphones in order to facilitate communication between them and the examiner. Children were introduced to the buttons by written instructions on the screen to press the red or the green button (e.g., “Please, push the red button”) followed by auditory instructions to press the red or green button, to familiarize them with both written and verbal cues and to allow for variability in reading skills. To introduce children to the discrimination task, four pairs of pictures (dogs, cats, rabbits, and birds) were presented sequentially and the child was asked to press the green button if they were the same and the red button if they were different pictures. The following instruction which the examiner read aloud appeared on the screen, “You are going to see two pictures. If they are the same, press the green button. If they are different press the red button. (Pictures presented.) See these pictures? Are they the same or different? Press the green button if they are the same or the red button if they are different.”

Training stimuli can be found in Figure 2. The children were given feedback on their responses and advised about any incorrect answers. Their questions were also answered at this time; the most frequent question was whether they needed to look for very small differences between the pictures.

Auditory discrimination was introduced through four auditory training pairs. Training pairs were CVC-CVCs similar to test items but did not include any of the CVCs used in the test phase (e.g., *zainbert* and *zainbert*). Two same and two different pairs were presented. Children received the following instructions on the screen, “Now we are going to do the same thing with some new words. You are going to hear two words. If they are the same press the green button, if they are different press the red button.” For lower verbal children, the following adjusted instructions were verbally implemented (Ellawadi et al. 2016), “Same? Yes, green, No, red.” The testing session consisted of two blocks of 40 pairs of novel words. The directions were identical to those of the auditory training. The following instructions were given on the screen “Now you are going to hear more pairs of words. If they are the same press the green button, if they are different press the red button”. The examiner read them with the children to ensure they understood before starting the experiment. Green and red circles similar to the buttons to be used came up on the screen indicating a new trial. A trial ended when the child pushed a button.

Phonological Discrimination Stimuli.

The discrimination task stimuli were pairs of novel bisyllabic CVC-CVC (consonant vowel consonant) novel words that differed minimally, that is by only one phonemic unit (e.g., *kulkeet* vs. *tulkeet*), or were identical (e.g., *kulkeet* vs. *kulkeet*). To create the stimulus list, CVCs were first taken from a list of CVC-CVCs in Luce and Pisoni (1998). The sound sequences of the novel words conformed to English phonology, and thus all pairs were possible words in English.

The words were recorded in a soundproof booth by an adult female native speaker of American English and concatenated in Praat (Boersma, 2001) so that each pair had 500ms of silence between words. Identical pairs contained two tokens of the same word. Eighty pairs were presented, half identical and the other half differing by one sound; in all cases the initial consonant varied on place of articulation.

Pairs also differed by neighborhood density, with half the identical pairs and half the different pairs drawn from dense neighborhoods and the other half from sparse neighborhoods. Neighborhood density was calculated for each CVC separately using the IPhOD online Dictionary (Vaden, Halpin, and Hickok, 2009), which calculates the number of English neighbors for each novel CVC. Pairs were created in the following manner. Ten CVCs were chosen for the high density set ('original' CVCs), each of which had a minimum of 27 neighbors (e.g., MIDE). Ten 'change' CVCs were then created by changing the initial sound of the 'original' CVCs by place of articulation (e.g., NIDE). Each 'change' CVC had a minimum of 26 neighbors. For the low neighborhood density set, the 'original' 10 CVCs had a maximum of 6 neighbors while the 'change' CVCs had a maximum of 8 neighbors.

The ten 'original' CVCs from within each set were paired, creating five CVC-CVCs for each set (e.g., MIDE-ZSUN). Each CVC-CVC was then reversed (e.g., BIS-KAR to KAR-BIS) to make a total of ten CVC-CVCs from the 'original' CVCs. The first CVC from each of the CVC-CVCs was then replaced with a 'change' CVC, yielding a set of 20 CVC-CVCs for each set. Each of the 20 CVC-CVCs was made into identical pairs (e.g., BIS-KAR and BIS-KAR) and forward and reverse different pairs (BIS-KAR, DIS-KAR, and DIS-KAR, BIS-KAR) were created for a total of 40 pairs from high neighborhood and 40 pairs from low neighborhood density. The first block of 40 trials contained all the pairs derived from the 'original' CVCs,

both identical and different pairs, and the second block of 40 trials contained the CVC-CVC pairs derived from the ‘change’ CVCs. Trials within each block were randomized across participants and coded for accuracy and reaction times.

Overall Procedure

All assessments were conducted in the children’s homes, usually in a living room or family room. Parents were allowed to be present during testing but were asked to refrain from participating in any way. Assessments were conducted over the course of two visits which were on average six months apart (range 0-14). ABRs were collected during the first visit, and phonological discrimination, nonverbal cognition, language performance, and diagnosis were assessed at the second visit.

Prior to both ABR and behavioral testing, parents gave written consent and participants provided written assent prior to the behavioral testing. For lower verbal children a variation of the following script was used: “Do you want to do some fun stuff with us today? You can stop any time you want to. Write your name here if you want to do some fun stuff. Remember you can stop anytime you want.” All children were able to write their names indicating they were willing to participate.

Hearing screenings were conducted immediately prior to ABR collection. ABR collection took between 30 and 45 minutes including the electrode application time, with breaks as needed. During the recordings, participants sat comfortably on a couch or chair while watching a movie on a laptop computer/tablet at a low volume.

At the second visit the phonological discrimination task was administered first, followed by the DAS, the CELF 5, and the ADOS 2. Breaks were given as needed and the entire session averaged 2.5 hours in length.

Analysis

Analysis of variance tests (ANOVA) were used to determine the degree of group level differences in the electrophysiological and phonological discrimination measures. Individual differences in the relationships between the ABR measures and syntax, semantics, and phonology were investigated using Pearson's product moment correlation coefficients. These analyses were performed for the entire sample as well as TD and ASD groups individually. Given that we expect significant relationships between ABR and semantics and syntax, a series of regression analysis were performed to determine whether phonological discrimination mediates the relationship between /da/ stability and concurrent language. Due to small numbers of participants, the regression was performed on the entire sample to increase power.

Results

Results are first presented for group level differences without respect to individual differences. Then correlational analyses will be presented to examine the relationship between variables on the individual level both with and without respect to diagnosis. Results are organized around three central questions. First, how do the groups differ on the ABR and phonological discrimination measures? Second, to what degree does one of the ABR measures, /da/ stability, correlate with the language components: syntax, semantics, and phonology? Third, if relationships are found, what is their nature, specifically, does phonological discrimination mediate neural encoding and semantic and syntactic performance?

Group Level Differences

Electrophysiological results will be reported first, followed by the behavioral results. Nonverbal cognition will not be used as a control variable for group level differences as the

groups only differed significantly on one subtest and group level differences at this stage are raw differences.

Electrophysiological measures.

Results for ABR tests can be found in Table 3. No significant group differences were found for click wave V latency, /da/ wave 5 latency, click response stability, or /da/ response stability, although the means for click and /da/ wave V latency and /da/ stability are in the predicted directions. The larger standard deviations for the ASD group for /da/ stability, (0.20 compared to 0.14) suggests differences in the distribution of stability responses across groups and Figure 5 depicts the group distributions for the /da/ Z scores. Furthermore, when individual /da/ stability values were compared to age relevant norms (Skoe, Krizman, Anderson, & Kraus, 2013) five of the 12 children with ASD fell outside of age-related norms while only one TD child did. Thus, nearly half of the ASD group did not have age-appropriate stability scores.

Phonological discrimination task.

Both TD ($M=73.64$, $SD= 4.08$) and ASD ($M=66.08$, $SD=11.07$) groups performed significantly above chance (40) on the phonological discrimination task (maximum=80). A significant group difference was found for overall performance on the phonological discrimination task [$F(1, 21) =4.54$, $p=0.045$], with the TD group on average correctly distinguishing same from different pairs more often than the ASD group. There was also a significant effect of group on reaction times for correct responses [$F(1, 1609) =17.17$, $p<.001$], with the TD group ($M=4.87$ seconds, $SD=1.16$) responding more quickly on average than the ASD group ($M=5.17$ seconds, $SD=1.72$).

No effect of neighborhood density was found on accuracy [$F(1,1838) =1.44$, $p=0.230$] nor was there a significant interaction effect of group and neighborhood density was found

[$F(1,1836) = 0.001, p = 0.985$], indicating neighborhood density was not a factor in correctly judging the pairs for either group. No main effect of neighborhood density was found on reaction time [$F(1,183809) = 0.837, p = 0.360$] as the overall time to respond was similar for both high neighborhood density pairs and low ones. However a marginally significant interaction effect was found between group and neighborhood density [$F(1,1607) = 3.28, p = 0.07$] for correct responses. Post-hoc exploratory tests indicated that the TD group [$F(1,816) = 4.21, p = .04$] was faster to indicate correct responses for high neighborhood density words ($M = 4.78, SD = .96$) compared to low neighborhood density ones ($M = 4.95, SD = 1.32$), while the ASD group took similar amounts of time to respond to both ($M = 5.21, SD = 2.05$; and $M = 5.22, SD = 1.30$).

Relationships Between /Da/ Stability and Language Performance

ABR /da/ stability scores were converted via Fisher transforms to Z scores based on the results of the entire sample for all analyses given the very small actual numerical differences in /da/ stability correlations (Russo et al., 2009; Skoe, Brody, & Theodore, 2017).

Semantics and syntax on standardized tests.

Pearson's product-moment correlation coefficients were computed to assess the relationship between /da/ response stability and the Word Classes subtest of the CELF 5, a measure of semantic knowledge. No relationship emerged between raw scores for Word Classes and /da/ stability for either group. However significant positive correlations were found between raw scores for Formulated Sentences, a measure of syntactic skill, and /da/ stability for the entire group, the TD group, and the ASD group, indicating children with more stable neural responses to /da/ stability show greater syntactic ability.

When age and DAS composite were entered as covariates the relationships between /da/ stability and Formulated Sentences remained. Correlations between /da/ Stability Z scores and

CELF subtests raw scores can be found in Table 4. The relationship between /da/ Stability Z scores and Formulated Sentences raw scores can be seen in Figure 7, and Figure 8 depicts the relationship between /da/ Stability Z scores and Word Classes raw scores.

Phonological discrimination

Pearson's product-moment correlation coefficients were computed to assess the relationship between /da/ response stability and phonological discrimination performance. Statistically significant positive correlations were found for the entire group ($r=.494$, $n=23$, $p=.017$) and ASD group ($r=.575$, $n=12$, $p=.05$); while the relationship for the TD group alone was not statistically significant ($r=.497$, $n=11$, $p=.12$), the correlation is fairly large and in the expected direction. When age and DAS composite were included as covariates, the relationships for the entire group ($r(19)=.509$, $n=23$, $p=.018$) and the ASD group ($r(8)=.647$, $n=12$, $p=.043$) remained, and the relationship for the TD still did not reach statistical significance ($r(7)=.374$, $n=11$, $p=.322$). Figure 6 depicts the relationship between /da/ Stability Z scores and results from the phonological discrimination task.

Interrelationships

Relationship between phonology and semantics and syntax.

In order to investigate the degree to which phonological discrimination links sensory processing and semantic and syntactic performance the relationship between phonology and semantics and phonology and syntax were individually examined. Pearson's product-moment correlation coefficients were computed to assess the relationship between performance on the phonological discrimination task and language performance on the CELF 5. Statistically significant positive correlations were found for the entire group between phonological discrimination and raw scores for Formulated Sentences, and Word Classes. This appears to be

driven by the ASD group as no statistically significant relationships were found within the TD group alone for any of the subtests. For the ASD group alone, statistically significant positive correlations were found between phonological discrimination and raw scores for Formulated Sentences, Word Classes, Repeated Sentences, and Following Directions.

When age and DAS composite were entered as covariates statistically significant positive relationships were maintained for the entire group for Formulated Sentences and Repeated Sentences. A significant negative correlation between Following Directions and phonological discrimination was seen in the TD group, and within the ASD group significant positive correlations were maintained for Formulated Sentences, and Word Classes. Correlations between phonological discrimination and CELF subtests can be found in Table 6. Figure 9 depicts the relationship between phonological discrimination and Formulated Sentences raw scores and Figure 10 depicts the relationship between phonological discrimination and Word Classes raw scores.

Mediation of phonological discrimination.

Multiple regression analyses were conducted to assess individual components of the proposed mediation model. The first regression found that /da/ stability Z scores were positively associated with Formulated Sentences raw scores (i.e., c-path) ($b = 17.13$, $t(21) = 3.21$, $p = .004$). It was also found that /da/ stability Z scores were positively related to phonological discrimination (i.e., a-path) ($b = 11.52$, $t(21) = 2.6$, $p = .02$). Lastly, results indicated that the mediator, phonological discrimination, was positively associated with Formulated Sentences (i.e., b-path) ($b = 1.02$, $t(21) = 7.0$, $p < .001$). In addition, results indicated that the direct effect of /da/ Stability on Formulated Sentences became non-significant when controlling for phonological discrimination (i.e., c'-path), thus suggesting full mediation ($b = 5.42$, $t(21) = 1.6$, p

= .126). As both the a-path and b-path were significant, the indirect effect was tested using a bootstrap estimation approach with 5000 samples (Preacher & Hayes, 2004). Results indicated the indirect coefficient was significant, $b = 11.71$, $SE = 4.15$, $95\% CI = 3.5-20.24$ confirming the mediation role of phonological discrimination. Figure 11 displays the results. No such mediation relationship was investigated for Word Classes.

Discussion

The current study investigated the relationship between neural encoding of speech in the brainstem and concurrent macro level language performance at the levels of syntax, semantics, and phonology in school-aged TD children and children with ASD. Given the large empirical and theoretical distance between subcortical auditory processing and semantic or syntactic ability this study further investigated the interrelationships between language levels to find evidence for phonology mediating any relationship found between brainstem and semantics and syntax. Previous research had revealed more robust brainstem encoding of speech was related to higher language performance, primarily reading ability, in both TD (Skoe, Brody, & Theodore, 2017; Neef, Schaadt, & Friederici, 2017; Hornickel & Kraus, 2013) and ASD (Russo et al., 2009) populations, but the individual differences in school age children's semantic and syntactic performance in relation to the stability of brainstem encoding of speech had not been investigated. ABRs were collected to /da/, a complex speech sound, and clicks, as well as to tasks designed to elicit phonological discrimination ability, semantic ability and syntactic ability. The three major questions the study attempted to answer were 1) do ABRs to click and /da/ differ between groups? 2) Does /da/ stability predict language (syntax, semantics, and phonology)? And 3) To what degree does phonological discrimination act as a mediator if relationships are found?

Results did not reveal group level differences on ABR click wave V latency, click stability, /da/ wave V latency, or /da/ stability. Group level differences were found for syntax, semantics and phonological discrimination, with the TD group out-performing the ASD group. /Da/ stability was related to syntactic performance and phonological discrimination, but not semantic performance (see Figures 6-8) and phonological discrimination was a successful mediator of the relationship between /da/ stability and syntactic performance on the CELF 5.

Although click findings are not uniform in the ASD literature (see Miron et al., 2018 for an overview), and for example Russo and colleagues found typical click ABRs in a group of children with ASD and atypical encoding of speech sounds, the lack of group level difference in click stimuli was not unexpected. This was not the case with finding no group differences with respect to /da/ stability, as this runs counter to Otto-Meyer and colleagues (2017)'s report that ABR stability across several stimuli was lower among children with ASD than TD peers. Several differences between the participants in this study and those in the Otto-Meyer study, however, bear noting as they may have contributed to the differences found in /da/ stability. The TD and ASD groups in the Otto-Meyer study were matched on language ability, nonverbal cognition, and age while the participants in this study were not matched in this way. Additionally, their overall age range was 7 to 13 years, while the participants in this study spanned 7 to 17 years. Given the continual maturation of the auditory system across this period (Skoe et al., 2013) lack of homogeneity in this study may have prevented fine scale group differences to emerge. Despite this, the direction of the relationships was in line with expectations, especially for /da/ stability. The ASD group also had more variability in their stability, with five of the 13 falling out of range of age-established norms (Skoe et al., 2013). Most interestingly, a potential bimodal distribution could be emerging for individuals with ASD

in this study, as both the very low and very high stability ends of the continuum were populated by the ASD children with the TD children fell mostly in the middle. The TD children were in fact more similar in their responses and only one child did not fall within age norms. A larger number of children would, preferably with a narrower age range, would need to be studied to make this more than speculative.

With respect to phonological discrimination, the TD group was better able to accurately classify pairs of bisyllabic non-words as being the same or different than the ASD group. In addition to being more accurate, they were also faster to respond. Neighborhood density did not appear to influence accuracy or reaction time for either group, although a trend was seen for the TD group to be faster at responding to words from high density neighborhoods than low density ones, while the ASD group showed no sensitivity to neighborhood density. This trend in the TD group is in line with findings that high neighborhood density leads to an advantage in processing. It is possible that a ceiling effect for the TD group is masking in part any contribution of neighborhood density. A more demanding assessment of the effects of neighborhood density on phonological discrimination would be needed to test this. The phonological discrimination task used in this study was designed to be accomplishable by young children with ASD who may have additional cognitive difficulties. This affected how difficult the phonological discrimination task could be, as it had to be easily explained to and understood by all participants. In general terms this meant that the load of the task (i.e., word length) was constrained. In this task only bisyllabic CVC-CVCs were used and did not include four-syllable words. It was difficult and took a little practice for the children with more modest cognitive ability to understand that they needed to compare the two words of two syllables each and not the first syllable to the second. A more rigorous test of phonological discrimination can increase

load by increasing the number of syllables, but this would have not been possible in our sample. It would have increased the variability in the TD group however, and possible allowed for more robust relationships to emerge.

The first main question of individual differences was whether /da/ stability related to language at the levels of phonology, semantics, and syntax. Following the Auditory Stability Hypothesis, it was predicted that children with more stable neural encoding of speech sounds would have better phonological discrimination skills, as well as stronger performance on semantic and syntactic assessments. Results showed that /da/ stability was directly related to the ability to discriminate nonwords, as children with more stable /da/ encoding had better performance on phonological discrimination. This suggests that stable neural encoding of speech at the level of the brainstem may engender more robust phonological representations. Although categorization of speech itself is a cortical process, more stable auditory encoding may facilitate this process. This is in line with findings from Weiss and Bidelman (2015) where more robust auditory brainstem encoding of speech sounds was categorized faster and more accurately than less robust encoding. The relationship between /da/ stability and phonological discrimination appeared to be driven by the ASD group, however, this relationship was present, albeit not to the same degree, in the TD group. Again, near ceiling performance on the part of the TD group on the phonological discrimination task, coupled with a narrower range of /da/ stability scores, could make a relationship harder to detect in a small sample. This would need to be investigated in a larger number of TD children with a more rigorous phonological discrimination task. A visual overview of the relationship showed no obvious outliers (see Figure 6) further indicating the existence of the relationship.

With respect to /da/ stability and semantic performance no statistically significant relationships emerged. Despite the lack of statistical significance, the relationships for the entire group, as well as the TD and ASD groups individually, were not absent; all had correlation coefficients of .36 or greater. The small sample size might have left the study too underpowered to detect a significant relationship. In addition, the CELF 5 Word Classes subtest may not be a rigorous test of semantic knowledge; assessments targeted at vocabulary knowledge such as the Peabody Picture Vocabulary Test, may be a better index. While the Word Classes examined the ability to see connections between words in interesting ways (e.g., synonyms, antonyms, and semantic features such as shared characteristics, associations, or function), the total number of questions was quite low, thus testing specific knowledge of a few words, rather than more general contours of semantic ability. Furthermore, the ASD group showed a definite trend towards /da/ stability influencing semantics, especially when age was taken into consideration. When age was accounted for, the ASD group showed considerably less semantic knowledge, which may indicate that /da/ stability is more important at the lower end of the continuum. This perhaps indicates that children with ASD rely more on neural stability in acquiring semantic knowledge, possible due to TD children with poor stability utilizing compensatory strategies. Likewise, semantic knowledge in TD children may be more dependent on other factors, such as working memory which was not examined here. It is also possible that the TD sample was too small to provide enough variability, even within the typical range, in these areas.

Results showed that syntax and /da/ stability were related in the entire sample of children, indicating that more robust brainstem encoding of speech may facilitate better syntactic skill. The Formulated Sentences subtest of the CELF 5 is a demanding task in which children are shown a picture and given words to use to make a sentence about the picture. The given words

are for the most part conjunctions, and they become increasingly more challenging. For example, early sentences require use of ‘and’ and ‘if,’ while intermediate require use of ‘instead,’ and later sentences require use of ‘before’ and ‘until’ in the same sentence. Responses are judged on syntactic correctness and good sentences can require skill. This could indicate that poor /da/ stability can indeed form a bottleneck in syntactic development. Perhaps better encoding reduces demands on working memory or attentional demands and thus allows young learners to develop and refine syntactic knowledge.

This study also investigated whether or not the levels of language interact, specifically whether phonological discrimination mediates a relationship between neural encoding stability and semantic and /or syntactic performance. Results showed that while more /da/ stability relates to better syntactic performance, it does so by way of phonological discrimination. This indicates that it may be the more robust phonological representations afford syntactic development. While this study cannot make any claim as to whether the current lack of stability existed earlier, for example from birth or during the early stages of language development, it is likely, especially given the relationships found between /da/ stability in childhood and adolescence and language performance in advanced toddlerhood.

Overall the findings support the idea that lack of neural stability in subcortical encoding of sound may affect language development. This study also supports Tomblin (2015) in that typical and atypical development form a continuum, rather than following completely distinct trajectories. Children with better phonological, syntactic, and semantic performance tended to have more stable neural encoding of /da/ than children with poorer language performance. And for syntactic development, phonology mediated this relationship. One possible explanation of the mediation is that less stable encoding of speech precipitates less robust phonological

representations, and this slows syntactic development by limiting input. The process may work in a similar way to what happens in speech in noise ability. Although speech in noise can be influenced by top down factors, it has also been shown to relate to neural encoding at the level of the brainstem (White-Schwoch et al., 2015; Russo et al., 2009). White-Schwoch and colleagues (2015) reported that neural encoding of stop consonants in noise predicted four-year old's phonological abilities, while Russo and colleagues (2009) found that less degradation of encoding in noise predicted better language outcomes. Much of the time, people, including very young language learners, receive input in noisy environments whether that be home, school, or community settings. If children with less stable encoding of speech struggle to process speech in these settings to an even greater degree than they do in quiet, this may effectively constrain the actual language input they receive. This could impact, for infants, statistical learning and the formation of robust phonological representations. A similar situation may be at work with respect to auditory encoding stability; more variable neural encoding of speech in the brainstem may constrain input. Children with less stable neural encoding of speech may not be able to capitalize on language input in noisy environments, effectively reducing the actual amount of input they can receive.

Limitations and Future Directions

While the results found in this study are intriguing, this study is hampered by a lack of power, heterogeneity of the sample, and does not represent the full ASD spectrum. Larger numbers of children would need to take part in order to see some of the more subtle relationships emerge. The possible bimodal distribution for /da/ stability of the ASD group for example could only emerge if more children were examined. The children assessed in this study were part of a multi-cohort longitudinal study, leading to diversity in their ages at the time of this study.

Because both language skill and the auditory system matures over childhood and adolescence, this group may have been too heterogeneous (given how small it was) to allow for meaningful patterns to emerge. This heterogeneity extended to cognitive ability in the ASD group, with some children showing much more modest general cognitive functioning on the DAS. That being said, all of our ASD sample had enough language ability to be able to complete both the phonological discrimination task and the CELF 5. Given that roughly 15%-30% of individuals with ASD are nonverbal many with few or no demonstrable language skills (Pickett, Pullara, O'Grady, & Gorden, 2009) this study in no way spanned the length of the ASD spectrum. The sensory demands of the ABR are also an issue. Although there are far fewer sensory demands with just three electrodes that need to be applied, compared to a full EEG cap or going into an fMRI scanner, this does limit who can participate.

The results of this study do invite further study in several directions. In the future the relationship between brainstem encoding of speech and syntax, semantics, and phonology should be examined in younger children. All of the children in this study had learned to read. Once a child learns to read, auditory processing is not the sole driver of language development. Working memory should also be examined, as well as differences in working memory may contribute to the relationship between stability of neural encoding of speech and language. Last of all, a more robust look at semantic abilities, including vocabulary and categorization should be investigated with respect to auditory processing.

In conclusion, stable neural encoding of speech by the brainstem appears to facilitate language development at several levels in both TD and ASD populations. Furthermore, phonological discrimination appears to mediate the relationship between encoding stability of speech and syntactic development. These findings lend support to the growing body of literature

investigating subcortical contributions to language (Skoe, Brody, & Theodore, 2017; Banai et al., 2009; Hornickel & Kraus, 2013). These findings also indicate that children with ASD and TD children have similar developmental patterns with respect to the stability of encoding of speech by the brainstem. Lack of stability affects both groups in a similar fashion, although there are more children with ASD who show this phenomenon.

References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychiatric Publishing.
- Banai, K., Hornickel, J., Skoe, E., Nicol, T., Zecker, S., & Kraus, N. (2009). Reading and subcortical auditory function. *Cerebral Cortex*, *19*(11), 2699-2707.
- Basu, M., Krishnan, A., & Weber-Fox, C. (2010). Brainstem correlates of temporal auditory processing in children with specific language impairment. *Developmental Science*, *13*(1), 77-91.
- Bates, E. (1979). *The Emergence of Symbols: Cognition and Communication in Infancy*. New York: Academic Press.
- Bavin, E. L., & Naigles, L. R. (Eds.). (2015). *The Cambridge Handbook of Child Language*. Cambridge University Press.
- Bidelman, G. M., Gandour, J. T., & Krishnan, A. (2011). Musicians and tone-language speakers share enhanced brainstem encoding but not perceptual benefits for musical pitch. *Brain and Cognition*, *77*(1), 1-10.
- Boersma, Paul (2001). Praat, a system for doing phonetics by computer. *Glott International* *5*:9/10, 341-345.
- Charles-Luce, J., & Luce, P. A. (1990). Similarity neighbourhoods of words in young children's lexicons. *Journal of Child Language*, *17*(1), 205-215.
- Cohen, I.L., J.M. Gardner, B.Z. Karmel, H.T. Phan, P. Kittler, T.R. Gomez, M.G. Gonzalez, E.M. Lennon, S. Parab, and A. Barone. (2013) Neonatal Brainstem Function and 4-Month Arousal-Modulated Attention Are Jointly Associated with Autism. *Autism Research*, *6*(1): p. 11-22.
- Courchesne, E. (1997). Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. *Current Opinion in Neurobiology*, *7*(2), 269-278.

- Courchesne, E., R.Y. Courchesne, G. Hicks, and A.J. Lincoln. (1985) Functioning of the Brain-Stem Auditory Pathway in Non-Retarded Autistic Individuals. *Electroencephalography and Clinical Neurophysiology*, 61(6): p. 491-501.
- Crain, S. (1989). Why Poor Readers Misunderstand Spoken Sentences. In Eds. D. Shankweiler & I. Y. (Eds.). *Phonology and Reading Disability* (pp.133-165). Ann Arbor: The University of Michigan Press.
- Edwards, J., Fox, R. A., & Rogers, C. L. (2002). Final consonant discrimination in children: Effects of phonological disorder, vocabulary size, and articulatory accuracy. *Journal of Speech, Language, and Hearing Research*, 45(2), 231-242.
- Eigsti, I. M., Bennetto, L., & Dadlani, M. B. (2007). Beyond pragmatics: Morphosyntactic development in autism. *Journal of Autism and Developmental Disorders*, 37(6), 1007-1023.
- Ellawadi, A. B., Fein, D., & Naigles, L. R. (2016). Category structure and processing in 6-year-old children with autism. *Autism Research*.
- Elliott, C. D. (2007). *Differential Ability Scales – Second edition (DAS-II)*. San Antonio, TX: Harcourt.
- Felsenfeld, S., Broen, P. A., & McGue, M. (1992). A 28-year follow-up of adults with a history of moderate phonological disorder: Linguistic and personality results. *Journal of Speech, Language, and Hearing Research*, 35(5), 1114-1125.
- Fernald, A., & Marchman, V. A. (2012). Individual differences in lexical processing at 18 months predict vocabulary growth in typically developing and late-talking toddlers. *Child development*, 83(1), 203-222.
- Fernald, Performs Marchman, 2012

- Flöel, A., de Vries, M. H., Scholz, J., Breitenstein, C., & Johansen-Berg, H. (2009). White matter integrity in the vicinity of Broca's area predicts grammar learning success. *Neuroimage*, *47*(4), 1974-1981.
- Friederici, A. D., & Skeide, M. A. (2015). Neurocognition of language development. In E. L. Bavin & L. R. Naigles, (Eds.). *The Cambridge Handbook of Child Language* (pp. 61-88). Cambridge, United Kingdom: Cambridge University Press.
- Frost, S. J., Landi, N., Mencl, W. E., Sandak, R., Fulbright, R. K., Tejada, E. T., ... & Pugh, K. R. (2009). Phonological awareness predicts activation patterns for print and speech. *Annals of Dyslexia*, *59*(1), 78-97.
- Gabr, T. A., & Darwish, M. E. (2016). Speech auditory brainstem response audiometry in children with specific language impairment. *Hearing, Balance and Communication*, *14*(1), 50-58.
- German, D. J., & Newman, R. S. (2004). The impact of lexical factors on children's word-finding errors. *Journal of Speech, Language, and Hearing Research*, *47*(3), 624-636.
- Geva, R., K. Sopher, L. Kurtzman, G. Galili, R. Feldman, and J. Kuint. (2013) Neonatal Brainstem Dysfunction Risks Infant Social Engagement. *Social Cognitive and Affective Neuroscience*, *8*(2): p. 158-64.
- Golestani, N. (2014). Brain structural correlates of individual differences at low-to high-levels of the language processing hierarchy: A review of new approaches to imaging research. *International Journal of Bilingualism*, *18*(1), 6-34.
- Grieser, D., & Kuhl, P. K. (1989). Categorization of speech by infants: Support for speech-sound prototypes. *Developmental Psychology*, *25*(4), 577.
- Hall JW. (2006). *New Handbook of auditory evoked responses*. Boston, MA: Allyn and Bacon.

- Hoff, E., & Naigles, L. (2002). How children use input to acquire a lexicon. *Child Development, 73*(2), 418-433.
- Hood LJ. (1998.) Clinical applications of the auditory brainstem response. San Diego, CA: Singular Publishing Group.
- Hornickel, J., & Kraus, N. (2013). Unstable representation of sound: a biological marker of dyslexia. *Journal of Neuroscience, 33*(8), 3500-3504.
- Hornickel, J., Anderson, S., Skoe, E., Yi, H. G., & Kraus, N. (2012). Subcortical representation of speech fine structure relates to reading ability. *Neuroreport, 23*(1), 6.
- Hornickel, J., Skoe, E., Nicol, T., Zecker, S., & Kraus, N. (2009). Subcortical differentiation of stop consonants relates to reading and speech-in-noise perception. *Proceedings of the National Academy of Sciences, 106*(31), 13022-13027.
- Huttenlocher, J., Waterfall, H., Vasilyeva, M., Vevea, J., & Hedges, L. V. (2010). Sources of variability in children's language growth. *Cognitive Psychology, 61*(4), 343-365.
- Jacola, L. M., Byars, A. W., Hickey, F., Vannest, J., Holland, S. K., & Schapiro, M. B. (2014). Functional magnetic resonance imaging of story listening in adolescents and young adults with D own syndrome: evidence for atypical neurodevelopment. *Journal of Intellectual Disability Research, 58*(10), 892-902.
- Johns, A. R., Myers, E. B., Skoe, E., & Magnuson, J. S. (2017). Speed of lexical access relates to quality of neural response to sound, not cognitive abilities, in younger and older adults. *The Journal of the Acoustical Society of America, 141*(5), 3747-3747.
- Johnson, K. L., Nicol, T. G., & Kraus, N. (2005). Brain stem response to speech: a biological marker of auditory processing. *Ear and Hearing, 26*(5), 424-434.

- Jones, M., Meagher, C., Figueiredo, M., Naigles, L., Skoe, E., & Fein, D. (April, 2017). Relationships between auditory brainstem responses and early language in typically developing children and children with autism spectrum disorder. Poster presented at the *Society for Research in Child Development Annual Meeting*, Austin, TX.
- Jusczyk, P. W., & Aslin, R. N. (1995). Infants' detection of the sound patterns of words in fluent speech. *Cognitive Psychology*, 29(1), 1-23.
- Kjelgaard, M. M., & Tager-Flusberg, H. (2001). An investigation of language impairment in autism: Implications for genetic subgroups. *Language and Cognitive Processes*, 16(2-3), 287-308.
- Kulesza Jr, R. J., Lukose, R., & Stevens, L. V. (2011). Malformation of the human superior olive in autistic spectrum disorders. *Brain Research*, 1367, 360-371.
- Lee, H., Devlin, J. T., Shakeshaft, C., Stewart, L. H., Brennan, A., Glensman, J., Pitcher, K., Mechelli, A., Frackowiak, R. S. J., Green, D. W., & Price, C. J. (2007). Anatomical traces of vocabulary acquisition in the adolescent brain. *Journal of Neuroscience*, 27(5), 1184-1189.
- Liberman, I. Y., Shankweiler, D., & Liberman, A. M. (1989). The Alphabetic Principle and Learning to Read. In Eds. D. Shankweiler & I. Y. (Eds.). *Phonology and Reading Disability* (pp.1-33). Ann Arbor: The University of Michigan Press.
- Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., & Bishop, S. (2012). Autism diagnostic observation schedule—2nd edition (ADOS-2). Los Angeles, CA: Western Psychological Corporation.
- Lovio, R., Näätänen, R., & Kujala, T. (2010). Abnormal pattern of cortical speech feature discrimination in 6-year-old children at risk for dyslexia. *Brain Research*, 1335, 53-62.
- Luce, P. A., & Pisoni, D. B. (1998). Recognizing spoken words: The neighborhood activation model. *Ear and Hearing*, 19(1), 1.

- Lukose, R., Beebe, K., & Kulesza Jr, R. J. (2015). Organization of the human superior olivary complex in 15q duplication syndromes and autism spectrum disorders. *Neuroscience*, *286*, 216-230.
- McClelland, J. L., & Elman, J. L. (1986). The TRACE model of speech perception. *Cognitive Psychology*, *18*(1), 1-86.
- Meagher, C., Jones, M., Tecoulesco, L., Figueiredo, M., Fein, D., Skoe, E., & Naigles, L. (2017, May). Relationships between auditory brainstem responses and early language in typically-developing children and children with autism spectrum disorders. Poster presented at the *International Meetings for Autism Research*, San Francisco, CA.
- Metsala, J. L., & Walley, A. C. (1998). Spoken vocabulary growth and the segmental restructuring of lexical representations: Precursors to phonemic awareness and early reading ability.
- Miron, O., Beam, A. L., & Kohane, I. S. (2018). Auditory brainstem response in infants and children with autism spectrum disorder: A meta-analysis of wave V. *Autism Research*, *11*(2), 355-363.
- Miron, O., D. Ari-Even Roth, L.V. Gabis, Y. Henkin, S. Shefer, I. Dinstein, and R. Geva. (2016) Prolonged Auditory Brainstem Responses in Infants with Autism. *Autism Research*, *9*(6): p. 689-95.
- Molfese, D. L. (2000). Predicting dyslexia at 8 years of age using neonatal brain responses. *Brain and Language*, *72*(3), 238-245.
- Morales, M., Mundy, P., Delgado, C. E., Yale, M., Messinger, D., Neal, R., & Schwartz, H. K. (2000). Responding to joint attention across the 6-through 24-month age period and early language acquisition. *Journal of applied developmental psychology*, *21*(3), 283-298.
- Morales, M., Mundy, P., Delgado, C. E., Yale, M., Messinger, D., Neal, R., & Schwartz, H. K. (2000). Responding to joint attention across the 6-through 24-month age period and early language acquisition. *Journal of Applied Developmental Psychology*, *21*(3), 283-298.

- Naigles, L. R., & Fein, D. (2017). Looking through their eyes: tracking early language comprehension in ASD. *Innovative Investigations of Language in Autism Spectrum Disorder*, 49-69.
- Naigles, L. R., & Hoff-Ginsberg, E. (1998). Why are some verbs learned before other verbs? Effects of input frequency and structure on children's early verb use. *Journal of Child Language*, 25(1), 95-120.
- Naigles, L. R., Johnson, R., Mastergeorge, A., Ozonoff, S., Rogers, S. J., Amaral, D. G., & Nordahl, C. W. (2017). Neural correlates of language variability in preschool-aged boys with autism spectrum disorder. *Autism Research*, 10(6), 1107-1119.
- Naigles, L. R., Kelty, E., Jaffery, R., & Fein, D. (2011). Abstractness and continuity in the syntactic development of young children with autism. *Autism Research*, 4(6), 422-437.
- Neef, N. E., Müller, B., Liebig, J., Schaadt, G., Grigutsch, M., Gunter, T. C., ... & Kraus, N. (2017). Dyslexia risk gene relates to representation of sound in the auditory brainstem. *Developmental Cognitive Neuroscience*, 24, 63-71.
- Neef, N. E., Schaadt, G., & Friederici, A. D. (2017). Auditory brainstem responses to stop consonants predict literacy. *Clinical Neurophysiology*, 128(3), 484-494.
- Nelson, K. (1973). Structure and strategy in learning to talk. *Monographs of the Society for Research in Child Development*, 38(1-2) serial no. 149.
- Newman, R., Ratner, N. B., Jusczyk, A. M., Jusczyk, P. W., & Dow, K. A. (2006). Infants' early ability to segment the conversational speech signal predicts later language development: a retrospective analysis. *Developmental Psychology*, 42(4), 643.
- Newman, R., Ratner, N. B., Jusczyk, A. M., Jusczyk, P. W., & Dow, K. A. (2006). Infants' early ability to segment the conversational speech signal predicts later language development: a retrospective analysis. *Developmental Psychology*, 42(4), 643.

- Norton, E. S., Beach, S. D., & Gabrieli, J. D. (2015). Neurobiology of dyslexia. *Current Opinion in Neurobiology*, 30, 73-78.
- Otto-Meyer S, Krizman J, White-Schwoch T, Kraus N. (2018) Children with autism spectrum disorder have unstable neural responses to sound. *Experimental Brain Research*. 236:3 (733-743).
- Peirce, JW (2007) PsychoPy - Psychophysics software in Python. *Journal of Neuroscience Methods*, 162 (1-2), 8-13.
- Pickett, E., Pullara, O., O'grady, J., & Gordon, B. (2009). Speech acquisition in older nonverbal individuals with autism: a review of features, methods, and prognosis. *Cognitive and Behavioral Neurology*, 22(1), 1-21.
- Piotroski, J., & Naigles, L. R. (2011). Intermodal preferential looking. *Research Methods in Child Language: A Practical Guide*, 17-28.
- Pisoni, D. B., & Luce, P. A. (1987). Acoustic-phonetic representations in word recognition. *Cognition*, 25(1-2), 21.
- Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers*, 36(4), 717-731.
- Pugh, K. R., Mencl, W. E., Jenner, A. R., Katz, L., Frost, S. J., Lee, J. R., Shaywitz, S. E., & Shaywitz, B. A. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental retardation and developmental disabilities research reviews*, 6(3), 207-213.
- Richlan, F., Kronbichler, M., & Wimmer, H. (2013). Structural abnormalities in the dyslexic brain: a meta-analysis of voxel-based morphometry studies. *Human Brain Mapping*, 34(11), 3055-3065.
- Rumsey, J.M., A.M. Grimes, A.M. Pikus, R. Duara, and D.R. Ismond. (1984) Auditory Brainstem Responses in Pervasive Developmental Disorders. *Biological Psychiatry*, 19(10): p. 1403-18.

- Russo, N. M., Skoe, E., Trommer, B., Nicol, T., Zecker, S., Bradlow, A., & Kraus, N. (2008). Deficient brainstem encoding of pitch in children with autism spectrum disorders. *Clinical Neurophysiology, 119*(8), 1720-1731.
- Russo, N.M., E. Skoe, B. Trommer, T. Nicol, S. Zecker, A. Bradlow, and N. Kraus. (2008) *Deficient Brainstem Encoding of Pitch in Children with Autism Spectrum Disorders*. *Clinical Neurophysiology, 119*(8): p. 1720-31.
- Saffran, J. R., & Thiessen, E. D. (2007). Domain-general learning capacities. *Blackwell handbook of language development, 68-86*.
- Skoe, E., & Kraus, N. (2010). Auditory brainstem response to complex sounds: a tutorial. *Ear and Hearing, 31*(3), 302.
- Skoe, E., Brody, L., & Theodore, R. M. (2017). Reading ability reflects individual differences in auditory brainstem function, even into adulthood. *Brain and Language, 164*, 25-31.
- Skoe, E., Krizman, J., & Kraus, N. (2013). The impoverished brain: disparities in maternal education affect the neural response to sound. *Journal of Neuroscience, 33*(44), 17221-17231.
- Skoe, E., Krizman, J., Anderson, S., & Kraus, N. (2013). Stability and plasticity of auditory brainstem function across the lifespan. *Cerebral Cortex, 25*(6), 1415-1426.
- Song, J. H., Banai, K., Russo, N. M., & Kraus, N. (2006). On the relationship between speech-and nonspeech-evoked auditory brainstem responses. *Audiology and Neurotology, 11*(4), 233-241.
- Song, J. H., Skoe, E., Banai, K., & Kraus, N. (2011). Perception of speech in noise: neural correlates. *Journal of Cognitive Neuroscience, 23*(9), 2268-2279.
- Song, J.H., K. Banai, and N. Kraus. (2008) Brainstem Timing Deficits in Children with Learning Impairment May Result from Corticofugal Origins. *Audiology and Neurotology, 13*(5): p. 335-44.

- Tager-Flusberg, H., Paul, R., & Lord, C. (2005). Language and communication in autism. In F. Volkmar, R. Paul, A. Klin, & D. J. Cohen (eds.), *Handbook of Autism and Pervasive Developmental Disorders*, 3rd edn, vol 1, , (pp. 335-364). New York: Wiley.
- Tecoulesco, L., Skoe, E., & Naigles, L. (2018, March) Linking Auditory Processing and Lexical Representation Via Phonological Discrimination. Poster presented at the *Cognitive Neuroscience Society Annual Meeting*, Boston, MA.
- Tek, S., Mesite, L., Fein, D., & Naigles, L. (2014). Longitudinal analyses of expressive language development reveal two distinct language profiles among young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 44(1), 75-89.
- Tharpe, A.M., F.H. Bess, D.P. Sladen, H. Schissel, S. Couch, and T. Schery. (2006) Auditory Characteristics of Children with Autism. *Ear and Hearing*, 27(4): p. 430-41.
- Tomasello, M., & Farrar, M. J. (1986). Joint attention and early language. *Child development*, 1454-1463.
- Tomblin, J. B. (2015). Children with Specific Language Impairment (SLI). In E. L. Bavin & L. R. Naigles, (Eds.). *The Cambridge Handbook of Child Language* (pp. 527-544). Cambridge, United Kingdom: Cambridge University Press.
- Vitevitch, M. S. (2002). The influence of phonological similarity neighborhoods on speech production. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 28(4), 735.
- Vitevitch, M. S., & Luce, P. A. (1999). Probabilistic phonotactics and neighborhood activation in spoken word recognition. *Journal of Memory and Language*, 40(3), 374-408.
- Vydrova, R., Komarek, V., Sanda, J., Sterbova, K., Jahodova, A., Maulisova, A., ... & Kyncl, M. (2015). Structural alterations of the language connectome in children with specific language impairment. *Brain and Language*, 151, 35-41.

- Wiig E. H., Semel E., Secord W. A. (2013). *Clinical Evaluation of Language Fundamentals–Fifth Edition (CELF-5)*. Bloomington, MN: NCS Pearson.
- Weiss, M. W., & Bidelman, G. M. (2015). Listening to the brainstem: musicianship enhances intelligibility of subcortical representations for speech. *Journal of Neuroscience*, 35(4), 1687-1691.
- White-Schwoch, T., Carr, K. W., Thompson, E. C., Anderson, S., Nicol, T., Bradlow, A. R., ... & Kraus, N. (2015). Auditory processing in noise: A preschool biomarker for literacy. *PLoS biology*, 13(7), e1002196.

Table 1. Characteristics of Typically Developing (TD) and Autism Spectrum Disorder (ASD) groups at visit 1

	TD M(SD) range	ASD M(SD) range	F	<i>p</i>	η_p^2
Age	19.93 (1.24)	31.59 (6.09)	37.81	<.001	.643
(months)	19.01-23.3	18.77-41			
ADOS	0.55(.93)	12.67(3.65)	113.9	<.001	.844
	0-3	7-18			
CDI	118.09(117.45)	116.50(116.69)	.001	.974	<.001
Understands and Says	11-317	7-328			
Mean Length Utterance	1.39(.24)	1.89(.89)	2.77	0.112	0.112
	1-1.75	1-3.58			
MSEL					
Fine Motor	22.27(2.65)	26.11(3.67)	7.41	.014	.29
	19-28	20-34			
Expressive Language	20(4.31)	21(7.35)	.155	.698	.007
Receptive Language	25.09(3.36)	24.92(7.79)	.005	.95	<.001
	20-31	12-38			
Visual Receptive	26.09(3.08)	26.67(6.51)	0.07	.792	.003
	21-30	12-34			

ADOS , Autism Diagnostic Observation Schedule; CDI, MacArthur-Bates Communicative Development Inventory; MSEL, Mullen Scales of Early Learning

Table 2. Characteristics of TD and ASD groups at time of current study

	TD M(SD) Range (<i>n</i> =11)	ASD M(SD) Range (<i>n</i> =12)	F	<i>p</i>	η_p^2
Age (years)	10.72(2.10) 7-13	12.33(3.34) 7-17	1.86	.187	0.08
ADOS-2	1.6(2.41) 0-6	9.45(5.37) 3-17	25.424	<.001	.57
CELF 5 Raw Scores					
Formulated Sentences	38.82(7.42) 21-47	29.42(13.35) 7-46	4.24	0.05	0.17
Word Classes	32.28(4.79) 22-38	27.42(7.01) 15-35	3.55	0.07	0.14
Repeated Sentences	59.27(11.32) 41-77	45.67(20.81) 12-71	3.69	0.07	0.15
Following Directions	25.82(6.69) 10-32	21.33(7.52) 9-32	2.26	0.15	0.10
CELF 5 Standard Scores					
Formulated Sentences	11(2.24) 7-15	6.92(3.75) 1-14	9.807	.005	.318
Word Classes	12.73(2.9) 10-19	8.42(2.78) 2-12	13.243	.002	.387
Repeated Sentences	12.0(3.3) 6-19	7.7(3.7) 1-13	3.692	.068	.15

	TD <i>M(SD)</i> Range (n=11)	ASD <i>M(SD)</i> Range (n=12)	F	<i>p</i>	η_p^2
Following directions	11.73(2.9) 7-17	8.67(3.9) 3-15	4.395	.048	.173
DAS Raw Scores					
Pattern Construction	47.09(6.35) 34-52	35.83(12.71) 17-52	7.01	0.02	0.25
Recall of Digits	21.64(4.23) 14-29	20.75(5.63) 11-30	0.18	0.68	0.01
Matrices	20.91(5.59) 11-32	15.83(8.76) 2-32	2.69	0.12	0.11
Composite	89.63(13.00) 66-105	72.42(25.32) 31-112	4.09	0.06	0.16

ADOS 2, Autism Diagnostic Observation Schedule; CELF 5, Clinical Evaluation of Language Fundamentals, Fifth edition; DAS, Differential Ability Scales

Table 3. ABR results for TD and ASD Groups

	TD M(SD)	ASD M(SD)	F	<i>p</i>	η_p^2
Click Wave V Latency	5.64(.17)	5.75(.16)	2.893	0.101	.104
Da Wave V Latency	6.50(.24)	6.53(.22)	0.091	0.765	.004
Click Stability	0.78(.15)	0.81(.15)	0.213	0.648	.008
Da Stability raw scores	0.74(.14)	0.72(.20)	0.077	0.784	.003
Da Stability Z scores	1.01(.29)	1.04(.46)	.043	.873	.002

Table 4. Correlations between CELF 5 Raw Scores and /da/ Stability Z scores for the entire sample, TD and ASD groups

	Raw Scores			Controlling for DAS and Age		
	ALL	TD	ASD	ALL	TD	ASD
Formulated Sentences	.573**	.696*	.619*	.671**	.881**	.697**
Word Classes	.390	.358	.457	.372	.129	.558 †
Repeated Sentences	.376	.028	.531	.342	-.565	.601 †
Following Directions	.337	.358	.371	.266	.093	.364

Note

† $p < .1$

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

Table 5. Correlations between Phonological Discrimination and CELF 5 Raw Scores for the entire group and TD and ASD groups

	Raw Scores			Controlling for DAS and Age		
	ALL	TD	ASD	ALL	TD	ASD
Formulated Sentences	.833**	.578 †	.923**	.695**	.219	.869**
Word Classes	.785**	.203	.896**	.38	-.511	.718*
Repeated Sentences	.845**	.516	.880**	.562*	.12	.701*
Following Directions	.622**	.166	.741**	-.008	-.687*	.47

Note

† $p=.06$

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

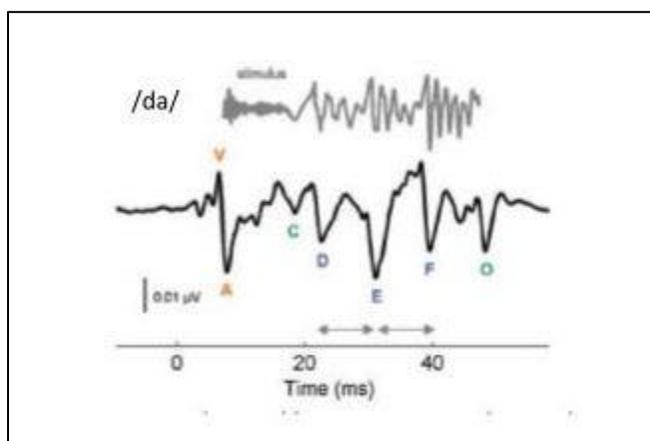


Figure 1. /Da/ stimulus and typical response waveform
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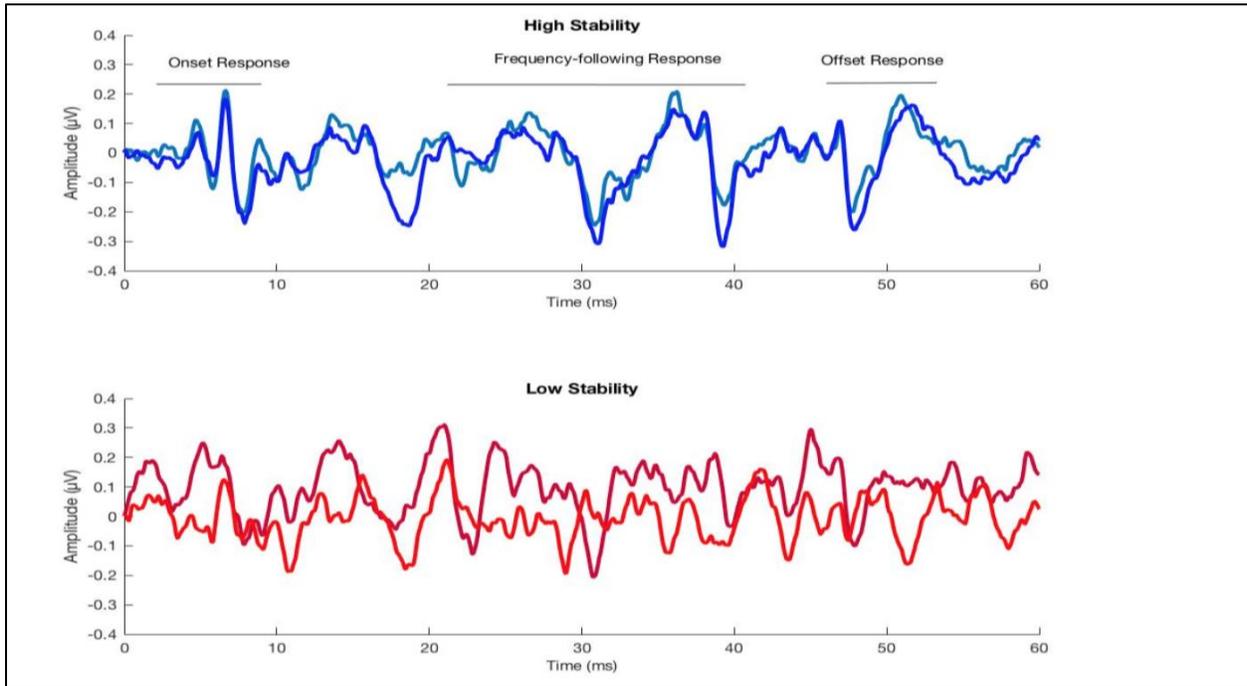


Figure 2. Waveform comparison of High Stability Responder and Low Stability Responder. Each line represents an average waveform for 3000 trials. The first 3000 trials and the second 3000 trials can be compared using a linear correlation.



Figure 3. Training stimuli for Discrimination task, same (top) and different (bottom) pictures

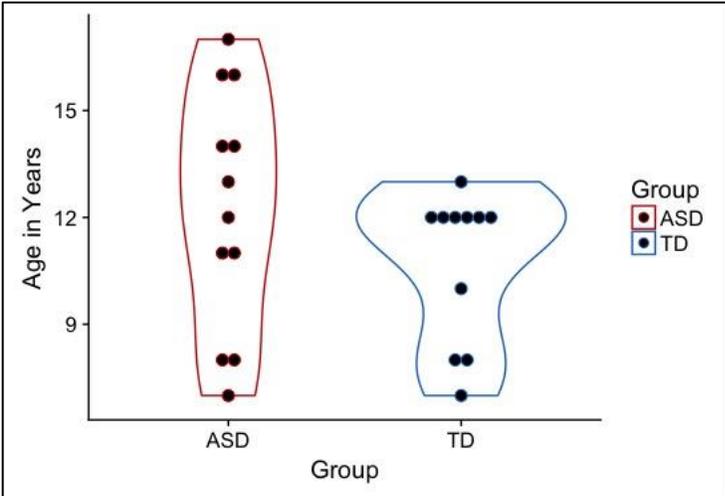


Figure 4. Trimmed violin plot depicting the age distributions of ASD and TD groups

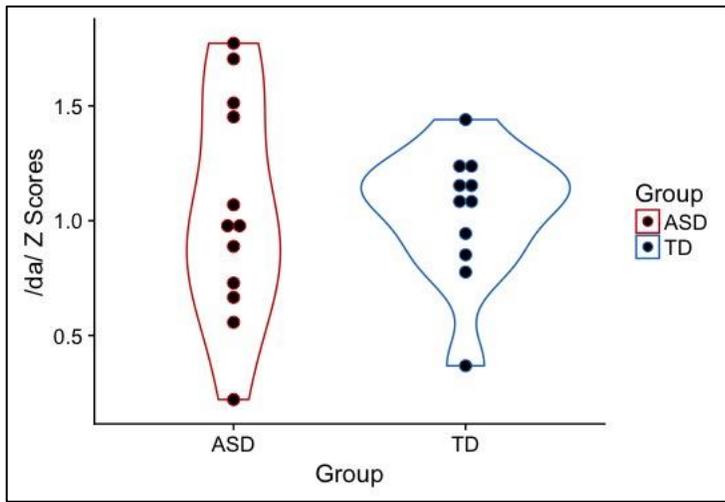


Figure 5. Trimmed violin plot of /da/ stability Z score distributions of ASD and TD groups

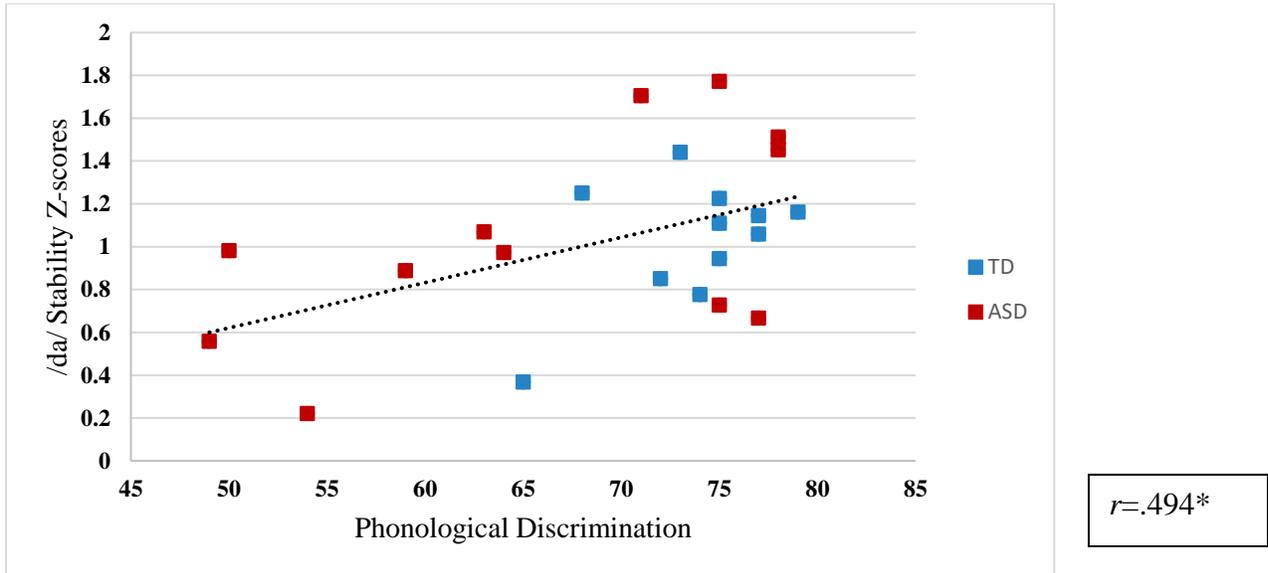


Figure 6. Relationship between /da/ Stability Z scores and Phonological Discrimination for TD and ASD children.

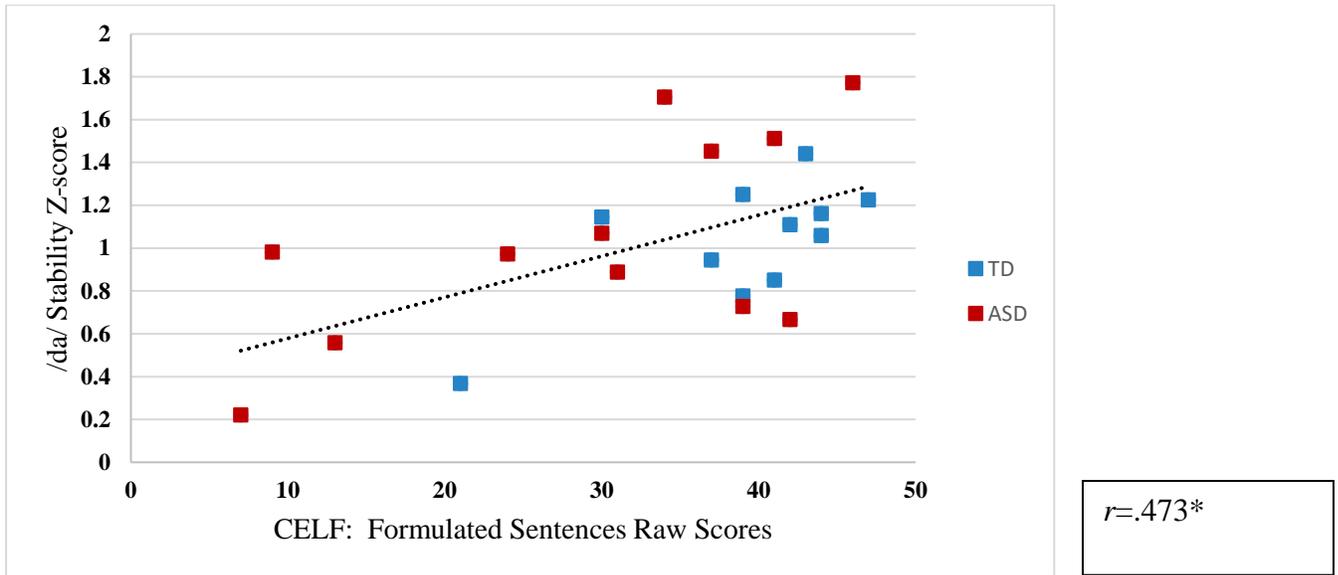


Figure 7. Relationship between /da/ Stability Z scores and syntactic ability in Formulated Sentences Raw Scores for TD and ASD children

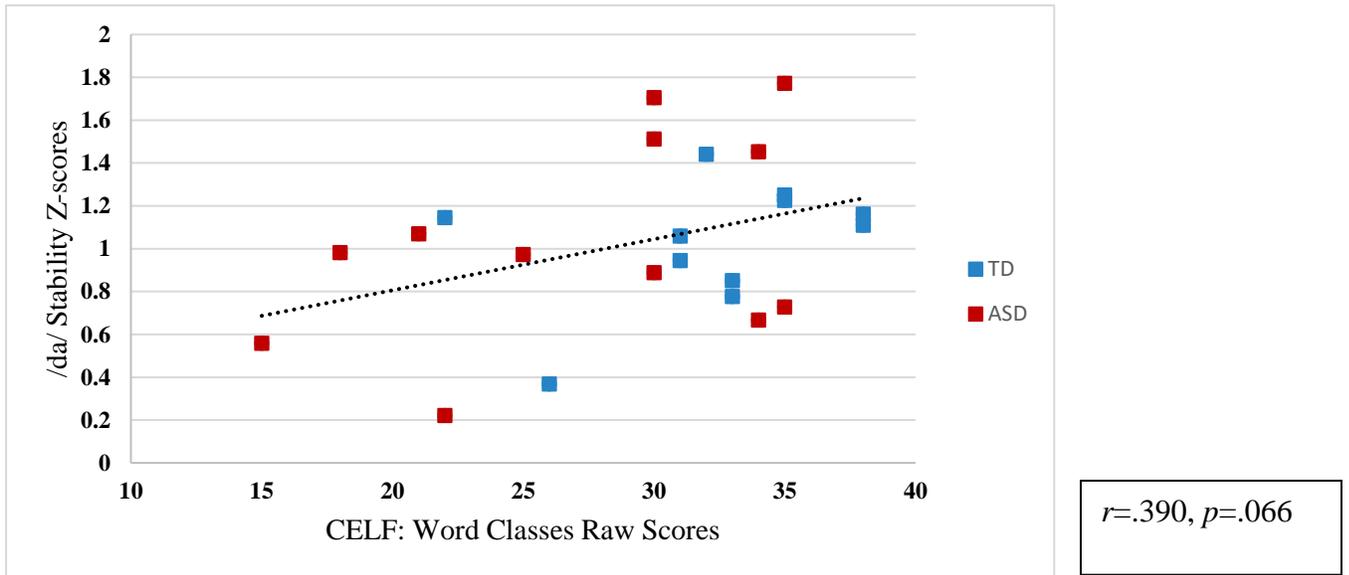


Figure 8. Relationship between /da/ Stability Z scores and semantic ability in Word Classes for TD and ASD children

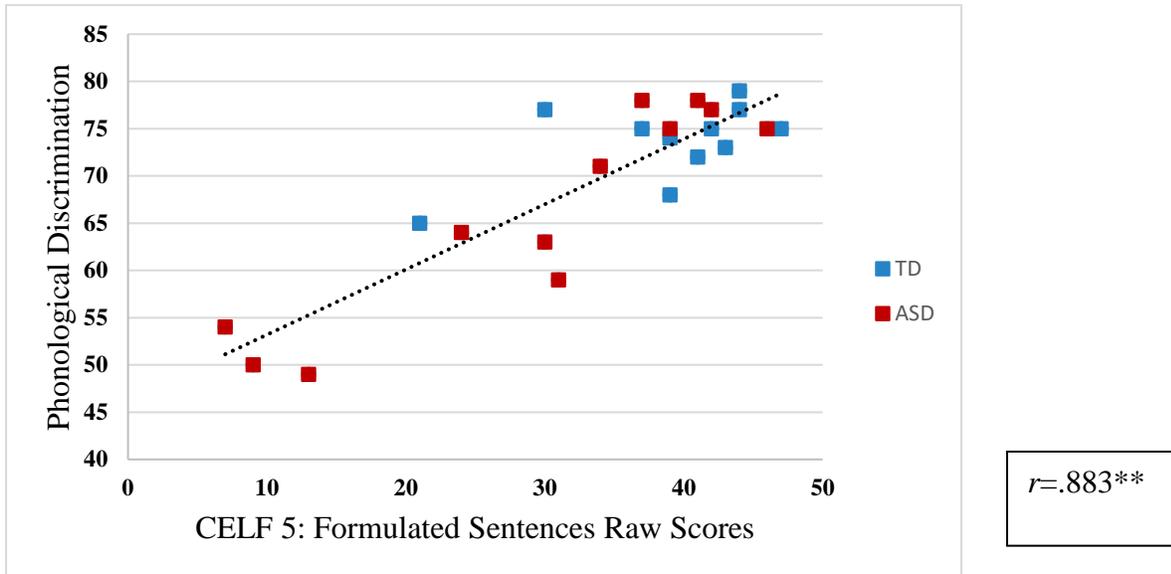


Figure 9. Relationship between phonological discrimination scores and syntactic ability in Formulated Sentences for TD and ASD children.

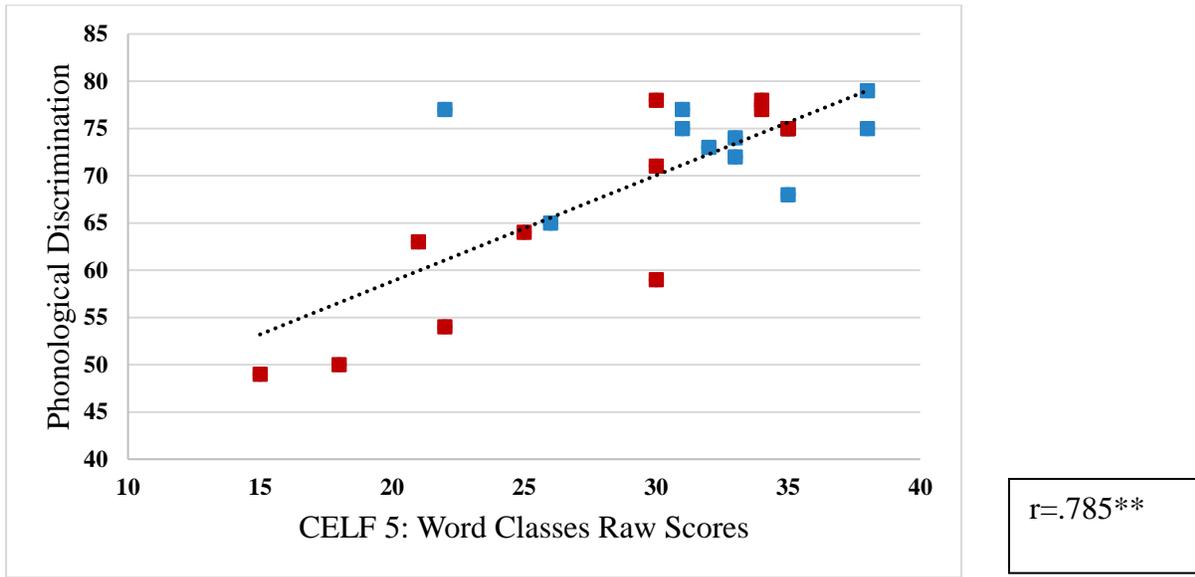


Figure 10. Relationship between /phonological discrimination scores and semantic ability in Word Classes for TD and ASD children.

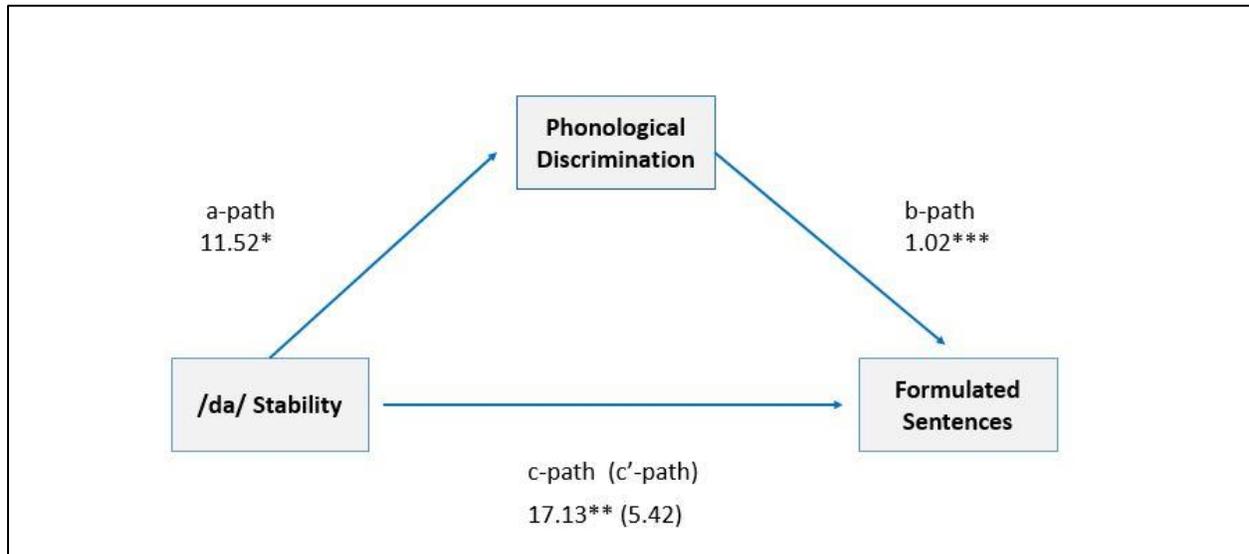


Figure 11. Phonological Discrimination Mediates the Relationship between /da/ Stability and Formulated Sentences. /Da/ Stability predicts Phonological Discrimination and Phonological Discrimination Predicts Formulated Sentences, as seen by the a and b paths respectively. The total effect of /da/ Stability on Formulated Sentences is represented by the c-path. The direct effect, represented by the c'-path is not significant.