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Approaches to examining the role of auditory evoked potentials in early language development

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Abstract

Previous research has suggested a relationship between auditory evoked potentials (AEPs) and spoken language proficiency, but their interactions during the earliest stages of development are not well understood. *AEP-Age*, an index that estimates the maturity of a child’s AEP relative to same-aged peers, has been effective in investigating this relationship in school-aged children, but has yet to be applied to younger populations. This thesis includes two Stage 1 Manuscripts (Registered Reports) for future studies to (a) assess the utility of *AEP-Age* to predict chronological age and language ability in 18-48-month-old children, and (b) investigate the relationship between *AEP-Age* and language ability longitudinally in children with three different trajectories (children with typical development, late talkers who resolve, and children with persistent developmental language disorder). This thesis sets the stage for a new line of research examining the role of AEP maturation in the earliest stages of typical and atypical language development.

Keywords

Auditory Evoked Potentials, Language, Development, Child, Infant, Electroencephalography, Sensory, Event-Related Potentials, Developmental Language Disorder.

Summary for Lay Audience

Past research demonstrates a relationship between our brain's response to sound, called auditory evoked potentials (AEPs), and language abilities. AEPs can be captured as a waveform using electroencephalography (EEG), and like our language skills, have been shown to mature and change as we age. A newly developed index called AEP-Age has been shown to successfully estimate auditory brain maturity in school-aged children. To collect a child's AEP, EEG records brain responses to a simple tone over 5 minutes, then these responses are compared to overall averages of AEP responses from groups of children of different ages. Recent research has shown that AEP maturity (captured using AEP-Age) is related to language proficiency in school-age children with typical and atypical language development.

This thesis includes two papers that provide a detailed plan for two future studies that will validate the use of AEP-Age in toddlers. The first of the two papers describes a study that will examine groups of children at different ages between 18 and 48 months in order to create average AEP responses for each age group, assessing whether AEP-Age is a good measure in children this young. The second paper describes a study that will follow a group of children from the age of 18 months to the age of 48 months. This study will investigate the relationship between AEP-Age and language ability in children with three different developmental trajectories (children with typical development, late talkers whose difficulties resolve, and children with persistent developmental language disorder). Together, these studies set the stage for a new line of research examining auditory maturity in the earliest stages of typical and atypical language development.

Co-Authorship Statement

This work consists of four chapters: an introductory chapter (Chapter 1), two Stage 1 Manuscripts (Chapter 2 and 3), and a concluding chapter (Chapter 4) of which, I, Alyssa Janes, am the lead author. This project was conceptualized with contributions from my supervisor, Dr. Janis Oram Cardy, and my Advisory Committee: Drs. Nichole Scheerer, Lisa Archibald, and David Purcell. Chapters 2 and 3 will be submitted for publication as Stage 1 Registered Reports with co-authors Drs. Oram Cardy, Nichole Scheerer, and Elaine Kwok. All co-authors supported the project design and analysis plans, and Drs. Oram Cardy and Dr. Nichole Scheerer reviewed and provided feedback on the final thesis, including both manuscripts.

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Chapter 1

1 Introduction

Developmental disorders of language learning affect a child's ability to communicate and can range from mild and transient to more severe, persistent cases (Paul, 2020). Why some children have such difficulties is not well understood, but one proposal has been that deficits in rapid auditory processing of both linguistic and non-linguistic sounds play a role (Benasich et al., 2002). Neuroscientific methods such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and electroencephalography (EEG) have all proven useful in the investigation of the relations between auditory cortical processing and language development. However, these methods have had limitations. For example, studies using EEG have focused on evaluating the characteristic auditory evoked potential (AEP) through methods such as the measurement of peak amplitudes and latencies or mean amplitude over a specific time window (van Zuijenfor et al, 2012; for review see Hämäläinen et al., 2013). However, these conventional analyses are limited in their ability to deal with obstacles such as abrupt age-related changes or late emergence of key components in the AEP waveform during childhood (Ponton et al., 2000). As a result, Intraclass Correlation (ICC), which measures the overall AEP without reliance on identifying individual peaks, has emerged as a new approach to examining the relationship between language development and auditory cortical maturation. While ICC has been successfully used to predict the language abilities of school-aged children (Bishop et al., 2011; Kwok et al., 2018a), to my knowledge, it has not been applied to younger populations. Given this, the interaction between auditory cortical maturation and language abilities during the earliest stages of development is still not well understood. The overall goal of this thesis is to set the stage for a new line of research examining the relationship between the maturity of AEPs and spoken language abilities in young children aged 18 to 48 months.

To provide background, the current introductory chapter will provide an overview of early language development, the role of auditory cortical processing during this period, common methods of analysis of AEPs, and gaps in the literature. A brief overview of the present thesis will be provided as an introduction to the chapters that follow, which include two Registered Report (Stage 1) manuscripts (Chapters 2 and 3) and a discussion of progress towards their implementation, future plans, and implications of this line of research (Chapter 4).

1.1 Early Spoken Language Development

The development of spoken language is a complex process that shows variability in its exact manifestation in individual children and can be influenced by a range of environmental factors including socioeconomic status (Hoff & Tian, 2005), quality of mother-infant interactions and attachment security (Morisset et al., 2008), and maternal education level (Reilly et al., 2010). Despite this individual variation, typical language development appears to follow a universal and predictable timeline regardless of culture (Conti-Ramsden & Durkin, 2012; Kuhl, 2004), which is no doubt attributable to the biological bases of language acquisition. The first three years of life are a particularly intense period of both neural and language development. For example, at the same time that synaptic density and concentration are rapidly increasing (Huttenlocher, 1979), young infants are becoming more sensitive to subtle acoustic differences between the sounds of the language(s) they are learning, laying a foundation for their rapidly growing language system (Kuhl, 2004, 2010).

In the first year of life, children develop building blocks for language including nonverbal communication and emerging awareness and comprehension of the language of input (Krentz & Corina, 2008). For example, before the emergence of a child’s first words, their caregiver(s) will often witness communicative gestures such as pointing (Behne et al., 2011; Tomasello et al., 2007) and head gestures (Fusaro et al., 2012). Infants will engage in babbling and production of sounds that mimic adult intonation (Locke, 1989; Saaristo-Helin et al., 2011). These skills are indicators that the infant is displaying communicative intent, the beginnings of language comprehension, and acquiring knowledge of the phonemes of their language. Despite the fact that humans are born with the ability to discriminate phonemes of all languages (McMurray & Aslin, 2005), this capability decreases with age as the child becomes attuned to their first language (Krentz & Corina, 2008). It is proposed that this refinement is a result of a learning process in which the infant is forming mental, speech sound categories for commonly heard acoustic signals (Kuhl et al., 2005).

Although much occurs prior to the onset of the child's first word, this event is seen as the beginning of language production (Majorano & D'Odorico, 2010). Commonly, this happens near the first birthday, and vocabulary will continue to grow at a steady pace (~10 words/month) until the acquisition of about 50 words (Benedict, 1979). At this point, a child will begin to acquire new words at a rate of nearly 30 words a month (Goldfield & Reznick, 1990). During this period, a child's growing phonological system provides them with the foundation needed for both semantic and syntactic development, which becomes more dominant in the second and third years of life (Foorman et al., 2002). Around this time, the child continues to develop their understanding and use of new words and begins to form multiword phrases. Typically, the first multiword utterance will be short (2-3 words) (Braine & Bowerman, 1976), and lack grammatical morphemes such as those used to mark possession (possessive -'s), number (plural -s) or tense (progressive -ing, past -ed) (Tyack & Ingram, 1977). Throughout the preschool years, phrases grow longer, and children refine their use of grammar including the addition of articles (e.g., a, the), auxiliary verbs (e.g., am, is, are, has, have), and pronouns (e.g., him, her), and begin to produce multiclause phrases (Kirjavainen et al., 2009). As their use and understanding of their language increases, children will also become more proficient in pragmatic elements such as turn taking (Rutter & Durkin, 1987), repairing conversational misunderstandings (Laakso & Soininen, 2010), and discussing future events (Atance & O'Neill, 2005).

Given the supportive role of auditory processing in the extraction of key acoustic features early in life, and the role of the developing phonological system in other building blocks of language such as vocabulary and grammar, it has been suggested that auditory processing plays an important role in the development of spoken language.

1.2 The Development of Auditory Processing

Humans are born with an immature auditory system that continues to develop well into adolescence (Eggermont & Ponton, 2003). Continual maturation of the auditory system involves changes in specific pathways of both the peripheral and central nervous systems, although predominantly the latter. These changes are a consequence of physiological development and ongoing exposure to auditory stimuli (Litovsky, 2015, Chapter 3). At birth, several mature neurons are already present in the auditory cortex, however, research using immunostaining techniques suggest that the axons carrying information through the cortex are in varying stages of immaturity (Moore & Guan, 2001). Mature axons are distinct in the sense that they contain a highly complex network of neurofilaments and have undergone myelination, that is, formation of a fatty sheath around the axon that increases rapid transmission between neurons (Hoffman et al., 1984). Axonal development in the cortex continues through childhood in a predictable pattern that parallels the electrophysiological and perceptual development of auditory processing (discussed in detail below) (Moore & Guan, 2001). In newborns, mature axons are only present in the marginal layer of the cortex (layer I). Layer I is considered to be the most primary layer of the cortex and provides only the most basic information about auditory stimuli due to its lack of intracortical connections (Moore, 2002). During early childhood, dendritic branching (the process of dendritic growth and synapse formation) gradually enhances intracortical connections in the auditory cortex, driving activity in cells of deeper layers IV, V, and VI (Marin-Padilla & Marin-Padilla, 1982). It is not until about 5 years of age that mature axons are detectable in layers II and III of the auditory cortex. These intermediary layers represent maturing corticocortical connections linked to communication in the cortex between, and within, hemispheres. Typically, by 11 or 12 years of age, the density of mature neurons in all layers of the auditory cortex will reflect those of a young adult (Moore, 2002)

As physiological development progresses, a child will also experience perceptual changes that influence their processing of acoustic inputs. Infants in the first few months of life have the ability to distinguish speech sounds of varying acoustic characteristics (intensity, frequency, etc.). Despite an immaturity in deeper levels of the cortex, infants younger than 4.5 months are able to differentiate between individual speech sounds (Eggermont & Ponton, 2003) and speakers (Jusczyk et al., 1992). In fact, young infants have proven more accurate than adults at detecting phonemic contrasts outside of their native language. However, between the ages of 6 and 12 months, as the deeper layers of the auditory cortex mature, an infant's ability to detect phonemic contrasts outside their language of input decreases (Bar-On et al., 2018). This may be the result of the maturation in deeper levels of the auditory cortex, leading to phonetic categorization that prioritizes common sounds (i.e., phonemes in the language of input) (Werker & Tees, 2002; Kuhl et al, 1992). Around 5 years of age, while layers II and III of the auditory cortex begin to develop to appear more adult-like, synaptic connections become gradually more specialized and children are increasingly able to process masked and degraded speech (Elliot, 1979; Eisenberg et al., 2000). Throughout childhood, speech perception and sound localization skills continue to improve along a maturational timeline that is considered complete by young adolescence (Eggermont & Moore, 2012)

Often, auditory maturation is classified through progressive changes in electrophysiological responses, with development reflected in changes to distinct peaks in the auditory evoked potential (AEP). The AEP waveform itself is comprised of a set of measurable peaks (P1-N1-P2-N2) that represent electrical activity at the scalp and can be used to approximate auditory cortical maturation (Tomlin & Rance, 2016). Peak amplitude, peak latency, and the morphology of individual components have been studied extensively over the years (reviewed in Wunderlich & Cone-Wesson, 2006). Measures of peak latency appear relatively stable from birth to 6 years old for all components, at which point they begin to decrease through later childhood (Ponton et al., 2002). This is assumed to be a result of increased myelination in layers II and III of the auditory cortex and improving synaptic efficiency (Wunderlich et al., 2006). In 5–6-year-old children, the AEP waveform is dominated by the P1 component (Ponton et al., 2000). Similar relationships between peak amplitude and physiological maturation of the auditory cortex are observed for later emerging components as well. For example, maturational trends in N1 peak magnitude are opposite to those of P1 (Ponton et al., 2002). Although the N1 peak does not develop until 9-10 years old, researchers speculate that the physiological source of the N1 peak is the same as that of P1, with electrical signals being superimposed on P1. It is proposed that the neural generators of P1 are nearly adult-like at the emergence of the N1 peak (Ponton et al., 2002). A systematic decline in magnitude similar to that of P1 has also been shown for the N2 peak (Cunningham et al., 2000; Johnstone et al., 1996; Oades et al., 2007). The declining amplitude of the N2 peak from about 5-15 years old provides further evidence for a continuum of maturation in the auditory cortex from birth to adolescence. The timeline of auditory cortical maturation and its reflection in the AEP waveform is of particular interest in this thesis, because differences within the P1-N1-P2-N2 complex have also been tied to children's language proficiency (Choudhury & Benasich, 2011).

1.3 Auditory Evoked Potentials and Language Development

Auditory evoked responses recorded during early childhood have been shown to be strong predictors of spoken and written language abilities later in life. Specifically, early work by Molfese and colleagues demonstrated the predictive potential of AEP morphology for reading and verbal skills from birth to 8 years of age (Molfese & Molfese, 1985, 1997). Using both speech and non-speech stimuli, they evoked neonatal AEPs for use in the prediction of language development and auditory maturation. Two components of AEPs elicited by speech sounds (occurring between 88-240 ms and 664 ms, respectively) were able to effectively identify children who performed better or worse on the McCarthy Scales of Children's Abilities (McCarthy, 1979) verbal index at age 3 years (Molfese & Molfese, 1985).

A follow-up study conducted years later provides further evidence for the relation between AEPs and verbal abilities (Molfese & Molfese, 1997). Neonatal AEPs were collected from 71 infants (aged 36 hours or less) and principal component analysis was used to isolate the two factors matching the latency configuration previously identified (i.e., occurring between 88-240ms and at 664 ms) (Molfese & Molfese, 1985). These neonatal AEPs had high accuracy in classifying children according to whether they demonstrated higher or lower verbal IQ on the Stanford-Binet Intelligence Scales (Thorndike et al., 1986) at 5 years of age, suggesting that the relation between verbal IQ and auditory maturation holds through the preschool period.

Further work by these authors (Molfese et al., 1999) has demonstrated that the latency of the N2 peak may also be used to successfully predict both verbal and reading skills at 8 years old. Hierarchical growth curve models of change investigating ERPs from the ages 1 through 8 years old were shown to predict verbal intelligence skills at age 8. The mean latency of the N2 peak for those who perform worse on the verbal intelligence scale of the Wechsler Intelligence Scale for Children (WASI) was delayed by 25 ms in comparison to those with higher verbal intelligence scores. Additionally, the linear rate of decline in N2 latency was slower in individuals with lower verbal intelligence across the ages of 1 to 8 years old (Molfese et al., 1999).

Several other studies have supported the findings of Molfese and colleagues (1985, 1997, 1999) and the association between language development and auditory cortical maturation (Benasich et al., 2002; Benaisch et al., 2006; Choudhury & Benasich, 2003; also see review, Heim & Benasich, 2006). In children with typical development, changes in the mean amplitude of the AEP waveform have been related to language and verbal memory skills. Research has also shown that larger, more positive mean amplitudes of the AEP in the right hemisphere at birth correspond to poor receptive language skills at 2.5 years old. Specifically, correlation and regression analyses supported a relation between "at-risk" or deviant AEP morphology to weaker language skills through development (Guttorm et al., 2005). Additional analyses of AEPs collected at birth show an association between larger, more positive ERP waveforms in the left hemisphere and poorer verbal memory skills at 5 years old (Guttorm et al., 2005).

Additional evidence for the relation between auditory cortical maturation and language proficiency can be found in studies of atypical development. Although some individual variation in maturational changes is expected, significant age-related changes in AEPs have been well documented and seem to follow a standard maturational progression (Bruneau et al., 1997; Ponton et al., 2000; Shafer et al., 2015). This is particularly useful in the context of developmental research, as immature auditory processing has been linked to impaired language development (Bishop & McArthur, 2004). To date, researchers have identified a range of atypical neurophysiological responses to auditory stimuli in children with language impairments. Infants with a family history of language impairment, who were thus at increased risk of language disorder, showed significant differences in their rate of cortical auditory maturation. Specifically, those identified as having an increased risk for language disorders showed delayed maturation of AEPs in childhood in comparison to controls (Choudhury & Benasich, 2011). Similar findings have been reported in populations of children with developmental language disorder (DLD, also known as specific language impairment, Bishop et al., 2017). Atypical auditory cortical responses to tones in pre- and mid-adolescent children with DLD have been characterized by several researchers (Lincoln et al., 1995; Tonnquist-Uhlen et al., 1996, Adams et al., 1987). Tonnquiest-Uhlen (1996) demonstrated that latencies of both the P2 and N2 components appear to be delayed in populations with language impairment, with the most pronounced differences observed in the latency of the P2 peak. Children with DLD demonstrated N1 peaks that were longer than those of typically developing children, perhaps due to slower processing in central auditory pathways (Tonnquiest-Uhlen et al., 1996). Significantly delayed latencies in the N2 peak have also been demonstrated in children with impaired language development between the ages of 8 to 10 years old compared to age-matched controls (Włodarczyk et al., 2018).

By contrast, other studies of children with DLD found typical N1 or P2 responses to auditory stimuli (Courchesne et al., 1989; Marler et al., 2002; Mason and Mellor, 1984; Ors et al., 2002; Włodarczyk et al., 2018; see review by Bailey & Snowling, 2003). It has been suggested that the inconsistencies in the literature may be due to the varying experimental paradigms (Bishop & McArthur, 2004). In addition, differences across studies in sample size, inclusion criteria, and age may all contribute to the discrepant findings. The maturation of AEPs involves several ongoing changes in morphology from birth to adolescence (Ponton et al., 2000). This makes it difficult for researchers to capture later emerging components such as N1 and P2 peaks in younger populations. One potential solution to this issue that has begun to be used in the literature involves the use of intra-class correlation (ICC), which allows for the estimation of the overall maturity of the AEP without having to identify and measure individual peaks within the waveform.

1.4 AEP Measurement using Intra-Class Correlation

Given the changes in the AEP waveform through development, a method of analysis that does not rely on identifying specific peaks is needed. This problem has been addressed using ICC in studies of cortical responses in school-aged children, adolescents, and adults (McArthur & Bishop, 2004; Bishop et al., 2007; Bishop et al., 2011; Kwok et al., 2018a, Kwok et al., 2018b). The ICC coefficient serves as an indication of how similar two waveforms are in shape and absolute voltage, and allows researchers to measure global resemblance rather than relying on single components. The ICC value itself ranges from 1.0 (identical) to -1.0 (opposite).

ICC allows researchers to specify a temporal window to be compared between two waveforms (as opposed to individual peaks). This is particularly useful for comparison of AEPs across age groups, since some components such as the N1 and P2 are not identifiable until later childhood (Ponton et al., 2002). Using this method, researchers can compare overall amplitude and morphology of AEP waveforms between a single participant and grand averages that represent the AEP of different age groups. The higher the degree of similarity between two waveforms, the higher the resultant ICC value. When comparing one child's AEP to a series of grand-averaged AEPs representing different chronological ages, the comparison that yields the highest ICC value can be considered to be a reliable estimate of the maturity of that child's auditory cortical response, that is, their auditory cortical "brain age".

In recent years, ICC has been employed in several studies of auditory cortical maturation. Given the large differences between children, adolescents, and adults in auditory cortical responses, Bishop et al. (2007) proposed that ICC could be a sensitive measure of variation both within and between age groups. While there was evidence of three separate developmental periods using ICC estimates of AEP maturity (5-12 years, 13-16 years, and adulthood), results showed no sensitivity to auditory maturation within these age groups. The authors suggested the lack of acuity was due to the wide age range, as group differences may have been masked by significant age-associated variation (Bishop et al., 2007). These limitations were addressed in later AEP studies that show increased sensitivity to maturation in a smaller age range of children aged 7 to 11 years old. Bishop et al. (2011) demonstrated that ICC analysis could be used to detect maturational differences in auditory processing in two-year age bands (7 -9 and 9-11 years), a sensitivity that was not evident in their previous study. Although the authors demonstrated that other methods of analysis show evidence of age-related changes in

AEPs (i.e., principal component analysis, time-frequency analysis, source localisation), ICC alone appeared to be the best measure of auditory cortical maturation (Bishop et al., 2011).

The use of a maturational index of auditory cortical processing derived using ICC is especially relevant for studies of children from a broad range of developmental abilities. This has been advantageous in studies of language development, given the proposed role of auditory processing (Bishop & McArthur, 2004). More recent evidence from studies of auditory maturation not only support the notion that ICC may be sensitive to chronological age in school-aged children, but also demonstrated the ability of the ICC-derived estimate of AEP maturity (*AEP-Age*) to predict unique variance in language ability. In an attempt to replicate and expand previous findings from Bishop et al. (2011), Kwok and colleagues (2018a) measured AEPs in response to simple tones in a sample of children aged 7-10 years old. Similar to Bishop et al. (2011), it was confirmed that ICC analyses were able to differentiate auditory maturity in two-year age bands (between 7 and 9 years, and 8 and 10 years), but also across a one-year age band between 8 and 9 years. Additionally, *AEP-Age* was found to be a significant predictor of language ability, explaining 7.8% of the variance in language ability beyond that explained by chronological age (Kwok et al., 2018a).

The relationship observed by Kwok et al (2018a) between *AEP-Age* and language ability is congruent with earlier evidence that individuals with language disorders exhibit immature auditory processing (Bishop et al., 2004). The association between language proficiency and *AEP-Age* was further explored by Kwok et al. (2018b) in a sample of school-aged children with DLD using ICC and their previously established normative AEP waveforms (Kwok et al., 2018a). Children who had below average language skills on the CELF-4 Core Language Score (Semel et al., 2003) were divided into two groups: those with mild DLD (11-16th percentile) and those with moderate-severe DLD (at or below the 10th percentile). Although these two groups did not significantly differ in chronological age, the authors found immature AEPs only in those with moderate-severe DLD. In other words, those with mild DLD had an *AEP-Age* similar to their chronological age but participants with moderate-severe DLD had *AEP-Age* estimates significantly younger than their own chronological age. *AEP-Age* accounted for 31% of the variation in language abilities in this sample of children with DLD (Kwok et al., 2018b).

Despite the growing evidence for a relationship between auditory cortical processing and language skills, a number of issues remain. First, the utility of *AEP-Age* has not yet been examined in younger populations. Although it has proven successful in predicting language variation in school-age children (Bishop et al., 2011, Kwok et al., 2018a), auditory maturation is a highly dynamic process, particularly in the early years. The relation between auditory cortical maturation and language proficiency during early language acquisition is not well understood. Second, the directionality of this influence remains unclear. To gain a better understanding of the role that auditory maturity plays in language development (or conversely, that language development plays in auditory maturity), there needs to be greater comprehension of the age-related changes in both language and auditory maturity during the early and extremely dynamic period of language acquisition occurring from 18 to 48 months.

1.5 The Present Work

The original goal of this thesis was to validate the use of the *AEP-Age* index in a cross-sectional study of children aged 18-48 months. However, due to the COVID-19 pandemic, data collection was not possible. Therefore, the remainder of this thesis will present two manuscripts in the format of Registered Reports (Stage 1) that have been prepared in anticipation of submission to a peer-reviewed scholarly journal. The Registered Report format of both of these chapters was chosen to align with that required by the *European Journal of Neuroscience* (EJN). Each of these manuscripts includes a preliminary abstract, background, methodology, and proposed analyses. Each of these studies will examine the relationship of *AEP-Age* to spoken language abilities in toddlers and will contribute foundational knowledge crucial to understanding how the maturation of auditory and spoken language skills interact in early childhood.

Chapter 2 of this thesis is a Stage 1 Manuscript entitled “Auditory evoked potential maturity and its relation to early language acquisition. A stage 1 registered report” that aims to address the following questions:

1. Are there significant differences in AEP maturity between 18, 24, 30, 26 and 48 months of age?
2. Can AEP maturity predict language ability beyond that which is explained by chronological age?

Chapter 3 is a Stage 1 Manuscript entitled “Longitudinal relations between auditory evoked potentials and language from 18 to 48 months in children with typical and atypical language acquisition. A stage 1 registered report” that aims to investigate the following questions:

1. Does AEP maturity at younger ages demonstrate a larger impact on language maturity at later ages or does earlier language maturity have a larger impact on later AEP maturity?
2. Do patterns of AEP maturation over time closely follow patterns on language maturation in children with different trajectories of language acquisition?

Chapter 2

2 Auditory evoked potential maturity and its relation to early language acquisition. A stage 1 registered report.

2.1 Abstract

A relationship between auditory evoked potentials (AEPs) and language proficiency has been previously demonstrated in children. *AEP-Age*, an index that uses intraclass correlation (ICC) to estimate the maturity of individual children's AEPs, has proven to be an effective tool to investigate this relationship in school-aged children. The objective of this proposed study is to assess the utility of *AEP-Age* to predict chronological age and language ability in 18–48-month-old children. AEPs in response to simple tones will be measured in 140 participants via recording of passive electroencephalography (EEG) activity as the participants watch a silent movie. A battery of standardized language tests will estimate participants' spoken language abilities. ICC will then be used to calculate an estimate of each child's cortical maturity. Results will indicate whether maturational differences in the neural processing of auditory information can be identified at particular developmental time points and will support future investigations of whether deviations at these time points may be related to difficulties in early language development.

2.2 Introduction

The development of spoken language includes acquisition of the grammar, vocabulary, and phonology (speech sounds) of the language of exposure. Acquisition of these skills happens with little conscious effort in childhood yet is dependent on environmental input (Brooks & Kempe, 2012). That is, linguistic and non-linguistic auditory input play a crucial role in the development of the understanding and use of spoken language (May-Mederake, 2012). Auditory processing supports the extraction of critical acoustic features in the speech signal and the establishment of the phonological system from a very young age (Benasich et al., 2006). This input, in turn, is used to build mental representations of sounds that ultimately influence and interact with other components of a child's growing language system (Tsao et al., 2004). Several studies conducted with both typically (Bishop et al., 2017) and atypically (Tallal, 2014; Archibald & Joanisse, 2012) developing children support the idea that processing of auditory information in the brain influences the characteristic development of spoken language. However, the extent to which this applies in the toddler years and its potential to function as a marker of the quality of language development has yet to be explored in detail.

Much like the development of language abilities, auditory cortical responses continue to mature through late adolescence or adulthood (Ponton et al., 2000, Sussman et al., 2008, Wunderlich et al., 2006). Auditory evoked potentials (AEPs) are often used as an index of auditory processing maturation and are of particular interest in research with young children because they can be measured using electroencephalography (EEG) without active responding by the participant. Of particular interest is a sequence of long-latency AEP components characterized by alternating positive and negative peaks, labelled P1-N1-P2-N2, typically occurring between 40 and 300 ms after the onset of an auditory stimulus (Ponton et al., 2000). Age-related changes to the amplitude and latency of the P1-N1-P2-N2 peaks parallel maturational changes in auditory cortical areas (Ponton et al., 2000), making this complex of AEP components ideal for studying developmental processes. While the amplitude and latency of these components can be indicative of auditory cortical maturation (Ponton et al., 2002, Wunderlich et al., 2006, McArthur & Bishop, 2002), strict reliance on measurement of these components when investigating changes across development can produce spurious results. This is because the components making up the P1-N1-P2-N2 complex demonstrate abrupt age-related changes (e.g., P1), don’t emerge until later in childhood (e.g., N1), or become adult-like by age 5 or earlier (e.g. P2; Ponton et al., 2002). By contrast, intraclass correlation (ICC) allows researchers to assess the global resemblance of two AEP waveforms without having to isolate particular AEP components (McArthur & Bishop, 2004). One advantage of ICC for developmental research is that it allows a participant’s AEP waveform to be compared to averaged waveforms computed for different age groups. The more similar a participant’s AEP waveform is to the averaged waveform representing a particular age group, the higher their ICC with that age group will be. Therefore, the age group with which a child’s individual AEP has the highest ICC will provide an age estimate of that participant’s auditory cortical maturation, or their *AEP-Age* (Bishop et al., 2011; Kwok et al., 2018a, 2018b). Thus, ICC allows researchers to use global age-related changes to the P1-N1-P2-N2 complex to track auditory cortical maturation, while avoiding the challenges associated with focusing on a single AEP component.

By comparing several methods of analysis (i.e., computing mean amplitudes, time frequency analysis, source localization, ICC), Bishop and colleagues (2011) concluded that ICC is the most effective method for distinguishing chronological age bands using AEPs in school-aged children (7 to 11 years old). Auditory cortical responses were initially collected from participants aged 7 and 9 years old, then again two years later, when the children were 9 and 11 years old, respectively. Participants were categorized as part of the *younger* group (those first measured at 7 years of age) or as part of the *older* group (those first measured at 9 years). Grand average AEP waveforms were calculated for ages 7, 9, and 11 years old. Using ICC, participants were assigned an *AEP-Age* age based on their individual cortical responses. Significant differences were found both within each age group and between the younger and the older groups, which suggests maturational differences in AEPs between the ages of 7 and 11 years. However, high levels of variance suggested that factors beyond chronological age affect AEPs (Bishop et al., 2011). With the goal of both replicating and expanding these findings, Kwok and colleagues (2018a) measured AEPs in response to simple tones in a cross-sectional sample of children aged 7, 8, 9, and 10 years old. Analyzing children in one-year bins, *AEP-Age* was able to differentiate children aged 7 and 8 years old from those who were 9 and 10 years old. Further, *AEP-Age* accounted for significant variance in language ability beyond that explained by chronological age but showed no relation to nonverbal IQ. Together these studies provide evidence that auditory cortical maturation is a process that displays significantly different AEP responses across 1- to 2-year age ranges during the school-age period of development. Further, these results suggest that changes in AEP responses across development can be predictive of a child’s language ability at certain ages, highlighting the relationship between auditory cortical maturation and spoken language development.

Despite the identified relationship between auditory cortical maturity and language abilities in older children, there is a paucity of research investigating the relationship between AEPs and language in infants and toddlers. Infants and toddlers are of particular interest due to the rapid language acquisition that occurs during these developmental periods. In the first year of life, infants have limited understanding of their language, but by soon after their first birthday, they show increasing comprehension and begin to produce many words on their own. By 24 months, many toddlers can produce short phrases and by 30 months, they begin to use spatial, emotional, and temporal utterances (Morse & Cangelosi, 2017). Even toddlers as young as 36 months are beginning to follow some basic rules of grammar and sentence structure (Zardini, 2006). Several studies, including those of children as young as 2 months old, provide evidence that the cortical skills and acoustic abilities necessary for language perception are in place at a very young age (Aslin, 1989; Irwin et al., 1985; Jensen & Neff, 1993). While infant AEPs have been used to successfully predict later language abilities (Choudhury & Benasich, 2011), the predictive variables were measured using individual components identifiable in infancy. By contrast, *AEP-Age* accounts for the entire waveform morphology and has the potential to be measured across ages. Given its efficacy in the investigation of language proficiency and cortical maturity in school-aged children, the expansion of the *AEP-Age* index to the early years is the next logical step.

The objectives of this study are to (a) evaluate whether ICC is a reliable method for capturing developmental changes in AEPs between 18 to 48 months, and (b) examine the relationship between auditory cortical maturation estimated using *AEP-Age* and spoken language development. Based on the significant changes that occur between 18, 24, 30, 36, and 48 months in language skills, we predict that there will be significant differences in AEP maturity between each of these age points. In addition, we predict that levels of AEP maturity will predict individual variation in language abilities beyond what is explained by chronological age. This study will provide valuable knowledge about the underlying contributions of and significant changes in AEPs at young ages, and will expand on our knowledge of the relation between the development of basic perceptual skills such as auditory processing and more complex cognitive processes such as language.

2.3 Methods

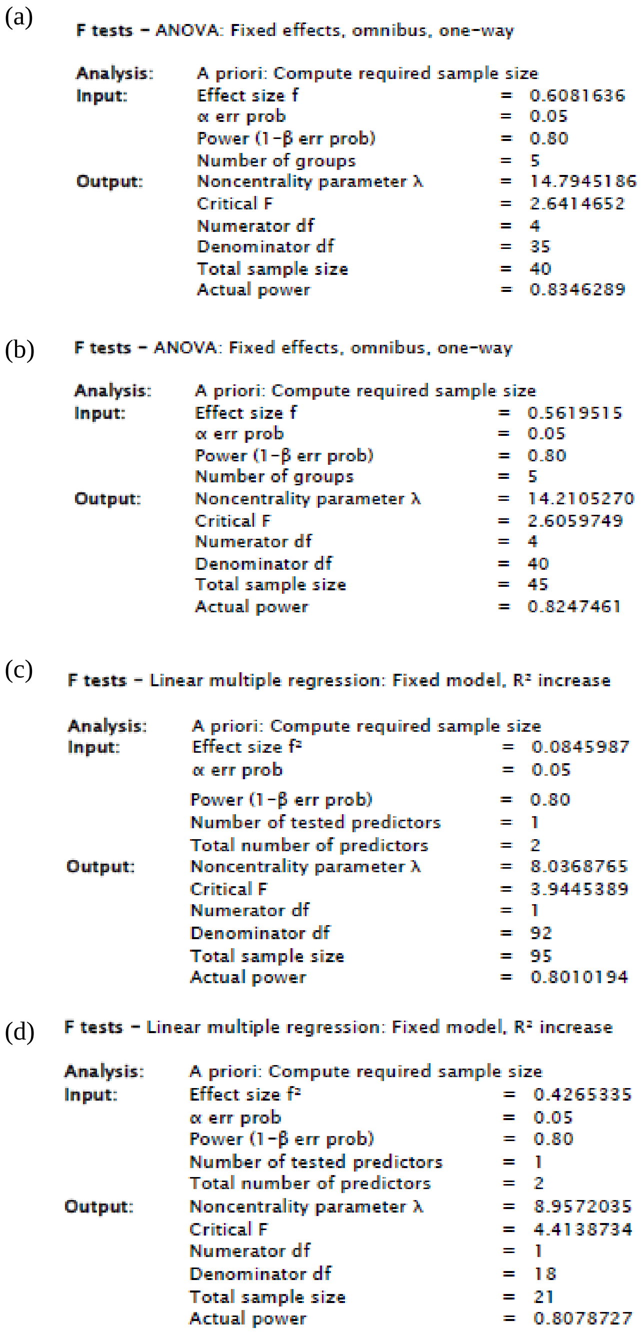
2.3.1 Participants

A total of 140 children with typical development and normal hearing will participate in this study, specifically, 20 children in each of the following age groups: 12, 18, 24, 30, 36, 48, and 60 months. Participants will be recruited from a variety of sources including Western University's Psychology Developmental Participant Pool, Western University's OurBrainsCAN Participant Pool, Western University's childcare centres, community advertisement, and word of mouth. For the purposes of this study, children will be recruited from English-speaking homes and be neurologically healthy with no developmental concerns by parent report. To be included, children must (a) pass a hearing screening (see *Measures*) b) meet age-appropriate developmental milestones on the LookSee checklist (previously known as the Nipissing District Developmental Screener; Dahinten et al., 2004), and c) have no known neurological impairments by parent report. Caregivers will be provided $20 to partially compensate them for their time and children will be provided with a small toy valued under $5 at the end of their participation. Western University's Health Sciences Research Ethics Board approved this study (see Appendix A), which will be undertaken with the written consent of each child's parent or guardian.

2.3.2 Sample size justification

For grand average computations for each age group, including more participants in each age band results in reduced high-frequency noise and more clearly defined peaks. Based on similar work in our and other labs, at least 15 participants per age band is sufficient for a clear grand average auditory ERP. As described in further detail in the Data Analysis section, the 12- and 60-month age groups will only be used for generating grand averaged waveforms to use in determining the *AEP-Age* for each child aged 18-48 months. Only those aged 18-48 months will be included in the statistical analyses.

To estimate sample size for one-way ANOVA of differences in *AEP-Age* across the 5 age groups, we calculated power based on Kwok et al. (2018a) for both the 9-channel and 5-channel analyses (see Figure 1, panels a and b), which estimated a total



(a)

```
F tests - ANOVA: Fixed effects, omnibus, one-way

Analysis:   A priori: Compute required sample size
Input:      Effect size f                    =  0.6081636
            α err prob                       =  0.05
            Power (1-β err prob)             =  0.80
            Number of groups                 =  5
Output:     Noncentrality parameter λ        =  14.7945186
            Critical F                       =  2.6414652
            Numerator df                     =  4
            Denominator df                   =  35
            Total sample size                =  40
            Actual power                     =  0.8346289
```

(b)

```
F tests - ANOVA: Fixed effects, omnibus, one-way

Analysis:   A priori: Compute required sample size
Input:      Effect size f                    =  0.5619515
            α err prob                       =  0.05
            Power (1-β err prob)             =  0.80
            Number of groups                 =  5
Output:     Noncentrality parameter λ        =  14.2105270
            Critical F                       =  2.6059749
            Numerator df                     =  4
            Denominator df                   =  40
            Total sample size                =  45
            Actual power                     =  0.8247461
```

(c)

```
F tests - Linear multiple regression: Fixed model, R² increase

Analysis:   A priori: Compute required sample size
Input:      Effect size f²                   =  0.0845987
            α err prob                       =  0.05
            Power (1-β err prob)             =  0.80
            Number of tested predictors      =  1
            Total number of predictors       =  2
Output:     Noncentrality parameter λ        =  8.0368765
            Critical F                       =  3.9445389
            Numerator df                     =  1
            Denominator df                   =  92
            Total sample size                =  95
            Actual power                     =  0.8010194
```

(d)

```
F tests - Linear multiple regression: Fixed model, R² increase

Analysis:   A priori: Compute required sample size
Input:      Effect size f²                   =  0.4265335
            α err prob                       =  0.05
            Power (1-β err prob)             =  0.80
            Number of tested predictors      =  1
            Total number of predictors       =  2
Output:     Noncentrality parameter λ        =  8.9572035
            Critical F                       =  4.4138734
            Numerator df                     =  1
            Denominator df                   =  18
            Total sample size                =  21
            Actual power                     =  0.8078727
```

Figure 1. A priori power analyses to estimate sample size. Screenshots from G*Power analyses for one-way ANOVA of 5 age groups by (a) 9 channels and (b) 5 channels, both based on effect size estimates from Kwok et al. (2018a), and hierarchical regression analysis with language ability as the independent variable, *AEP-Age* as the dependent variable, and chronological age as covariate based on effect sizes from (c) Kwok et al. (2018a) and (d) Kwok et al. (2018b).

sample size requirement of *N*=40-45, leading to a minimum requirement of *n*=9 per group. For a hierarchical regression examining the R^2 increase of *AEP-Age* predicting language functioning over and above chronological age, we estimated a total sample size requirement based on Kwok et al. (2018a) and Kwok et al. (2018b) regression analyses, which led to estimates of *N*=95 and *N*=21, respectively (see Figure 1, panels c and d). Therefore, a minimum of *n*=19 is required per group.

2.3.3 Procedure

Participants will be invited to attend a single, 1-2 hour visit to the university lab. During this time, AEPs will be collected using a 128-channel Electrical Geodesics system (Electrical Geodesics, Eugene, OR, USA). While seated alone or in their parent's lap (dependent on age) and watching a silent movie, participants will be presented with 225 repetitions of a 50 ms, 490 Hz tone over a period of roughly 5 minutes. Tones were digitized at a 41.1 kHz sampling rate using PRAAT software (Boersma & Weenink, 2011), with a 10 ms onset/offset ramp. The auditory stimuli will be controlled and played using E-Prime software (Psychology Software Tool Inc., Pittsburgh, PA), and presented with a jittered interstimulus rate in 100 ms intervals between 1000 and 1400 ms. Participants will be presented with the auditory stimuli in a comfortable sound field. A reverberant sound field has been previously calibrated, using a Tanoy I5 AW speaker, with placement of the participant 1 metre from the speaker and at least 0.6 metres from all walls. To ensure that auditory stimuli are presented at a consistent level, a sound level meter will be used prior to each participant to measure and achieve a peak-to-peak equivalent between 68 and 69 dbC SPL.

Upon completion of EEG acquisition, participants in the age groups between 18 and 48 months will participate in language assessment. Participants in the 12- and 60-month age groups will not complete language assessments because they are only being included for the purposes of establishing normative grand-averaged AEPs for these two age bands (see *Data Analysis* for future explanation). Participants aged 18-48 months will be administered the *Preschool Language Scale-5* (Zimmerman et al., 2011) in addition to other spoken language tests, dependent on age (see Table 1). The inclusion of additional language tests will help refine the investigation of *AEP-Age* and language. By administering tests of phonology, grammar, and vocabulary, it could be determined whether the potential relation between AEPs and language proficiency is more broad, or rather, specific to certain components of language (i.e., receptive/expressive language or phonology/grammar/vocabulary).

Table 1. Standardized Measures of Phonology, Vocabulary, and Grammar

Component	**18 mos**	**24 mos**	**30 mos**	**36 mos**	**48 mos**
Phonology	-	Goldman Fristoe Test of Articulation 3 -Sounds-in-Words subtest*			
Vocabulary	*MacArthur-Bates Communicative Development Inventories* - Words Produced subtest**		*Clinical Evaluations of Language Fundamentals Preschool, 3rd edition* - Basic Concepts & Expressive Vocabulary subtests***		
Grammar	*MacArthur-Bates Communicative Development Inventories* - Word Forms subtest**		*Clinical Evaluations of Language Fundamentals Preschool, 3rd edition* - Sentence Comprehension & Word Structure subtests***		

*Goldman & Fristoe (2015), **Fenson et al. (2007), ***(Wiig et al. (2020)

2.3.4 Measures

Hearing screening. To ensure that participants have normal hearing, a screening will be completed at the beginning of the visit. The assessment method will vary based on participant age and ability. Children aged 12, 18, and 24 months will undergo automated distortion-product otoacoustic emission (DPOAE) testing in both ears using the Madsen Accuscreen DP 5. As per the protocol used in the provincial infant hearing detection and intervention program, a *refer* result is indicated if the DPOAE signal-to-noise ratio is less than 8 dB on two or more frequencies. Re-screening of an ear for which there was a refer result is permitted up to a maximum of two times. For the remaining age groups, tones will be played through a Tanoy I5 AW speaker sound field in conformity with the Hughson-Westlake procedure (Valente, 2009). This procedure involves testing the child's perception of the frequencies 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz at multiple volume levels. Presentation will begin at 30 dB HL at each frequency and moves in a stepwise direction down 10 dB and up 5 dB. Those who are 30 and 36 months of age will undergo visual reinforcement audiometry (VRA). Reinforcement toys will be positioned at 90 degrees on either side of the child. With this procedure, the toys will light up as a reward when a child correctly detects a tone by turning their head towards the audio speaker it originated from. Children aged 48 and 60 months will participate in conditioned play audiometry (CPA), where they will be given a bucket of toys or a puzzle and trained to drop or insert a piece in response to detecting a tone. The goal of the VRA and CPA screening is to ensure that participants are able to detect all frequencies when presented at 25 dB HL. Should a child receive a final result of refer on DPOAE or fail to detect all frequencies at 25 dB HL on VRA and CPA, they will be excluded from further participation and parents will be counselled about follow-up assessment of hearing.

LookSee. To confirm typical development, a LookSee checklist will be completed by the caregiver present at the time of testing. LookSee checklists are available for 13 different key stages of development, 7 of which will be used in this study (12 months, 18 months, 2 years, 30 months, 3 years, 4 years, and 5 years; Cairney et al, 2016). Because the LookSee checklist uses milestones that children should have mastered by a specific age, it is recommended to use the earlier checklist if the child falls between two ages. A *two-flag* rule (i.e., two skills on the checklist not mastered) will be used as criterion for exclusion, as this has been shown to provide higher levels of sensitivity and specificity in comparison to a one-flag rule (Currie et al., 2012).

Preschool Language Scale-5 (PLS-5; Zimmerman et al., 2011*)*. The PLS-5 examines a range of language skills using play-based activities to provide a comprehensive developmental assessment of oral language abilities. It will be administered to all participants aged 18 to 48 months, and will generate standardized scores (*M* = 100, *SD* = 10) reflecting children's overall, receptive, and expressive language abilities (Total Language Score, Auditory Comprehension Score, Expressive Communication Score, respectively) relative to same-age peers.

Goldman Fristoe Test of Articulation-3 (GFTA-3; Goldman & Fristoe, 2015). The Sounds-in-words subtest will be administered to participants between the ages of 24 and

48 months as a measure of expressive phonological development. During this test, children are asked to name pictures and the accuracy of their production of consonants and consonant clusters in single words is recorded. This will generate a Sounds-in-words standard score (*M* = 100, *SD* = 10) that reflects the child's speech sound production abilities relative to peers of the same age and sex.

MacArthur Bates Communicative Development Inventories (CDI; Fenson et al., 2011*).* The CDI Words and Sentences (Toddler) form is a parent-report instrument designed to examine children's developing language abilities. Caregivers of children aged 18, 24 and 30 months will be asked to complete two sections of the form. The Vocabulary Checklist asks caregivers to mark words they have heard their child use from a list of 680 words common to children's early vocabularies. The Word Forms section ask caregivers to mark words they have heard their children use from a list of 25 irregular plural nouns and irregular past tense verbs (e.g., mice, ate). Responses will generate percentile ranks for Words Produced and Words Forms, which respectively estimate children's expressive vocabulary and expressive grammar relative to same-age peers.

Clinical Evaluation of Language Fundamentals- Preschool, 3rd edition (CELF-P3; Wiig et al., 2020*).* Four subtests of the *CELF-P3* will be administered as measures of early vocabulary and grammar development in participants aged 36 and 48 months. The Basic Concepts subtest estimates receptive vocabulary by asking children to point to the picture of a word spoken by the examiner from a choice of three. In the Expressive Vocabulary subtest, children are asked to name pictures that target verbs and nouns. The Sentence Comprehension subtest estimates receptive grammar by asking the child to choose the picture that best matches a spoken sentence from a choice of four. The Word Structure subtest estimates expressive grammar via a cloze task paradigm in which the child is asked to provide the missing word or phrase at the end of a sentence that describes a picture, where the missing element is a grammatical construction. Each subtest generates a scaled score (*M* = 10, *SD* = 3) that estimates the child's ability in the target areas of language relative to same-aged peers.

2.3.5 EEG Acquisition and Processing

EEG data will be recorded using a 128-channel HydroCel Geodesic Sensor Net and amplified with a Net Amps 400 system. Data will be bandpass filtered (0.1-100 Hz), notch filtered (60 Hz) and digitized (16-bit precision) at 250 samples per second. Post-collection, data will be passed through an offline filter using 2 to 30 Hz finite impulse response (FIR) filter. Electrode impedances will be adjusted with a goal to be maintained below 50 kΩ (Ferree et al., 2001). Channels with impedances above 75 kΩ will be excluded from further analyses. Average referenced data will be segmented into 1200 ms epochs that are time-locked to the presentation of the tone, which include a 200 ms baseline. Trials with sudden spikes in electrical energy of 50 μV or greater (i.e., artifacts such as eye movement, blinks, etc.) will be identified and removed so that only those trials that are artifact-free will be used in creating the averaged AEP waveform for each individual. A one-way (1 x 7) ANOVA will be run to ensure there are no significant differences in the number of accepted trials across groups. These AEPs will be used to create 7 grand average, baseline-corrected AEP waveforms, one for each age group (12, 18, 24, 20, 36, 48, and 60 months).

2.4 Analyses

2.4.1 Calculating AEP-Age

At our sampling rate of 250 Hz, 125 data points will be acquired for each 500 ms AEP waveform (500 ms x 250 Hz sampling rate = 125 data points). Using a customized script in MATLAB (see Appendix B), the 125 data points for each participant will be then compared to the 125 data points comprising each of the 7 AEP grand average waveforms using the following formula:

$(\text{Mean Square}_{\text{between}} - \text{Mean Square}_{\text{within}}) / (\text{Mean Square}_{\text{between}} + \text{Mean Square}_{\text{within}})$, where

1 $\text{Mean Square}_{\text{between}} = \{[\Sigma X^2 + \Sigma Y^2 + 2 \times \Sigma(X.Y)] / 2 - (\Sigma X + \Sigma Y)^2 / 2N\}/(N - 1)$,

2 $\text{Mean Square}_{\text{within}} = [0.5 \times (\Sigma X^2 + \Sigma Y^2) \_ \Sigma(X.Y)]/N$,

3 N = number of EEG data points entered into the ICC calculation

4 X, Y = the two AEP waveforms under comparison.

The resulting ICC value represents an estimate of the reliability between the participant’s AEP waveform and the grand average waveform, which reflects the similarity of the two waveforms. The age comparison that yields the highest ICC value will be assigned as the participant’s age equivalent for that channel. In order to avoid inflating ICC values, each participant’s AEP waveform will be removed from their own age groups’ grand average AEP prior to ICC calculations. For each participant analyzed, the age equivalent assigned at each channel will then be averaged for an overall *AEP-Age*, which is an estimate of AEP maturity across all viable channels. See Figure 2 for an example.

As per Kwok et al., (2018a) two different *AEP-Age* estimates will be calculated for each child. The first *AEP-Age* will be derived from nine electrodes (F3, Fz, F4, C3, Cz, C4, T7, Pz, and T8) to capture responses across frontal, temporal, and parietal, as well as left, right, and central electrodes. The second estimate of auditory maturity will be a refined *AEP-Age* (*AEP-AgeR*) that is an average of only those channels that best reflect age-related changes. Previous work in school-aged children (7-10 years old) suggested that only 5 of the 9 channels (F3, F4, C3, Cz and T7) were correlated with chronological age (Kwok et al., 2018a). This is consistent with previous observations that AEPs are maximal at fronto-central and temporal electrodes (Bishop et al., 2011). Subsequent regression analyses indicated that *AEP-Age* based on 9 channels was not a significant predictor of language ability but that their *AEP-AgeR* based on 5 channels was (Kwok et al., 2018a). The current study focuses on a younger population; therefore, a new *AEP-AgeR* will be generated. First, one-tailed correlational analysis between age equivalents (selected based on highest ICC) and chronological age at each of the original nine channels will be conducted, using Bonferroni correction to reduce the risk of type I error ($\alpha = 0.05/9 = 0.0055$). Only those channels that show a significant ($p < 0.0055$) correlation with chronological age would then be selected to be averaged together to create the refined *AEP-Age* estimate, *AEP-AgeR*, for each child.

Note that *AEP-Age* and *AEP-AgeR* will not be calculated for children in the 12- and 60-month age groups. Their AEPs will be collected solely for the purpose of having 12-month and 60-month-old grand average reference AEPs for comparison purposes. By

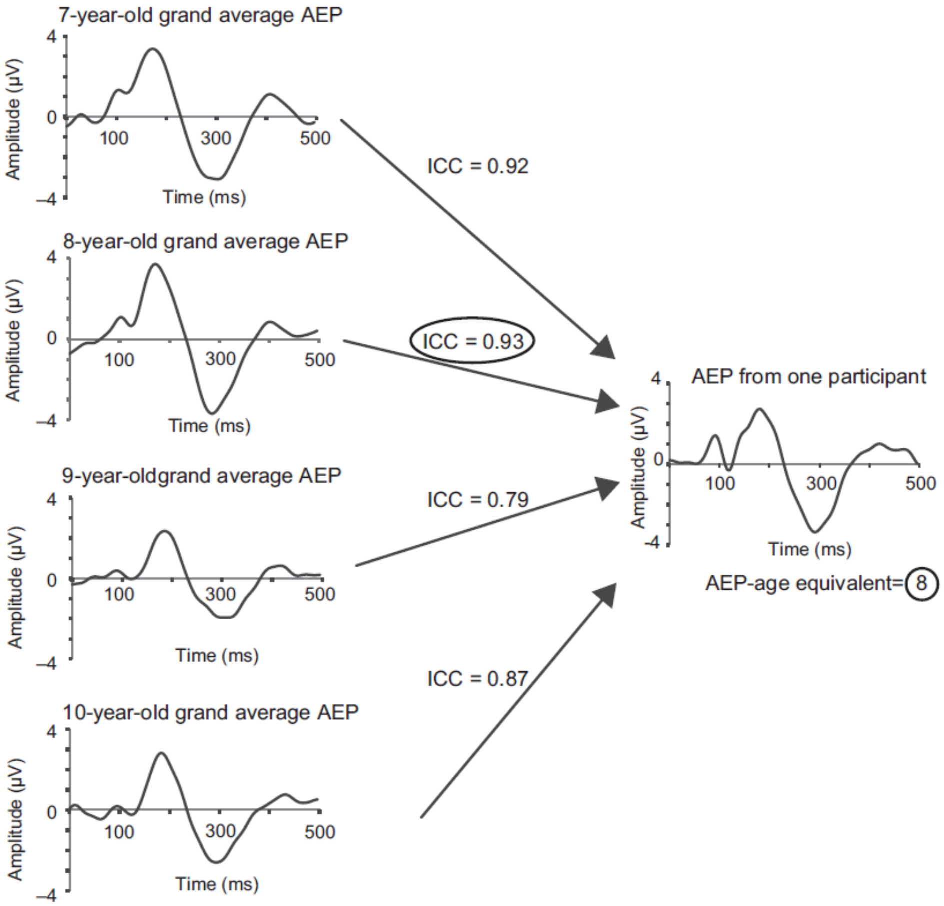


Figure 2. Example of ICC Calculations. ICC calculations in school-aged children from Kwok et al (2018a). The average AEP waveform from all electrodes of a single participant are compared to the AEP average waveform of each of the four normative age groups. The resultant ICC calculation with the highest value (in this instance, the 8-year-old grand average) is taken as the *AEP-Age* equivalent for that channel. This process is repeated for all channels and averaged to assign *AEP-Age* for that participant.

having grand average AEPs representing chronological ages both younger than and older than the youngest (18-month) and oldest (48-month) participant groups in the sample, it provides the potential to identify immaturity in the youngest children (e.g., a 18-month-old's AEP best correlating with that of 12-month old children) or advanced development in the oldest children (e.g., a 48-month-old's AEP waveform best correlating with that of children aged 60 months), thereby not artificially deflating or inflating their *AEP-Age* estimate.

2.4.2 Statistical analyses

To determine whether there are significant differences in *AEP-Age* between children aged 18, 24, 30, 36, and 48 months, one-way ANOVAs will be calculated to evaluate whether there is a significant effect of group. Should there be significant group effects, Tukey's HSD post hoc comparisons will be conducted to evaluate which specific ages significantly differ from each other. Further, to establish how much of the variance in chronological age is explained by *AEP-Age*, linear regression analysis will be conducted in which *AEP-Age* will serve as the predictor and chronological age is the dependent (criterion) variable. Should the model prove significant ($p < 0.05$), the coefficient of determination (R^2) will indicate the proportion of variance in chronological age that is explained by maturity of children's AEPs.

To investigate whether AEP maturity is a predictor of language beyond the influence of chronological age, regression analyses will be conducted. Specifically, they will be used to evaluate the ability of *AEP-Age* (and *AEP-AgeR*) to predict both chronological age and children's overall language ability relative to their same-age peers. A hierarchical regression will be conducted with PLS-5 Total Language Score as the dependent variable and both chronological age and *AEP-Age* as the predictors. Chronological age will be entered into the first step and *AEP-Age* entered into the second step to determine whether *AEP-Age* can account for variance in Total Language scores over and above chronological age. This analysis will be repeated using *AEP-AgeR*.

There is also the possibility that *AEP-Age* is more closely tied to certain aspects of language development relative to others. Some evidence suggests that auditory cortical maturity may be particularly linked to receptive language ability (Bishop et al., 2007; Oram Cardy et al., 2008). For example, Kwok et al. (2018b) found *AEP-Age* predicted 20% of the variance in receptive language ability but did not predict expressive language in school-aged children with DLD. To account for this potential association, the two hierarchical regressions using PLS-5 Total Language Score will be repeated using (a) PLS-5 Auditory Comprehension Score and (b) PLS-5 Expressive Communication Score as the dependent variable, and both chronological age and either *AEP-Age* or *AEP-AgeR* (whichever resulted in the strongest model in the original analysis) as the two predictors.

To assess which domains of early language development (phonology, vocabulary, grammar) correlate with AEP maturity, several subtests will be employed. Using the strongest *AEP-Age* predictor (*AEP-Age* or *AEP-AgeR*), correlations will be run with each of the following measures as the dependent variable, acknowledging that sample size will differ depending on how many of the age groups were administered each measure:

Phonology

1. GFTA-3 Sound-in-words (*N*=80)

Vocabulary

2. CDI Words Produced (N=60)
3. Combined scaled scores of the CELF-P3 Basic Concepts and Expressive Vocabulary subtests (N=40)

Grammar

4. CDI Word Forms (N=60)
5. Combined scaled scores of the CELF-P3 Sentence Comprehension and Word Structure subtests (N=40)

To reduce type 1 error associated with these 5 comparisons, Bonferroni correction will be used ($\alpha = 0.05/5 = 0.01$). Early domains of language that significantly correlate ($p < 0.01$) with the *AEP-Age* variable will be used to drive further exploratory regression analyses. The objective of the exploratory analyses is to identify and evaluate whether the inclusion of certain domains of language may improve the regression model completed using PLS-5 Total Language Score. Given that the development of this model is data-driven, it will not be possible to identify the dependent variables until data collection and the correlational analysis have been completed.

Chapter 3

3 Longitudinal relations between auditory evoked potential and language from 18 to 48 months in children with typical and atypical acquisition. A stage 1 registered report

3.1 Abstract

Despite evidence for a relationship between auditory cortical maturity and language proficiency (Bishop et al., 2007, Ponton et al., 2000), the direction of this influence remains unclear. *AEP-Age,* an index that uses intraclass correlation to compare individual children's auditory evoked potentials (AEPs) with the grand-averaged AEPs of different age groups, has proven successful in estimating auditory cortical maturity in school-aged children. The objective of the current study is to investigate the relationship between *AEP-Age* and language ability longitudinally throughout early development in children with three different trajectories (children with typical development, late talkers who resolve, and children with persistent developmental language disorder), in order to better understand whether maturation of auditory cortical processing contributes to or rather is influenced by maturation of language. AEPs in response to simple tones and spoken language ability will be measured in 90 18-month-old children and again when they are 24, 30, 36, and 48 months. By comparing changes in *AEP-Age* and language ability over time in children with typical and atypical language development, we will provide insight into the direction of influence of auditory cortical processing and language proficiency and determine whether *AEP-Age* has the potential to predict which children will grow out of their early language delays and which will not.

3.2 Introduction

In order to use and understand a spoken language, an individual must have comprehension of the sounds (phonology) and words used in that language (lexical knowledge), as well as how to put those words together (grammatical knowledge) (Bamberg, 2011). Mastery of these skills begins during infancy, and exposure to auditory input is essential to the development of the understanding and use of spoken language

(May-Mederake, 2012). Early speech perception abilities, such as an infant's ability to rapidly extract critical features from a speech signal, have been proposed to support the establishment of the phonological system, where mental representations of the sound units of the language are formed (Tsao et al., 2004; Benasich et al., 2006). A growing body of literature suggests that impaired auditory processing may be an underlying contributor to impaired language and reading development (Bishop et al., 1999; Godfrey et al., 1981; Kraus et al., 1996; McAnally & Stein, 1997; Nagarajan et al., 1999; Snowling et al., 1986; Stark & Heinz, 1996a, 1996b; Werker & Tees, 1987). Studies have suggested that even in infancy, cortical responses to sound differ between those who do versus do not have a family history of language impairment and appear to be related to later language abilities (Choudhury & Benasich, 2011). Together, these studies have supported the proposal that auditory processing plays a critical role in supporting spoken language acquisition.

Auditory evoked potentials (AEPs), or their magnetic equivalent, auditory evoked fields, are often measured to estimate auditory cortical maturation (Bishop et al., 2007, Yoshimura et al., 2014, Kwok et al., 2018a). AEPs are discrete waveforms elicited in response to an auditory stimulus that are collected using electroencephalography (EEG). Auditory stimuli typically elicit a characteristic complex of positive and negative peaks labelled P1-N1-P2-N2 that occur between 50 and 300 ms after the onset of the stimulus. It has been established and widely accepted that there are significant changes in the AEP complex with age and that these changes reflect auditory cortical maturation (Ponton et al., 2000, Wunderlich et al. 2006, Sussman et al., 2008). Ponton et al. (2000) demonstrated a range of significant maturational changes in the AEP complex from 5 to 20 years old. Perhaps the most noteworthy maturational changes occur in the amplitude of the P1 and N1 peaks. Generally, the P1 peak decreases and the N1 peak increases with chronological age (Tonnquist et al., 1995). Decreased latency of the P1 and N1 peaks with age has been shown to be a strong indicator of cortical maturation (Sharma et al., 1997, Ponton et al., 2000, Lippé et al., 2009), and continues to shorten until reaching adult levels around 14-16 years of age (Polich et al., 1985; Ponton et al., 2002) This is likely a result of axonal maturation and increased myelination in the auditory cortex (Eggermont & Ponton, 2003).

Many of the studies to date that have examined the relationship between auditory cortical processing and language development have focused on the amplitude and latency of individual components in the P1-N1-P2-N2 complex (Ponton et al., 2000, Sussman et al., 2008, Wunderlich et al., 2006). For example, Oram Cardy et al. (2008) reported latencies of the M50 (the magnetic equivalent of the P1) predicted language ability and impairment, and the amplitude of a component of the N1 peak (N1b) has been showed to be significantly decreased in individuals with ASD (Bruneau et al., 1999, Seri et al., 1999). Molfese et al. (1999) reported that delayed N2 latency in the left hemisphere was linked to lower verbal intelligence in 8-year-old children. Despite these useful contributions, reliance in the measurement of individual peaks has the potential to provide an imprecise estimate of auditory cortical maturity because individual components are not always identifiable at different ages in earlier childhood. For example, the N1 peak often does not emerge until later in development while other peaks (e.g., P2) become adult-like by age 5 or earlier (Ponton et al., 2002). AEP measurement is complicated by significant developmental changes in the topography and morphology for various evoked components (Wunderlich et al., 2006). As a result, standard component peak detection techniques may return incorrect values when components are missing, delayed, or of opposing polarity across children (McArthur & Bishop, 2004). These issues can make it particularly difficult to compare the AEPs of children across different ages or stages of development, especially in the early years.

To circumvent issues with measuring individual AEP components, intraclass correlation (ICC) has emerged as novel method for estimating AEP maturity. ICC compares an individual participant's averaged AEP waveform to the grand-averaged AEP waveforms for different age groups. The resultant ICC value reflects the level of similarity between the individual's AEP waveform and that of the age group of interest. Therefore, the age group comparison that yields the highest ICC value is deemed to be that child's AEP age-equivalent or *AEP-Age*, providing an estimate of their auditory cortical maturation (Bishop et al., 2011; Kwok et al., 2018a, 2018b). ICC has the benefit of being sensitive to changes in amplitude and waveform shape, unlike the conceptually similar Pearson's correlation coefficient.

Applying ICC to the analysis of AEPs has been effective for examining auditory cortical maturation in children with typical development. Originally, Bishop et al. (2007) used the ICC method to characterize cortical maturation in a sample of 5- to 30-year-olds. In this study, differences in *AEP-Age* emerged across three maturational groups: 5-12 years, 13-16 years, and adulthood. Using a larger sample and smaller age range, Bishop and colleagues (2011) demonstrated that the ICC calculation is sensitive to developmental changes between 7-11 years. After estimating *AEP-Age* for children in groups aged 7, 9, and 11 years, they demonstrated a significant group effect, with *AEP-Age* increasing at each age. In addition, *AEP-Age* accounted for a significant portion of the variance in chronological age in this sample. Kwok et al. (2018a) also used the ICC approach to discern developmental cortical changes between groups of children 7, 8, 9, and 10 years old. In this study, *AEP-Age* was significantly higher in children aged 9-10 years compared to those aged 7-8 years. In addition, children's language abilities were not only predicted by their chronological age, but also their *AEP-Age* (Kwok et al., 2018a). Researchers have also found that the AEPs of children with DLD are more like those of younger children (Bishop et al. 2004, Kwok et al. 2018b), providing further evidence that auditory cortical maturity, indexed by *AEP-Age*, may reflect not only chronological age but also language development.

Although evidence supports a relation between auditory cortical maturation and language development, what remains unknown is the direction of influence. Current theories suggest that early auditory maturation contributes to spoken language development (Benasich et al., 2006; Tallal, 2004). While these two processes have been clearly linked in prior research, this assumed direction of influence between them is in fact unconfirmed. Prior longitudinal studies have not considered alternate or more sophisticated directions of this relation. In these studies, the possibility remains that (a) early AEPs were already influenced by the extent of language acquisition at the time that they were measured, (b) a stronger predictive relation would have been found between earlier language and later AEPs, or c) the influence is better viewed as bidirectional. Measuring both AEP and language maturity at multiple time points during a dynamic period of language acquisition (18-48 months) would enable examination of associations between these processes over time, and, of key interest here, the direction of influence between them. Given the success of previous research using the *AEP-Age* index to examine auditory cortical maturation and its relation to language abilities, it is an ideal metric to investigate infants and toddlers longitudinally. Because *AEP-Age* can be acquired (a) with minimal participation, (b) over a short time period, (c) in response to a simple acoustic stimulus, and (d) via an analysis approach that does not rely on the identification of individual AEP components, it is ideally suited to the age range of interest.

Most toddlers meet expected language milestones such as speaking their first words by 18 months and producing two-word phrases by 24 months. However, up to 20% of children present with delayed onset of these spoken language milestones between 18-35 months (Reilly et al., 2018). For most, these difficulties resolve by 4 years old (*late bloomers*). However, roughly one quarter of children who display early difficulties will continue to show persistent and oftentimes lifelong impairments in language proficiency, that is, will go on to be diagnosed with DLD (Duff et al., 2015; Reilly et al., 2018). Both late bloomers and those with DLD can have similar presentation in the first few years of life including delayed onset of and fewer first words and fewer two-word combinations (Reilly et al., 2018). Comparing auditory cortical maturation with language skills in the three different groups of children (typical development, late bloomers, DLD) while they develop along these different trajectories of language acquisition has the potential to provide significant insight into the direction of influence between these two processes.

The objective of this study is to measure the development of AEPs and language longitudinally to evaluate the directional influence between auditory cortical maturation and language proficiency over time during the early years. The study will follow children aged 18 months as they develop to 48 months of age, and will include children who proceed along three early language development trajectories: children with typical development (TD), children who are late-to-talk at 18 months but resolve by 48 months, that is, late bloomers (LB), and children with persistent difficulties beyond the late talking period, that is, children who meet criteria for DLD at 48 months. Based on the direction of influence assumed by current theory, we predict that early auditory cortical development will have a larger impact on language skill at later ages when compared to the influence of early language maturity on later auditory cortical maturity. Further, we predict that differences in AEP maturity over time will closely reflect patterns of language maturity in all three trajectories.

Determining the direction of influence matters. Until now, it has been assumed, but not demonstrated, that early cortical maturation has a greater influence on later language proficiency than early language skills on later auditory cortical maturity. Results of this study will increase understanding of whether auditory cortical maturation is a consequence of or contributor to language development, thus informing theory and the direction of future research. For example, if *AEP-Age* shows promise in predicting the trajectory of early language acquisition, future research could examine clinical translation into predicting which infants and toddlers are most at risk for later problems in language development.

3.3 Methods

3.3.1 Participants

This study will involve the participation of at least 30, 18-month-old children in each of the three language development trajectory groups (TD, LB, DLD). At the time of recruitment, participants can only be classified as meeting language milestones (TD) or being late-to-talk, with determination of assignment into the LB or DLD groups only possible by the end of the study at 48 months (see Procedure for further detail). In order to achieve the targeted sample size, after accounting for attrition and the possibility of over or under sampling participants in the LB and DLD groups, we anticipate recruiting and following at least 120 children, with at least 90 of these being children who are late-to-talk at 18 months. Recruitment will be achieved through resources such as Western University’s Psychology Developmental Participant Pool, Western University’s BrainsCAN Participant Pool, Western University’s childcare centres, community advertisement, and word of mouth. In addition, participants will be recruited from Western University’s tykeTALK, a regional service provider in the Ontario Preschool Speech and Language Program. The inclusion of clinic-referred children in addition to those reported to be late-to-talk in the community will support our efforts to oversample late talkers, given that only 20-25% of these children will later be diagnosed with DLD (Chilosi et al., 2019). To be included in this study, participants must come from English speaking homes and have an absence of (a) permanent childhood hearing loss, (b) neurological disorders, (c) genetic syndromes, and (d) craniofacial anomalies, as declared by parent report.

3.3.2 Procedure

Over the course of the study, children and their caregivers will be invited to visit the lab at 18, 24, 30, 36, and 48 months. At each visit, caregivers will be provided $20 to partially compensate them for their time and children will be provided with a small toy valued under $5 at the end of their participation. Western University's Health Sciences Research Ethics Board approved this study, which will be undertaken with the written consent of each child's parent or guardian.

To be included in the study, participants must demonstrate normal hearing. To ensure this, a screening will be completed at the beginning of each visit. The assessment method will vary based on participant age and ability. At 18 and 24 months, children will undergo distortion-product otoacoustic emissions (DPOAE) testing in both ears using the Madsen Accuscreen DP 5. As per the protocol used in the provincial infant hearing detection and intervention program, a *refer* result is indicated if the DPOAE signal-to-noise ratio is less than 8 dB on two or more frequencies. Re-screening of an ear for which there was a refer result is permitted up to a maximum of two times. Tones will be played through a Tanoy I5 AW speaker sound field in conformity with the Hughson-Westlake procedure (Valente, 2009). This procedure involves testing the child's perception of the frequencies 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz at multiple volume levels. Presentation will begin at 30 dB HL at each frequency and moves in a stepwise direction down 10 dB and up 5 dB. At 30 and 36 months of age, children will undergo visual reinforcement audiometry (VRA). Reinforcement toys are positioned at 90 degrees on either side of the child. With this procedure, the toys will light up as a reward when a child correctly detects a tone by turning their head towards the audio speaker it originated from. At 48 and 60 months, children will participate in conditioned play audiometry (CPA), where they will be given a bucket of toys or a puzzle and trained to drop or insert a piece in response to detecting a tone. The goal of this screening is to ensure that participants are able to detect all frequencies when presented at 25 dB HL. Should a child fail a screening, testing will not continue and parents will be counselled about follow-up assessment of hearing. Should the child's hearing loss be determined to be transient (e.g., related to middle ear infection) at follow-up with a health care practitioner, children will be invited to resume participation following resolution. If a permanent hearing loss is identified at follow-up hearing assessment, they will be excluded from further participation.

As a part of each visit, the child will be entertained with a silent animation while their AEPs are collected using a 128 channel Electrical Geodesics EEG system (Electrical Geodesics, Eugene, OR, USA). While seated alone or in their caregivers lap (age dependent) auditory stimuli will be played for roughly 5 minutes over a calibrated sound field in a soundproof booth via E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA). The auditory stimuli will consist of 225 repetitions of a 50 ms, 490 Hz tone with an interstimulus rate jittered in 100 ms intervals between 1000 and 1400 ms presented. Using PRAAT (Boersma & Weenink, 2011), tones have been digitized at a sampling rate of 41.1 kHz with a 10 ms onset/offset ramp. To ensure a standardized presentation, a Tanoy I5 AW speaker has been calibrated and built into part of a reverberant speech field in which the speaker remains at least 1 metre from all speakers and 0.6 metres from all walls. Prior to each participation, a sound level metre will be used to standardize a presentation volume with a peak-to-peak equivalent between 68 and 69 dbC SPL.

The second portion of the visit will include standardized assessment of overall language functioning using the *Preschool Language Scale, 5th edition* (PLS-5; Zimmerman et al., 2011) at all timepoints. The *PLS-5* Total Language Score will provide a standardized estimate of language abilities relative to same age peers at each age and will be related to *AEP-Age* in statistical analyses. At the first visit at 18 months, caregivers will be asked to complete the *Macarthur-Bates Communicative Development Inventory* (CDI) Words and Gestures form (Fenson et al., 2007). Children will be classified as being late-to-talk (with future potential to be assigned in either the LB or

DLD groups) if they receive a raw score of 10 or fewer on the CDI Words Produced subtest. At the last visit at 48 months, children who were late-to-talk at 18 months will be further classified as LB or DLD based on parent report on the *Children's Communication Checklist-2* (CCC-2; Bishop, 2003) and standardized behavioural testing with the *Clinical Evaluation of Language Fundamentals-Preschool, 3rd edition* (CELF-P3; Wiig et al., 2020). To be classified as having DLD, children must receive scores of -1 *SD* below the mean on the CCC-2 Language and the CELF-P3 Core Language domains.

3.3.3 EEG Acquisition and Processing

EEG data will be recorded from 128, average referenced, scalp electrodes from a HydroCel Geodesic Sensor Net and amplified with a Net Amps 400 system. Data will be bandpass filtered (0.1-100 Hz), notch filtered (60 Hz), and digitized (16-bit precision) at 250 samples per second. Electrode impedances will be adjusted and ideally maintained below 50 kΩ (Ferree et al., 2001). Post-collection, data will be passed through an offline filter using 2 to 30 Hz finite impulse response (FIR) filter. Data will be segmented into 1200 ms epochs that are time-locked to the presentation of the tone, with a 200 ms pre-stimulus baseline. Only those epochs that are artifact free (i.e., no sudden spikes in electrical energy of 50 µV or greater) will be used in creating the averaged AEP waveform for each child. A one-way (1 x 7) ANOVA will be used to ensure there are no significant differences in the number of accepted trials across time points.

3.4 Analyses

3.4.1 Calculating AEP-Age

Each child's auditory cortical maturity for each age will be quantified through an *AEP-Age* estimation. To calculate *AEP-Age*, the Fisher-transformed ICC statistic will be used to measure the similarity of each child's AEP grand average at each of the 9 electrodes (F3, Fz, F4, C3, Cz, C4, T7, Pz, and T8) from 0 to 500 ms post tone onset as compared to normative AEP grand averaged reference waveforms from an independent sample of children 12, 18, 24, 20, 36, 48 and 60 months of age (see Chapter 2). At our sampling rate of 250 Hz, 125 data points will be acquired for each 500 ms AEP waveform (500 ms x 250 Hz sampling rate = 125 data points). The 125 data points for each participant will then be compared to the 125 data points comprising each of the seven AEP grand average waveforms (from the Chapter 2 study) using the following formula:

$$(\text{Mean Square}_{\text{between}} - \text{Mean Square}_{\text{within}}) / (\text{Mean Square}_{\text{between}} + \text{Mean Square}_{\text{within}}),$$

where

1 $\text{Mean Square}_{\text{between}} = \{[\Sigma X^2 + \Sigma Y^2 + 2 \times \Sigma(X.Y)] / 2$

$- (\Sigma X + \Sigma Y)^2 / 2N\}/(N - 1),$

2 $\text{Mean Square}_{\text{within}} = [0.5 \times (\Sigma X^2 + \Sigma Y^2) \_ \Sigma(X.Y)]/N,$

3 N = number of EEG data points entered into the ICC calculation

and

4 X, Y = the two AEP waveforms under comparison.

The resulting ICC value represents an estimate of the reliability between the child’s AEP waveform and the normative grand average waveform, which reflects the similarity of the two waveforms. This calculation will then be repeated until each child’s AEP waveform at each electrode are compared to each of the normative AEP waveforms at the same electrode. The age corresponding to the normative waveform that yields the highest ICC coefficient will be deemed the child's *AEP-Age* for that electrode. For each participant, age equivalents assigned to acceptable channels are then averaged for an overall *AEP-Age*, a measure of cortical maturity across all viable EEG channels.

Two different *AEP-Age* estimates will be calculated for each participant. The first *AEP-Age* will be derived from nine electrodes (F3, Fz, F4, C3, Cz, C4, T7, Pz, and T8) to capture responses across frontal, temporal, and parietal, as well as left, right, and central electrodes. The second *AEP-Age* model will be a refined estimate of auditory cortical maturity (*AEP-AgeR*) that is an average of only those channels that best reflect age-related changes. Research in older children shows evidence that only 5 of the 9 channels

(F3, F4, C3, Cz and T7) were correlated with chronological age (Kwok et al., 2018a). Further regression analyses suggested that *AEP-Age* based on 9 channels was not a significant predictor of language ability, but that *AEP-AgeR* was (Kwok et al., 2018a). Given these findings, an *AEP-AgeR* will also be calculated for the current sample. Repeated measures correlational analysis between age equivalents (selected based on highest ICC) and chronological age at each of the original nine channels will be conducted. Bonferroni correction will be employed to reduce the risk of type I error ($\alpha = 0.05/9 = 0.0055$). Channels that show a significant ($p < 0.0055$) correlation with chronological age would then be selected to be averaged together to create the refined *AEP-Age* estimate, *AEP-AgeR*, for each child at each age.

3.4.2 Statistical analyses

A first step will be to determine whether *AEP-Age* (based on 9 channels) or *AEP-AgeR* (based on a refined channel set) is a better predictor of language ability for use in subsequent analyses. A hierarchical regression will be conducted with PLS-5 Total Language Score as the dependent variable and both chronological age and either *AEP-Age* or *AEP-AgeR* as the predictors. Chronological age will be entered into the first step and the *AEP-Age* index entered into the second step to determine whether *AEP-Age* can account for variance in Total Language scores over and above chronological age. If only one model shows *AEP-Age* to be a significant predictor of language ability, then the *AEP-Age* index from that model will be selected. If *AEP-Age* is significant in both models, the index accounting for the highest proportion of variance in language ability will be selected.

To determine whether children who are TD, LB, and those with DLD differ in AEP maturity between 18 and 48 months, a 3 x 5 mixed ANOVA will be used, with group classification as the between-subject variable (TD, LB, DLD) and time as the repeated/within-subjects variable (18, 24, 30, 36, 48 months). A significant group effect will provide evidence for the fact that children with different trajectories differ in their overall AEP maturity (collapsed across all time points). A significant effect of time would indicate that overall (across groups) children change in their *AEP-Age* as they get older. Of key importance, a significant group by time interaction would support the prediction that children with different language trajectories differ in their *AEP-Age* over time. If there is a significant interaction, post-hoc analyses will be conducted to explore the nature of the interaction. To explore differences over time for each of the TD, LB, and DLD groups, 3 separate 1 x 5 repeated measure ANOVAs, one for each group, will be conducted. For each group in which a significant effect of time is found, paired-sample t-tests will be used comparing the 5 age points to determine time points at which there are significant differences in auditory cortical maturation for children from that group. To examine group differences as each age, 5 separate 1 x 3 one-way ANOVAs will compare the TD, LB, and DLD groups at the 5 age points, with post-hoc comparisons between the three group where applicable. One key question will be whether the two groups who were late-to-talk at 18 months (LB, DLD) differ from children who were not (TD) in their AEP-maturation at that age, and whether the LB and children with DLD differ from each other.

To examine whether AEP maturation at 18 months predicts later language ability at 48 months, two analyses will be conducted. First, to evaluate the effectiveness of *AEP-Age* in predicting children’s later language ability relative to their same-age peers, a hierarchical regression will be conducted with PLS-5 Total Language Score at 48 months as the dependent variable and *AEP-Age* at 18 months as the predictor to determine whether early *AEP-Age* can account for variance in later language abilities. Second, a simultaneous logistic regression model will be used to evaluate whether *AEP-Age* at 18 months can predict the presence of DLD diagnosis at 48 months. A positive (DLD) or negative (TD, LB) diagnosis at 48 months will act as the dependent variable and AEP-Age at 18 months will be used as the predictor. If the model is significant, it will be possible to identify the proportion of the variance in DLD status at 48 months that can be accounted for by *AEP-Age* at 18 months and the overall classification accuracy (sensitivity and specificity) of the model. A receiver operating characteristic (ROC) curve analysis will also be applied to the data to determine whether *AEP-Age* gives a better than chance prediction of ultimate DLD diagnosis in this sample, and if so, which *AEP-Age* cut-point provides optimal specificity and sensitivity.

Finally, a cross-lagged panel analysis (see example in Figure 3) will be conducted to evaluate the direction of influence between AEP and language maturity over time and to compare patterns of AEP maturity in children of both typical and atypical language acquisition. Cross-lagged associations across longitudinal intervals will be used to examine direction of influence, or lack thereof, between AEP maturity and language abilities. During analysis, particular attention will be given to those who were initially classified as late talkers (LB and DLD groups). This may serve to provide evidence for the idea that AEP maturity influences language maturity if, over time, AEP maturity parallels that of language. In contrast, the inverse influence may be suggested if LB present with an *AEP-Age* more similar to those who go on to be identified as having DLD, even as their linguistic skills move closer to children with typical language development. Note that the precise analytic parameters for this set of analyses is under development and will be completed with the support of a statistical consultant prior to submission of this manuscript as a registered report.

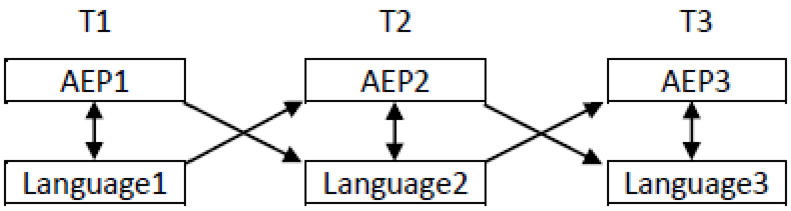


Figure 3. Cross-lagged panel analysis. Example of a 3 time-point cross lagged panel analysis of the type that will be used in data analysis comparing AEP's and language.

Chapter 4

4 Discussion

Recently, an index of auditory cortical maturity, *AEP-Age*, has been demonstrated to be capable of successfully estimating the maturity of AEPs in individual school-aged children. This ICC-derived index has also been shown to be able to explain some of the variance in language abilities in children with both typical and atypical language development (Kwok et al., 2018a; Kwok et al., 2018b). Given the accumulation of evidence supporting a relation between auditory cortical responses and language abilities, this thesis proposed two prospective studies (Chapters 2 and 3) that aim to refine and extend this *AEP-Age* index to the earliest stages of language acquisition. Overall, the studies proposed in this thesis aim to establish the utility of *AEP-Age* in (a) capturing maturational change in auditory cortical processing in the early years, (b) accounting for individual variations in language ability beyond that which is explained by chronological age, (c) evaluating whether auditory cortical maturation is a contributor to or consequence of early spoken language acquisition, and (d) predicting which late talkers with go on to develop DLD and which will not. To achieve this overall purpose, two Stage 1 Registered Report manuscripts were designed. This concluding chapter includes a brief review of the two planned studies, summary of activities completed in preparation for these studies before the onset of the pandemic, future directions and predictions, and overall implications of this line of research.

4.1 Study 1: Auditory evoked potential maturity and its relation to early language acquisition. A stage 1 registered report

Although *AEP-Age* has shown the ability to be an effective tool in predicting auditory cortical maturation and language abilities for school-age children, its utility has yet to assessed in preschoolers. The objective of this study is to examine the ability of *AEP-Age* to predict both chronological age and language proficiency in children aged 18, 24, 30, 36 and 48 months. To do so, participants will undergo passive EEG collection to record their neural responses to a tone while they watch a silent movie, and a battery of language tests will be administered to measure spoken language abilities. Using the Fisher-transformed ICC statistic, comparison will be made between individual participants' waveforms and age-binned grand averages to assign an *AEP-Age* to each child. One-way ANOVAs followed by Tukey's HSD post hoc comparisons will be used to determine whether and where there are significant differences in *AEP-Age* between children aged 18, 24, 30, 36, and 48 months. Linear regression analysis will be used to establish how much of the variance in chronological age is explained by *AEP-Age*. Hierarchical regression and correlational analyses will be used to further examine the association between *AEP-Age* and language, including overall language abilities, as well as more specific abilities in receptive, expressive, phonological, semantic, and grammatical domains of language. These results will inform our understanding of maturational differences in neural processing of sound through early childhood and whether these differences serve as a predictor of strength of language skills in individual children.

4.2 Study 2: Longitudinal relations between auditory evoked potentials and language from 18 to 48 months in children with typical and atypical language acquisition. A stage 1 registered report.

Despite evidence that suggests an association between auditory cortical maturity and language ability, the direction of this influence remains unclear. This study aims to longitudinally investigate the predictive ability of *AEP-Age* in toddlers between the ages of 18 and 48 months with respect to their language development. Recruitment for this study will target children with three different developmental trajectories: children with TD, late-talkers who resolve (LB), and late-talkers with persistent language difficulties (DLD). Children will complete passive EEG and assessment of their language abilities at each visit to the lab when they are 18, 24, 30, 36, and 48 months. The normative waveforms from the Study 1 sample will be used to estimate each child's *AEP-Age* at visit. Mixed ANOVA will determine whether children with different language trajectories differ in their *AEP-Age* over time. Hierarchical and logistic regression will evaluate the ability of *AEP-Age* at 18 months to predict children's overall language ability relative to their same-age peers at 48 months, and the presence of DLD diagnosis at 48 months, respectively. To evaluate the direction of influence between auditory cortical maturity and language, cross-lagged panel analysis will be conducted to compare patterns of AEP and language maturity across all three groups. Results will provide insight into the direction of influence (or potential lack of influence) between auditory cortical maturity and language abilities in children with different trajectories of language acquisition.

4.3 Preparation and the Role of COVID-19

Unfortunately, the spread of COVID-19 played a detrimental role in the progress of this research. Until the onset of the pandemic, the first study was in an excellent position for implementation and data collection. Alas, the nature of this research, namely placing EEG caps on the heads of toddlers while seated in their caregiver’s lap and administering standardized speech and language testing, made it prohibitive to continue given the necessary health and safety protocols (both in terms of being permitted to resume this type of data collection and in terms of the willingness of caregivers to bring their child on campus for such a study). However, I did complete much preparatory work, training, and pilot testing prior to March 2020.

In preparation to carry out Study 1, I contributed to the preparation of the ethics application, including letters of information, consent forms, and recruitment materials, which was submitted to the Western Research Ethics Board (WREB). Based on the correspondence and recommendations of the WREB, further amendments to the study paradigm were made, documented, and approved (see Appendix A). Following ethics approval, I developed a written plan similar to that of a pre-registration. This document detailed general study information in addition to an overall design plan, sampling plan, discussion of variables, and general plans for analyses.

In addition to obtaining ethical approval and writing the pre-registration, the lab had to be prepared for testing. To do so, I created a 24-page lab manual that provides an overview of the equipment, software, and protocols relevant to this study. This process involved extensive technological troubleshooting with the Net Station (NS) EEG acquisition system and extensive communication with support teams. Once the NS system was functional, a sound field that reflected the proposed paradigm for EEG acquisition had to be constructed. With the support of experienced audiologists and literature reviews, my lab members and I designed and calibrated an external sound field in the audiometric testing booth (see example in Figure 4).

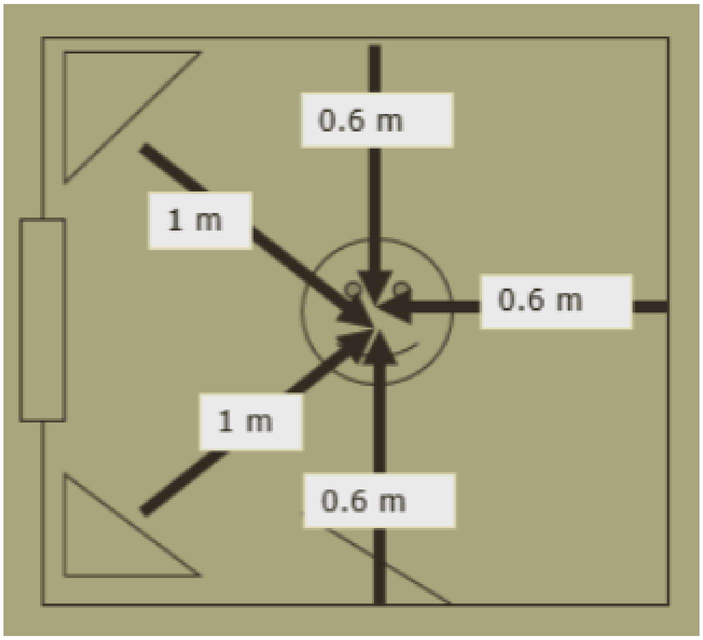


Figure 4. Example of Calibration in an External Sound Field. This image represents a reverberant sound field that has been previously calibrated with placement of the participant 1 metre from the speaker and at least 0.6 metres from all walls.

Prior to recruiting any participants, skill development was also required. This involved training and practicing for both EEG acquisition and administration of standardized language tests. To improve my EEG data collection skills with a diverse range of ages and developmental abilities, I participated in remote testing with Drs. Nichole Scheerer and Ryan Stevenson. My involvement included helping to collect EEG data from over 50 autistic and non-autistic children over a period of a few short days. This experience allowed for the refinement of both my functional and my technological skills involved in EEG acquisition in childhood that will be very beneficial to the proposed studies. To develop my skills in collection of language data, I was trained in the administration of the following standardized tests: Preschool Language Scales-5th Edition

(PLS-5), Goldman-Fristoe Test of Articulation-3 (GFTA-3) Sounds-in-Words subtest, and Clinical Evaluation of Language Fundamentals-Preschool, 2nd Edition (CELF-P2). During this time, recruitment and testing of several adult pilot participants occurred. This allowed me to practice these novel skills (EEG cap placement, measuring impedance values, etc.) before applying them to younger, and perhaps more temperamental, participants.

Prior to the onset of COVID, this study was finalized and primarily in the recruitment phase. As of the beginning of March, 2020, the majority of interest in participating was a result of word of mouth, but other methods of recruitment being used included Western Psychology's Developmental Participant Pool, community advertisement, flyers delivered within Western's childcare centres, and enrolment in Western's BrainsCan Participant Pool. Although recruitment was our primary focus at the time, I did have the opportunity to test one 30-month-old participant on March 6, 2020. During their visit, the child demonstrated some resistance to EEG acquisition but involvement of the primary caregiver (i.e., having the parent wear a cap, pretend to put it on the child, etc.) proved useful in encouraging the participant to cooperate. During this session, several predetermined silent movie options were prepared, however, the child insisted on watching a short video of a character they were familiar with. This was noted, and the lab setup was modified so that future children would be able to identify their own video to observe during testing (limited to Netflix or YouTube) with caregiver permission. As of June, 2021, data collection remains on hold due to the COVID-19 pandemic, nevertheless, the necessary skills and preparation are all in place to resume testing when possible.

4.4 Next Steps

Despite having to complete a modified thesis, plans are to submit both Chapters 2 and 3 for publication. Submission of a Stage 1 Manuscript is considered part one of two in the review process for Registered Reports. Registered Reports are a form of empirical article that include a detailed review of background, methods, and proposed analyses. The decision to embark on preparing Registered Reports, a new process for me, has provided the unique opportunity for improvement in scientific design and communication, in spite of not being able to collect data.

The benefits of pre-registering a study and having it reviewed prior to data collection include, but are not limited to, minimizing bias in deductive science while allowing for flexibility to conduct additional, unregistered analyses and report serendipitous findings. Evidence shows that the use of Registered Reports could improve research quality and credibility. Specifically, papers arising from Registered Reports show higher levels of rigour in methodology and analysis in comparison to those that do not (Soderberg et al., 2021). Regardless of whether the predictions in Chapters 2 and 3 are supported or not, completing a Registered Report will allow for publication and dissemination of results that may drive future research.

Should pandemic restrictions allow for it, testing is expected to resume in Fall 2021 with the integration of reviewers' edits. By completing a Stage 1 Manuscript, these studies are well positioned for a published, Stage 2 Manuscript in which reviewers consider the full study, including results and discussion.

4.5 Potential Results

The proposed studies aim to provide the foundation for long term exploration of whether auditory cortical maturation is a consequence of or contributor to language development. Both studies described in Chapters 2 and 3 focus on early stages of language acquisition to pursue this objective. It is predicted that the current research will support previous findings showing maturational development of AEPs (Ponton et al., 2000; Sussman et al., 2008, Wunderlich et al., 2006) and associations to language skill (Bishop et al., 2011, Kwok et al., 2018a).

4.5.1 Study 1

Given the success of ICC-derived index, *AEP-Age*, in accounting for partial variance of language in school-aged children (Bishop et al., 2011; Kwok et al., 2018a) this study aims to expand its utility in toddlers. As a result of ANOVA analyses, it is expected that there will be evidence for significant differences in auditory cortical maturity between 18, 24, 30, 36 and 48 months, as characterized by the *AEP-Age* index. It is anticipated that the variance in chronological age explained by *AEP-Age* will become evident through linear regression analyses and will align with the findings of Kwok and colleagues (2018a). Further, it is predicted that hierarchical and correlational regressions will demonstrate the ability of *AEP-Age* to predict language proficiency beyond skills explained by chronological age. Based on the results of Oram Cardy et al. (2008), it is expected that associations between overall and receptive language may be most evident.

4.5.2 Study 2

Evidence exists for a relation between immature or deviant auditory cortical responses and impaired language development (Bishop & McArthur, 2004, Bishop & McArther, 2005, Bishop et al., 2007; Kwok et al., 2018b). By following the development of children of different language trajectories, it is predicted that patterns of AEP maturation over time will closely parallel patterns of language maturation. It is expected that the use of mixed ANOVA analyses will determine whether children with different language trajectories differ in their *AEP-Age* as they develop. It is predicted that, using hierarchical regression, *AEP-Age* at 18 months will have a predictive relationship with overall language ability at 48 months. Further, it is anticipated that logistic regression will reveal that the assignment of *AEP-Age* at 18 months will predict the presence of DLD diagnosis at 48 months.

Based on previous findings regarding the timelines of language and auditory maturation, it is predicted that auditory maturity at younger ages will have a larger impact on language maturity at later ages, rather than the reverse (earlier language maturity having a larger effect on later AEP maturity). While not expected, there is the possibility that evidence will suggest a bidirectional or, possibly less likely, a non-existent influence between AEP and language abilities.

4.6 Implications

This research will contribute valuable knowledge about potential underlying contributors to and significant changes in AEPs at young ages, expanding on our knowledge of cognitive processes and mechanisms of language development. It will also serve to better inform the direction of future research in this area. If, as predicted, auditory cortical maturation does influence language maturation, this supports dedicating future resources to investigating the influences of auditory cortical maturation, the timing of these influences, and whether manipulation of said influences can impact language development. Finally, *AEP-Age* is a unique tool. It can be administered quickly and non-invasively and shows promise in predicting language trajectories in childhood. By establishing normative waveforms for children of a wide variety of ages, this research may lead to clinical translation into tools that could provide early identification of infants and toddlers at risk for language disorders, even before they are late to talk.

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Appendices

Appendix A: Human Ethics Approval and Materials

Western Research

Date: 3 December 2019

To: Dr. Janis Cardy

Project ID: 113186

Study Title: Relevance of auditory cortical maturation to early language acquisition

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 17Dec2019

Date Approval Issued: 03/Dec/2019 13:05

REB Approval Expiry Date: 01/Feb/2020

Dear Dr. Janis Cardy ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Cardy NSERC PROPOSAL 2018_Amendment	Protocol	15/Nov/2019	
NSERC EEG 2018 LOI Consent Aim 1	Consent Form	15/Nov/2019	
NSERC EEG 2018 LOI Consent Aim 2	Consent Form	15/Nov/2019	

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
NCA REDCap approval	Summary of Changes	Received 03Dec2019	

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western

PARTICIPANTS NEEDED FOR STUDY OF BRAIN MATURATION IN EARLY LANGUAGE DEVELOPMENT

IS YOUR CHILD 1-5 YEARS OLD?

We are looking for child volunteers to take part in a study of how the brain processes sounds and how this relates to language development. Participants must come from English-speaking homes and have no medical or developmental problems.

If you are interested and agree to participate, we will test your child's hearing and ask you to complete a short form about your child's development. We will briefly measure your child's brain response to sounds using electroencephalography (EEG). EEG is completely non-invasive and does not involve any form of radiation. If your child is 18-48 months old, we will also test your child's language skills.

Your child's participation would involve one visit to the university when your child is aged 12, 18, 24, 30, 36, 48 or 60 months. The visit will last between 1-2 hours.

You will be compensated for your time.

For more information or to volunteer for this study, please contact:
Allysa Janes, Graduate Student
ASLD, Communication Sciences and Disorders
[redacted] or
Email: [redacted]

PROJECT TITLE: *Relevance of auditory cortical maturation to early language acquisition*

PRINCIPAL INVESTIGATOR: Janis Cardy, PhD, S-LP(C)

Version Date: 2019-01-31

Letter of Information and Consent

Project Title: Relevance of auditory cortical maturation to early language acquisition (Aim 1)

Document Title: Letter of Information and Consent

Principal Investigator
Dr. Janis Cardy, PhD, S-LP(C)
[redacted]

Co-Investigators
Nichole Sheer, Ph.D
Tahereh Karami Shoar, M.Sc
Alyssa Janes, B.Sc
[redacted]

Sponsor/Funder Information
The funder of this research is the Natural Sciences and Engineering Research Council of Canada.

Conflict of Interest
There are no conflicts of interest to declare related to this study.

Introduction
In this Consent document, "you" always refers to the study participant. If you are a substitute decision maker (SDM) (i.e. someone who makes the decision of participation on behalf of a participant), please remember that "you" refers to the study participant. If an SDM is needed for this study, you will be asked to review and sign this consent form on behalf of the participant.

You are being invited to participate in research investigating how the brains of children with typical development process what they hear and how this relates to their early language development. You are being asked to participate because you have no developmental problems. Young children vary in how well their early language skills develop. Some children have very strong language abilities early on and some take longer to develop their language skills. In this study, we are trying to find out whether this has anything to do with how their brains process sounds. By examining the electrical signals emitted from the brain when sounds are presented, we can see if there are differences between children with different language abilities in the way their brains process sounds.

Why is this study being done?
The purpose of this study is to determine whether maturation of auditory processing in the brain is a consequence or contributor to early language development. The study plans to investigate maturational change in the brain from 18 to 48 months and its relations with language acquisition. If the results of our study suggest that we can predict strength of language development based on a child's brain response to sounds, we might be able to use this technique in the future to predict which children are at risk for problems with language development before they are late to talk.

How long will you be in this study?
There will be one study visit that will last about 1-2 hours during your participation in this study. This can be scheduled at your convenience.

What will happen during this study?
We plan to test 140 children aged 12, 18, 24, 30, 36, 48 and 60 months (20 per age group) for this study. All participants will come from English-speaking homes and will not have any medical or developmental problems.

If you agree to participate, you will visit Elborn College (on the northwest corner of Western Road and Sarnia Road) at the University of Western Ontario for 1-2 hours. Arrangements for parking will be provided. During this appointment, your hearing will be screened using foam ear tips and sound played at soft levels, and we will ask your parent or caregiver to complete a short checklist about your development. If you are aged between 18-48 months during the visit, we will also test your speech and language development using a variety of materials such as toys, pictures, and checklists.

In the second part of the session, you will be tested using electro-encephalography (EEG) while sitting on your parent or caregiver's lap in a sound-dampened booth. EEG is a recording of brain waves, or the electrical activity of the brain cells, made using a cap with wires that is placed on the head. Before you begin, you will practice wearing a net cap. Once you are comfortable wearing the practice cap, we will place the real net cap on your head. This cap is dipped in a salt water solution before placing it on your head, and a small amount of saline remains. A towel will catch any saline that might drip onto your clothes during placement. You will be asked to try to keep still while opening or closing your eyes (5 minutes) and while listening to beeps played on speakers (5 minutes). We will use videos and puppet shows to entertain you during the recording. You will not be required to do anything but try to sit still and watch the video/puppets. If, during the course of this study, new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you by the investigator.

What are the risks and harms of participating in this study?
There are no known or anticipated risks or discomforts associated with participating in this study. The testing session will take up to 2 hours, which may be inconvenient. Some of the questions you will be asked during the language testing may be too easy or too difficult, which may cause some boredom or anxiety. The examiner will make every effort to reduce frustration and provide breaks when needed. During the EEG portion, you may find the cap slightly uncomfortable or become tired of sitting still. We will make every effort to reduce any discomfort.

What are the benefits of participating in this study?
You will not receive direct benefit from being in this study. Information learned from this study may improve our current understanding of brain maturation and early language development and our future ability to identify children who struggle to learn language.

Are participants compensated to be in this study?
You will be compensated $20 for your participation in this research.

What are the rights of participants?
Your participation in this study is voluntary. You may decide not to be in this study. Even if you consent to participate, you have the right to not answer individual questions or to withdraw from the study at any time. If you choose not to participate or to leave the study at any time, it will

have no effect on your care. You do not waive any legal right by consenting to this study.

Can participants choose to leave the study?
If you decide to withdraw from the study, you have the right to request (e.g., by phone, in writing, etc.) withdrawal of information collected about you. If you wish to have your information removed, please let the researcher know and your information will be destroyed from our records. Once the study has been published, we will not be able to withdraw your information.

How will participants' information be kept confidential?
All identifiable information, such as your name and birthday (to calculate age) will collected separately from study data and linked only by a unique ID code that will be assigned to you child. The master list linking your study ID and identifiable information will only be available to the researchers. If the results of this study are published, only de-identified information will be made available. NO personal identifiers (such as your name, your parent/caregiver's name, address, date of birth, etc.) will be shared.

Your contact and demographic information including full name, telephone number, email address, full date of birth, and sex collected for this study will be stored in a secure, password-protected database (OurBrainsCAN) held at Western University. Only the researchers of this study and the BrainsCAN coordinator(s), who administers the database system, will have access to your identifiable information as stated above. The BrainsCAN coordinator will not need to review any of your information unless you have consented to be a part of the OurBrainsCAN registry. If you agree to be a part of the OurBrainsCAN registry and have indicated that the researchers of this study can enter your identifiable information, they will include the contact and demographic information collected for this study.

The de-identified data produced from this study (your test, questionnaire, and EEG data) will be stored electronically on a secure REDCap server at Western University and will be retained for a minimum of 7 years. These data will be coded by participant number and will not contain identifying information. Your de-identified data may be retained indefinitely and could be used for future research purposes (e.g., to answer a new research question). By consenting to participate in this study, you are agreeing that your de-identified data can be used beyond the purposes of this present study by either the current or other researchers. The de-identified data will be accessible by the study investigators as well as the broader scientific community. More specifically, the data may be posted on the Open Science Framework or made available to other researchers upon publication so that data may be inspected or analyzed by other researchers. The data that will be shared on the Open Science Framework will NOT contain any information that can identify you.

Qualified representatives of the Western University's Health Sciences Research Ethics Board that oversees the ethical conduct of this study may look at the study related records for quality assurance (to check that the information collected for the study is correct and follows proper laws and guidelines).

If you would like to be contacted about future research studies for which you may be eligible, you can choose to have your identifiable information as stated above entered into "OurBrainsCAN: University of Western Ontario's Cognitive Neuroscience Research Registry" by the researchers of this study OR alternatively you can be given the web address of OurBrainsCAN where you are able to enter your information. This is a secure database of potential participants for research at Western University, which aims to enrol 50,000 volunteers over a period of 5 years. The information in this database will be stored indefinitely. The records are used only for the purpose of recruiting research participants and will not be released to any third party. When you are invited to participate in future research studies, you will be given a full description of what your involvement would entail. You are, of course, free to turn down any invitation. If, at any time, you decide that you do not want to be a part of this database, please contact [redacted] to remove your information.

Whom do participants contact for questions?
If you have questions about this research study, please contact Principal Investigator, Dr. Janis Cardy, PhD, S-LP(C) at [redacted] .

If you have any questions about your rights as a research participant or the conduct of this study, you may contact The Office of Human Research Ethics ([redacted] The REB is a group of people who oversee the ethical conduct of research studies. The HSREB is not part of the study team. Everything that you discuss will be kept confidential.

If you agree to participate in this study, please complete the attached Consent Form.
You can also indicate if you are willing to be contacted for future studies. Your contact information will be confidentially stored for this purpose for 3 years.

This letter is yours to keep for future reference.

Consent Form

Project Title:
Relevance of auditory cortical maturation to early language acquisition (Aim 1)

This study has been explained to me and any questions I had have been answered.
I know that I may leave the study at any time. I agree to take part in this study

I agree to be contacted for future research studies.
___ YES
___ NO

Parent/Guardian: Your signature on this form indicates that you are acting as a substitute decision maker for your child and the study has been explained to you and all your questions have been answered to your satisfaction. You agree to allow your child to take part in the study. You know that your child can leave the study any time.

Child's Name: ____

______________________________________ ________________________________
Printed Name of Parent/Guardian Signature

____
Date (DD-MMM-YYYY)

My signature means that I have explained the study to the participant named above. I have answered all questions.

______________________________________ ________________________________
Print Name of Person Obtaining Consent Signature

____
Date (DD-MMM-YYYY)

*OPTIONAL: complete this portion **only** if you would like to consent to be added to OurBrainsCAN Recruitment Database.*

I consent to being added to the OurBrainsCAN: University of Western Ontario's Cognitive Neuroscience Research Registry to be contacted about future research studies for which you may be eligible:

Please initial your choice if you wish to be added to OurBrainsCAN:
____ Yes, I already signed-up.
____ Yes, the researcher can enter my information into the database on my behalf.
____ Yes, please provide me the link to join the database myself.

Child's Name (Please print): ____

Parent/Guardian's Signature: ___________________________ ____________________
Date (DD-MMM-YYYY

Version 2019-11-15

Appendix B: Custom MATLAB Script for ICC Analysis

```
% ----------------------------------------------------------------------
% INSTITUTE    : University of Western Ontario
% FILENAME     : runiccanalysis.m
% FILE TYPE    : Script
% VERSION      : 2.0
% AUTHOR       : Anthony Bertone
% ----------------------------------------------------------------------
% REVISION HISTORY
% ----------------------------------------------------------------------
%
%  1.0, 2010-09, Drew Morris (drew.j.morris@gmail.com)
%    - Initial release
%  2.0, 2014-08-05, Anthony Bertone (anthony.m.bertone@gmail.com)
%   - Modified Version
%
% ----------------------------------------------------------------------
% DESCRIPTION
% ----------------------------------------------------------------------
%
% Runs intra-class correlation (ICC) coefficient analysis of ERP data
% files.  Files should be in EGI simple binary format (.raw)
%
% ----------------------------------------------------------------------
% ----------------------------------------------------------------------
% ----------------------------------------------------------------------

disp(' ')

loadIccVariables;


try
   checkVariables;
catch e
   disp(['ERROR! ' e.message]);
   return;
end

%now add the paths to make file names fully specified
%full path to output files
ICC_table_file_path=fullfile(output_path, ICC_table_file);

%full path to config files

base_category_file=fullfile(config_path, base_category_file);
subjects_file_path=fullfile(config_path, subjects_file);
channels_to_analyze_file=fullfile(config_path, channels_to_analyze_file);
channel_names_file=fullfile(config_path, channel_names_file);
```

```
window_file=fullfile(config_path,window_file);
reference_file=fullfile(config_path, reference_file);


addpath(code_path);
cd(data_path);

%This file has the names for the 128 channel net. You can replace with
%another file that has the names of all the channels, 1 per line
try
   channel_names = read_channel_names(channel_names_file);
catch e
   disp(['ERROR! ' e.message]);
   return;
end


 % Read age group folders and filenames
try
   part_info = find_folder_file(data_path, subjects_file_path, subjects_file );
catch e
   disp(['ERROR! Searching for participant file. ' e.message]);
   return;
end


% Extract .raw file data into structure
try
   part_info = extract_data(part_info, data_path, channel_names, time0_code, byte_swap);
catch e
   disp(['ERROR! Extracting data. ' e.message]);
   return
end


% Calculate the grand average.
try
   GA = grandaverage(part_info, data_path, channel_names, time0_code, byte_swap);
catch e
   disp(['ERROR! Generating Grand Average. ' e.message]);
   return
end

% This reads in a list of channels you wish to include in the analysis
try
   selected_channels = readSelectedChannels(channels_to_analyze_file, channel_names);
catch e
   disp(['ERROR! In reading selected channels. ' e.message]);
   return
end
```

```
% This reads in the "base category" for ICC
try
    base_category = readBaseCategory(base_category_file);   % Tone
catch e
    disp(['ERROR reading base category: ' e.message]);
end

try
    win = readWindow(window_file);
catch e
    disp(['ERROR! ' e.message]);
    return
end

cd(code_path);

 for ch = 1:numel(part_info.patient)

    try
        [datablock, data_labels, comparison_labels] = createIccDataMatrix(part_info, GA, ch,
selected_channels, base_category, win(1),win(2));
    catch e
        disp(['ERROR creating data matrix: ' e.message]);
        return
    end

    ICCTABLE{ch} = do_ICC(datablock);

    str_ICC_table{ch} = ICCExcelTable(ICCTABLE{ch}, data_labels, comparison_labels);

    prompt_ICC_display(str_ICC_table{ch});

 end

 complete_ICC_table = vertcat(str_ICC_table{:});  % combine all ICC cell arrays into one cell
array


  try
      save_ICC_table(complete_ICC_table, ICC_table_file_path);
  catch e
      disp(['ERROR saving ICC table: ' e.message]);
      return
  end

  complete_ICC_table = [];
```

Curriculum Vitae

Name:	Alyssa Janes
Post-Secondary Education and Degrees:	McMaster University Hamilton, Ontario, Canada 2015-2019 BSc, Honours Life Science
	Western University London, Ontario, Canada 2019-2021 MSc, Health and Rehabilitation Sciences
Honours and Awards:	Spectra Energy Scholarship 2015-2019
	Natural Sciences and Engineering Research Council (NSERC) Undergraduate Student Research Award Summer 2019
	Province of Ontario Ontario Graduate Scholarship 2021-2022
Research Experience:	Rutherford Lab McMaster University Supervisor: Dr. Mel Rutherford 2017-2019
	Reading Lab McMaster University Supervisor: Dr Victor Kuperman 2017-2019
	Autism Spectrum and Language Disorders Lab Western University Supervisor: Dr. Janis Cardy 2019-Present
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