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Relation of spontaneous and evoked brain activity to language development in young children

Tahereh Karami Shoar, *The University of Western Ontario*

Supervisor: Cardy, Janis, *The University of Western Ontario*
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Abstract

Separate studies have shown connections between spontaneous alpha oscillations and language ability in 4-6 year-olds, and between auditory evoked potential (AEP) maturity and language in 7-10-year-olds. The thesis aimed to further our understanding of how these spontaneous and evoked neural measures relate to language development in younger children than previously studied.

In this thesis, I first propose a method to investigate spontaneous alpha oscillations and language in 1-4-year-olds. Next, I examined alpha oscillations, AEP maturity, and language ability in 5-6-year-olds. Results revealed that AEP maturity did not predict language ability and correlated with alpha long-range-temporal-correlation but not with alpha power or flexibility. Next, I examined the possibility that this study did not have enough AEP trials. Using a new index called standardized measurement error, I found that AEP trial-by-trial noise decreases with age between 4-7 years, suggesting that future studies of AEP maturity may need more trials for younger ages.

Keywords

Summary for Lay Audience

Previous studies have discovered a link between children's brain activity and language development. According to these studies, children's resting-state brain signals can provide vital details about how their language develops. Electroencephalography (EEG) can be used to record this brain activity. Recent research using EEG signals found that resting-state brain activity is connected to language development in 4-6-year-old children. Other studies found that children's language skills may be related to how their brains respond to sounds. This response to sound is called the auditory evoked potential (AEP) and is also collected using EEG. Recent research established a measure called AEP-Age to measure the maturation, or "brain age," of the auditory cortex. AEP-Age has been demonstrated to predict language ability in children aged 7-10 years. This thesis aimed to broaden our understanding of the potential connections of these resting-state and AEP measures with spoken language during the earliest stages of development.

The first paper in this thesis provides a detailed plan for a future study of the association between resting state EEG and language development in 1-4-year-old children. The second study examined whether AEP-Age predicts language development in 5-6 year-olds, and explored the relationship between AEP-Age, resting-state brain signals, and language proficiency in these children. Because I did not find the expected relationship between language and AEP-Age in this study, I conducted a third study to understand whether younger children have "noisier" brain activity and thus need more trials of sound presentation to get a reliable signal. Using a new analysis technique, I examined the noise level in the EEGs of children between the ages of 4 and 7 years, and found some evidence that younger children need more trials than older children to get reliable findings. Overall, this thesis contributes new information about, and new methods for studying, the relationship between resting-state brain signals, auditory maturity, and language development in young children.

Co-Authorship Statement

This work consists of five chapters: an introductory chapter (Chapter 1), a pre-registration manuscript (Chapter 2), two secondary data analysis studies (Chapters 3 and 4), and a concluding chapter (Chapter 5). My primary supervisor, Dr. Janis Oram Cardy, supervised the conceptualization, design, analysis, and the interpretation of results, and provided editing and feedback for all chapters in this thesis. The project design and analysis plans for the pre-registration manuscript in Chapter 2 were supported by co-authors Alyssa Janes and Dr. Nichole Scheerer. The studies in Chapters 3-4 were supported by co-investigator, Dr. Elaine Kwok, who co-supervised the design, analysis, and interpretation of results, and provided feedback on these chapters.

Acknowledgments

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Chapter 1

1   Introduction

Delayed onset of early language milestones can be a sign of the presence of a neurodevelopmental disorder (DSM-V, American Psychiatric Association, 2013). However, most children who are late-to-talk will catch up by 4 years of age and develop typically during subsequent stages of development (Duff et al., 2015; Reilly et al., 2018). Early brain markers of future, persistent language development difficulties could help with earlier diagnosis and intervention for those who are not going to grow out of their early delays. Numerous studies have examined the relationship between neural brain activity and spoken language skills from diverse angles. Electroencephalography (EEG), which has the advantage of being more child-friendly and less costly than to functional magnetic resonance imaging (fMRI), is one of the frequently utilized technologies for this aim. Information about how the brain functions at rest or during presentation of auditory stimuli can be gathered using EEG while children sleep or sit passively, making it a useful option for studying brain markers in young children.

Spontaneous EEG brain activity has been the subject of numerous studies in infants and children. According to some studies, spontaneous EEG activity can provide important details about a person's language growth and ability (Benasich et al., 2008; Cantiani et al., 2019; Gou et al., 2011; Lum et al., 2022). These studies have focused on different brain frequency bands in order to understand the neural correlates of language acquisition. However, alpha frequency has received the greatest attention in this field since, among other frequency ranges, its unique properties make it the ideal option (Jensen & Mazaheri, 2010a; Strauß et al., 2014). Research in our lab has demonstrated a substantial relationship between language skills and spontaneous alpha oscillation features, such as alpha power, alpha frequency flexibility, and alpha long-range temporal correlation, in young children (4-6 years old) (Kwok et al., 2019). However, the underlying mechanisms of these links are not well understood. A possibility could be that auditory processing may be involved in this function, which was the original aim of the present thesis research.

Another body of research has focused on the potential connections between language ability and auditory evoked potential (AEP) brain activity, which is generated when participants are exposed to auditory stimuli. Bishop et al. (2011) identified an intra-class correlation (ICC) method as the most reliable tool for capturing maturity in auditory cortical processing. This method generates an AEP-age index, or "brain age" equivalent, for each child, which has been found to be sensitive to developmental level (Bishop et al., 2011; Kwok et al., 2018). Additionally, Kwok et al. (2018) demonstrated that AEP-age could predict language ability in school-aged children. This study provided seminal insight into the possibility that brain activity could predict the path of later language development. Given both these findings and the previously discussed findings of relationships between measures of resting-state alpha oscillations and language, another aim of this thesis research was to explore the relations between both of these measures and language development in younger children.

A crucial factor that should be taken into account in AEP research is data quality. "Noisy" cortical responses, which can be more common in younger children, could result in potentially unreliable outcomes. Increasing the number of trials will attenuate the noise in an averaged AEP signal, but there is no standard way to calculate the necessary number of trials for ERP investigations. Many ERP experiments are built on tradition, using guidelines or experimental designs from earlier studies. No universally accepted approach exists for evaluating the quality of the data gathered in ERP studies (Luck et al., 2021). However, a few new methods have been proposed for this aim. Luck et al. (2021) suggested one way for data quality assessment, standardized measurement error (SME), which calculates the trial-by-trial variation of the data for each individual. As a result, higher SME indicates noisier and then less reliable data. Another aim of this thesis research was to demonstrate how this new SME approach can be used to conduct a data quality assessment of AEP data in children of different ages to evaluate whether more trials should be used for younger children .

Language abilities change dramatically in the early stages of development. Similarly, the human brain matures rapidly from birth through the first years of life. Therefore, investigating previously discovered connections between neural brain activity and

linguistic ability in children at the earliest stages of language acquisition will significantly advance our understanding of how the brain is involved in spoken language development.

1.1   The Present Work

The initial objective of my thesis research was to investigate the relationship between spontaneous alpha frequency oscillation and language abilities in 18- to 48 month-old children. We initiated recruitment and tested our first participant in early March 2020. Unfortunately, due to COVID-19, data collection has been suspended for the past two years. The present thesis instead presents three manuscripts that explore topics related to the relationship of both resting-state EEG and AEPs with language development in children

Chapter 2 of this thesis is presented in Stage 1 Registered Report format describing the background literature, research questions, methods, and planned analyses for the initially planned study. This study aims to examine the relationship between spontaneous alpha oscillation properties (including alpha power, alpha flexibility, and alpha long-range temporal correlation) and oral language development in children aged 1-4 years. We also aim to investigate how alpha properties, including alpha power, alpha flexibility, and alpha LRTC relate to each other and change during this development period.

Chapter 3 presents a study completed using secondary analysis of data from our lab, which included recording of both resting-state EEG and AEPs from 4-7 year-old children and administering behavioural tests of spoken language and non-verbal IQ. Portions of this dataset were published in Kwok et al. (2018) and Kwok et al. (2019), but another part of this dataset has not been published yet. This study aimed to determine whether: (a) the AEP-age index can differentiate between 5- and 6-year-old children, (b) AEP-age can predict language ability and non-verbal IQ in 5-6-year-olds, (c) AEP-age correlates with alpha oscillation properties including alpha power, alpha temporal correlation, and alpha frequency flexibility in the same sample, and (d) AEP-age, alpha oscillations, and language abilities are related.

Chapter 4 presents a study completed using secondary analysis of the same AEP data from 4-7 year-old children reported in Chapter 3. A part of this dataset was published in Kwok et al. (2018) but with different analyses and aims, while another part is unpublished. This study aimed to investigate within-subject variability across the age ranges used in our prior study (i.e., 4-7 years) in order to assess trial-by-trial noise trends in these participants, and to determine whether noise levels change with development.

Chapter 2

2   The Role of Alpha Oscillations in Early Language Acquisition. A stage 1 registered report

2.1   Introduction

Understanding the underlying neural mechanisms related to language development is an important step towards supporting children with language disorders. The brain has high plasticity and shows important developmental changes from infancy to early childhood (Gao et al., 2017). Similarly, language maturation begins in the first years of life (Brown, 1973). The late onset of language in the early stages of development may indicate neurodevelopmental difficulties such as autism spectrum disorder and language disorder (DSM-5; American Psychiatric Association, 2013). However, issues with language acquisition may not be entirely noticeable until the second postnatal year (Gabard-Durnam et al., 2015), such as failing to speak first words by about 18 months or combine words by about 24 months. In addition, delayed onset of these milestones does not necessarily mean children will go on to have a neurodevelopmental disorder. Most children who show these delays between 18-35 months will "catch up" by 4 years of age, with only about 25% showing persistent language impairments (Duff et al., 2015; Reilly et al., 2018). The challenge is that those who grow out of their early delays and those who do not can look the same during the first few years of life. Therefore, early neural indicators of future, persistent language development difficulties have the potential to aid in earlier diagnosis and intervention and consequently, better health outcomes.

Previous research has examined the relationship between language abilities and resting state brain oscillations recorded using electroencephalography (EEG) in order to better understand neural mechanisms connected to language development. Some studies have shown that infants (6 months) at high risk for language impairment have lower early gamma power (25–45 Hz) (Cantiani et al., 2019). Similarly, Benasich et al. (2008) found that children aged 16, 24, and 36 months with a family history of language difficulties showed lower gamma oscillation over frontal regions. Furthermore, it has been suggested that gamma power is strongly connected with subsequent language abilities (Cantiani et

al., 2019; Gou et al., 2011). Although gamma activity has been connected to a variety of cognitive functions, including language development (Benasich et al., 2008; Cantiani et al., 2019; Gou et al., 2011), its low signal-to-noise ratio raises challenges for some analytical approaches that we intend to utilize in the present study (Kwok et al., 2019).

Some studies have examined the role of other resting-state EEG frequency bands in language skills. A recent study used resting-state EEG to examine the relationship between spontaneous neural oscillation and children's language skills (Lum et al., 2022). The results of this study, which involved 10-year-old typically developing children, demonstrated that resting-state theta power was negatively correlated with the participants' performance on a sentence repetition test. However, they found no correlation with sentence repetition and delta, alpha, gamma, or beta power. In another study, researchers investigated whether the effect of sleep on memory would also affect sentence comprehension. EEG was recorded throughout a language learning task and an overnight sleep duration of 8 hours. They discovered that getting enough sleep was associated with higher alpha/beta power and better behavioral performance in the language task (Cross et al., 2021).

2.1.1   Alpha Oscillations

The alpha frequency has been the most commonly studied band given that it is the strongest frequency presenting in spontaneous neural oscillations (Jensen & Mazaheri, 2010a; Strauß et al., 2014). A few studies have specifically examined the relationship between alpha oscillations and language abilities. Boudewyn and Carter (2018) found that increased alpha activity is linked to attention lapses associated with poor language comprehension (Boudewyn & Carter, 2018). Another study found alpha frequency desynchronization in language-related regions in the left hemisphere during successful sentence encoding (Vassileiou et al., 2018). Seifi Ala et al. (2020) reported that hearing-aid users showed lower EEG alpha power in the parietal lobe during the more effortful conditions in a continuous speech-in-noise task (Seifi Ala et al., 2020). Rommers et al. (2017) investigated the effect of brain oscillations on sentence context prediction (Rommers et al., 2017). Using EEG, they studied brain activity in response to expected or unexpected sentences in strongly or weakly constraining contexts. They discovered that

alpha power in strongly constraining sentences is reduced before the onset of critical word appearance. Finally, a recent study of children aged 4 to 6 years in our lab revealed stronger oral language abilities were correlated with lower alpha frequency power, greater flexibility of alpha frequency, and longer temporal correlations in the alpha amplitude time course (Kwok et al., 2019).

2.1.1.1   Non-sinusoidal Features of Alpha Oscillations

Recent evidence shows that brain oscillation is non-sinusoidal and nonstationary (Cohen, 2014), which may carry critical information about neural activity and communication (Cohen, 2014; Cole & Voytek, 2017). Related research has demonstrated scale-free arrhythmic brain activity in EEG recordings that is distinguishable from brain oscillation (He, 2014). While brain oscillations have specific frequency bands, scale-free brain dynamics are arrhythmic and do not have distinctive frequencies (He, 2014). Although scale-free dynamics have been removed from analyses in previous literature, recent research has emphasized their importance for brain functions (He, 2014).

Alternative approaches to Fourier transform are required to analyze non-sinusoidal brain activity (Cole & Voytek, 2017). Being sinusoidal and stationary is a presumption for applying Fourier transform, so alternative methods may be more beneficial to capturing physiological characteristics of the brain signal (Cohen, 2014; Cole & Voytek, 2017). Kwok et al. (2019) used two characteristics of alpha oscillation in addition to alpha power to study this non-sinusoidal fluctuation of alpha oscillation, namely, frequency flexibility and long-range temporal correlation (LRTC). These two characteristics depict the brain's criticality and assist in capturing non-sinusoidal, moment-to-moment variability of brain signals (Kwok et al., 2019). Previous research has suggested that brain signals show brief bursts of energy (Lundqvist et al., 2016). These bursts of energy could occur at a fixed or flexible rate, resulting in changing frequency of the signal over time (Kwok et al., 2019). This means that the frequency of the underlying oscillator changes over time. Frequency flexibility represents the flexibility of the underlying neural oscillator generating the energy bursts of the signals (Kwok et al., 2019). In other words, it measures how fast the frequency band oscillator changes over time. LRTC reflects the correlation between a signal and itself at various time intervals (Linkenkaer-Hansen et al.,

2007). LRTC shows how rhythmic signals will spread over time (Thiery et al., 2018). In other words, it demonstrates whether a signal at a previous time point could anticipate a signal at a later time. For more details on these non-sinusoidal features, see Chapter 3 and Kwok et al. (2019).

A few studies have examined the relationship between sinusoidal and non-sinusoidal alpha features. Linkenkaer-Hansen et al. (2007) showed no correlation between alpha LRTC and alpha power in adolescents and young adults. Similarly, Kwok et al. (2019) discovered no association between alpha power and alpha LRTC in children aged 4-6 years, while alpha power was negatively correlated with alpha flexibility in this population. However, they found no correlation between alpha frequency and alpha LRTC. Given this indication that at least some aspects of non-sinusoidal neural activity may provide different information about brain oscillators in children, both frequency flexibility and LRTC of alpha oscillations will be evaluated in the present study in addition to alpha power.

2.1.1.2   Age-related Changes in Alpha Oscillations

A number of studies have examined how alpha neural oscillator features change throughout the lifespan. Most of these have examined age-related differences in alpha power. According to Srinivasan (1999), children (6–11 years old) have more power in alpha oscillation at both the anterior and posterior electrodes than adults (18-23 years) (Srinivasan, 1999). Similarly, Dustman et al. (1999) discovered that absolute alpha power declined from childhood to adulthood, with changes being more marked for occipital than for central recordings (Dustman et al., 1999). Chiang et al. (2011) found that participants aged 6 to 20 decreased average alpha power in the occipital regions (Chiang et al., 2011). Similar findings were made by Campbell et al. in 2022, who showed that participants' alpha power declined with age from 10 to 14 years (Campbell et al., 2022). However, Clarke et al. (2001) looked at age-related variations in EEG for children aged 8 to 12 years and discovered that while relative alpha power increased with age in both the frontal and posterior regions, absolute alpha power remained constant (Clarke et al., 2001). Few studies have examined alpha power in preschool-aged children to date.

Cellier et al. (2021) examined the alpha neural changes from 3 to 24 years of age and discovered no alteration in absolute alpha power with growing age (Cellier et al., 2021).

Several studies have examined changes in alpha LRTC during development. Nikulin and Brismar (2005) found that alpha oscillation LRTC did not change between 20 to 65 years (Nikulin & Brismar, 2005). Berthouze et al. (2010) investigated whether alpha LRTC alters during typical development by studying EEG data from subjects ranging in age from 0 to 660 months (Berthouze et al., 2010). They predicted that the scale-free nature of EEG LRTCs exists from early childhood through adulthood, but the magnitude of these effects changes with age. However, they found no such trend. Smit et al. (2011) examined how alpha LRTC changed in subjects aged 5 to 71 years. They noticed that alpha LRTCs increase from childhood to adolescence, and during adolescence and early adulthood (25 years), but stay stable beyond this (Smit et al., 2011).

Several studies in the past have revealed that variations in brain signals may not always be considered noise and may include crucial information about the brain (Garrett et al., 2013; McDonnell & Ward, 2011). Alpha frequency flexibility was a novel technique employed by Kwok et al. (2019) to capture this variability. We are unaware of any other study that has used this methodology to examine how alpha frequency flexibility changes with age. Kwok et al. (2019) found no association between age and alpha frequency flexibility in participants aged 4-6 years.

2.2   The Present Study

Even though the scientific literature has begun to pay more attention to the interconnections between brain activity and language development, there is still a scarcity of research in this area. Previous research has discovered essential information about resting-state alpha oscillation and linguistic ability in children, but these associations in infants and toddlers have yet to be investigated. These stages of development are crucial because children's language skills grow dramatically during this time, as do their brains. According to previous research, infants are sensitive to language from birth (Eimas et al., 1971). Around 10 to 12 months, they typically say their first words (Bates et al., 1997), and toddlers can usually generate nearly 10 concrete words by 18 months but can

understand more than what they can produce at that age. The extent of a child's production vocabulary begins to develop significantly around 20 months, and by the age of 30 months, the child's language expands to include more abstract content (Morse & Cangelosi, 2017). Beyond vocabulary, from 24 to 36 months, children start to use grammar morphemes, resulting in increasing mean length of utterance. From 36 to 48 months, they begin to use complex syntax, and by the time they are 60 months old, they have made significant improvement in using complex grammar structures (Zardini, 2006). Therefore, studying brain activity during the early stages of development will be crucial in identifying potential neural mechanisms underlying it.

This study aims to examine the relationship between spontaneous alpha oscillation properties and oral language development in children aged 1-4 years. We will recruit children aged 18, 24, 30, 36, and 48 months due to the considerable advancements in language skills that occur during this timeframe. Using resting-state EEG recordings and administrating standardized language tests to these participants, we will be able to examine whether resting-state alpha oscillation correlates with language skills. We predict that stronger oral language abilities will be associated with lower alpha power, higher alpha frequency flexibility, and higher LRTC. Note that Kwok et al. (2019) found that alpha LRTC could be predicted with both nonverbal IQ and language, which suggests it might not be a specific predictor of language. However, we will retain analysis of alpha LRTC given that Kwok et al. (2019) is only the first application of this alpha measure in children and the fact that our sample is younger than that studied by Kwok et al. (2019).

We also aim to investigate how alpha properties, including alpha power, alpha flexibility, and alpha LRTC relate to each other and change during these time points. Based on the prior literature, we anticipate that there will be no significant association between alpha power and alpha LRTC, but that there will be a negative correlation between alpha power and alpha flexibility. Since both alpha flexibility and alpha LRTC represent brain criticality, we anticipate detecting a correlation between these two characteristics. Furthermore, we anticipate that alpha power will decrease with age. Finally, as brain

criticality continues to develop throughout adulthood, we anticipate that the measures of brain criticality, namely, alpha flexibility and alpha LRTC, will increase with age.

This research will shed light on the fundamental roles of spontaneous brain activity in language development at young ages and how these associations change with age. It will also add to our understanding of how the brain can provide information about cognitive processes and development even when no overt task is being performed.

2.3   Methods

2.3.1   Participants

This study will include 120 children with typical development aged 18, 24, 30, 36, and 48 months (n=24 per age group). Children will be tested within (+/-) one month of the aforementioned age points. Children will be recruited from a variety of sources including Western Psychology's Developmental Participant Pool, Western's OurBrainsCAN Cognitive Neuroscience Research Registry, two Southwest Ontario YMCA childcare centres located on the Western campus, community advertisements including flyers and social media postings (Twitter, Facebook), and word of mouth. Children will be recruited from English-speaking homes and must be neurologically healthy with no developmental issues, according to parent reports. Children must (a) meet age-appropriate developmental milestones on the LookSee checklist (Previously known as Nipissing District Developmental screen (Dahinten et al., 2004), and (c) have no known neurological impairments by parent report to be included. Caregivers will receive $20 in compensation for their time, and children will receive a toy worth less than $5 at the end of their participation. This project has been approved by Western University's Health Sciences Research Ethics Board, and it will be carried out with the written consent of each child's parent or guardian.

2.3.2   Sample Size Justification

We estimate sample sizes for all the planned analyses (which will be explained in more detail later) using G*power. First, as shown in Figure 1, we estimate the sample sizes for the correlation analysis for alpha power, flexibility, and LRTC. We calculated the power

based on the effect sizes reported in Kwok et al. (2019). Based on the calculation, the minimum sample size for alpha power, alpha flexibility, and alpha LRTC are N= 57, N= 40, and N = 31, respectively.

a) alpha power

b) alpha flexibility

c) alpha LRTC

Figure 1. A priori power analysis to estimate sample size for correlation analyses. Screenshots from G*power analysis for correlation for alpha frequency properties. a) shows the minimum sample size for alpha power, b) shows the minimum sample size for alpha flexibility, and c) shows the minimum sample size for alpha LRTC.

For regression analysis, as shown in Figure 2, we estimated minimum sample sizes for alpha power, alpha frequency flexibility, and alpha LRTC based on Kwok et al. (2019) findings. The minimum total sample sizes are N = 73, N = 39, and N = 28, respectively.

a) alpha power

b) alpha frequency flexibility

b) alpha LRTC

Figure 2. A priori power analysis to estimate sample size for regression analyses. Screenshots from G*power analysis for regression analysis when language scores, chronological age, and PIQ are predictors and a) alpha power, b) alpha frequency flexibility, and c) LRTC are dependent variables.

We will conduct three independent ANOVA tests (1 x 5) for each of the three alpha measurements since we are also interested in knowing if the three alpha metrics change with age across each period (i.e., between these 5 age groups). The minimum sample size when the effect size is equal to the mean of medium and large effect sizes and with 5 groups is N = 120, thus requiring N = 24 subjects per age group (Figure 3).

Figure 3. A priori power analysis to estimate sample size for ANOVA tests.
Screenshots from G*power analysis for ANOVA analysis.

2.3.3   Procedure

Participants will be asked to attend the university lab for a single visit. First, EEG data will be collected from the participants. Participants will sit on their parent or caregiver's lap in a dimly lit soundproof booth while their spontaneous brain activity is recorded for three minutes. During this recording, we will show a silent animation to the participants to keep them engaged and relaxed, but not too excited. Parents will be asked to assist their children in remaining as calm as possible. Unlike Kwok et al. (2019), we will be unable to include specific eye-closed and eyes-open conditions due to the young age of the children in our sample. Following EEG recording, oral language ability will be examined using the Preschool Language Scale-5 (PLS-5) (Zimmerman et al., 2011), which evaluates both receptive and expressive language abilities.

2.3.4   Measures

Preschool Language Scale-5 (PLS-5; Zimmerman et al., 2011). The PLS-5 assesses a variety of language skills using play-based activities in order to give an estimate of oral

language abilities. Standardized scores (M = 100, SD = 10) will be generated that reflect children's overall, receptive, and expressive language abilities (Total Language Score, Auditory Comprehension Score, and Expressive Communication Score, respectively) in comparison to their peers of the same age.

Looksee Checklist. A LookSee checklist will be completed by the caregiver present at the time of testing to confirm typical development of the participants. LookSee has checklists for 13 different developmental phases, five of which will be used in this study (18 months, 2 years, 30 months, 3 years, and 4 years; (Cairney et al., 2016). Because the LookSee checklist uses milestones that children should have mastered by a certain age, it is recommended that if the child is between two ages, the earlier checklist be used. In compared to a one-flag rule, a two-flag rule (i.e., two skills on the checklist not achieved) will be employed as a criterion for exclusion because it has been proved to yield higher levels of sensitivity and specificity (Currie et al., 2012)

2.3.5   EEG Acquisition and Processing

Resting-state EEG will be recorded using a 128-channel DenseArray EEG system with HydroCel Geodesic Sensor Nets at a sampling frequency of 500 Hz (Electrical Geodesics, Inc., Eugene, OR, USA). The collected data will be filtered using an online hardware Bessel filter with a high-pass of 0.1 Hz and a low-pass of 100 Hz. We will ask parents to try to keep their child still for three minutes. Electrodes will be adjusted as needed to keep impedances below 50 kΩ (Ferree et al., 2001). Channels having impedances greater than 75 kΩ will be excluded from analysis.

The fieldtrip toolbox in Matlab software (Oostenveld et al., 2011) and custom Matlab scripts will be used to analyze the data offline. A 60 Hz elliptic notch filter will be used to reduce line noise (cut-off frequencies: 59.2 Hz and 60.8 Hz; 70 dB suppression). EEG recordings will be re- referenced to the average of the bilateral mastoid electrodes after being high-pass filtered (0.4 Hz, 2091 points, Hann window, zero phase lag) and low-pass filtered (100 Hz, 91 points, Hann window, zero phase lag). To lower the quantity of data files, the number of electrodes will be reduced to 60 channels. Artifacts caused by eye movements, eye blinks, muscle movements, and heart beats will be suppressed using

independent components analysis. We will examine whether language scores are connected to the dynamics of the cerebral alpha oscillator using three types of analyses (described in further detail below): (a) alpha power, (b) alpha frequency flexibility, and (b) temporal correlations in alpha-amplitude time series.

2.3.6   Planned Analyses

Specific methods to study frequency flexibility and long-range temporal correlation will be used. Fourier Transform, Hilbert Transform, and Detrended fluctuation analysis (Kwok et al., 2019) will be used to obtain alpha power, frequency flexibility, and long-range temporal correlation, respectively.

2.3.6.1   Alpha power analysis

The EEG data will be segmented into smaller epochs (7 s), and then a fast Fourier transform (FFT) will be applied for each epoch. FFT will result in complex values, and the squared magnitude of these complex values will be used to calculate power. For alpha frequency, we will consider the mean power of 7 to 10 Hz. The alpha power will be averaged together across all 7 s epochs (see Kwok et al., 2019 for more details).

2.3.6.2   Alpha frequency flexibility analysis

The EEG data will be segmented into 7 s epochs. Every 7-s epoch will go through a filter with a 5–12 Hz band-pass (broader than 7-10 Hz). For each filtered epoch, the Hilbert transform will be calculated, which results in complex values including amplitude and phase angle. Then, by calculating the derivatives of phase angle time series, we will determine the instantaneous frequency, which shows the speed of alpha frequency oscillator over time. This process results in a time series of instantaneous peak oscillation frequencies within the band-pass filter range. Then, the instantaneous frequency values will be binned into non-overlapping bins, and the probability of occurrence will be calculated. This will result in a histogram of instantaneous frequency values. Then a Gaussian function will be fitted to this histogram. The width of this Gaussian function will be calculated as alpha frequency flexibility (i.e., the wider width represents a more

flexible frequency). This process will apply to all epochs, and then they will be averaged together (see Kwok et al., 2019 for more details).

2.3.6.3   Alpha long-range temporal correlation analysis

The EEG signal will be segmented into 20 s epochs, and each epoch will be filtered with a 7-10 Hz filter to extract alpha frequency. We will require longer epochs in this analysis, as we are looking for how previous events could predict future events (i.e., how previous fluctuations can predict future fluctuations). Using detrended fluctuation analysis, we will obtain the LRTC for alpha frequency for each epoch. The alpha LRTC will be averaged across all epochs (see Kwok et al. (2019) for more details).

2.3.6.4   Statistical analysis

In order to test our prediction that stronger oral language abilities will be associated with lower alpha power, higher alpha frequency flexibility, and higher long-range temporal correlation, we will run correlation analyses. First, we test whether the alpha frequency properties are normally distributed (i.e., have Gaussian distribution). This will allow us to determine whether we will use parametric (e.g., Pearson) or non-parametric (e.g., Spearman) correlation tests. Three separate correlation analyses will be used between each of the alpha frequency properties and language scores.

To explore our prediction that language score will be a significant predictor of our alpha measures, we will run three separate regression analyses. In each, chronological age and language scores will be predictors and the alpha measure (power, flexibility, or LRTC) will be the dependent variable.

In order to evaluate our hypotheses regarding relationships between the alpha features, we will conduct another correlation analysis. Parametric and non-parametric correlation tests will be chosen depending on the normality test results. Then, we will run three separate correlation studies to examine the relationships between alpha power, alpha flexibility, and alpha LRTC.

In order to evaluate our hypothesis that alpha characteristics will differ across at the five ages, we will perform one-way analyses of variance (ANOVA). Three separate one-way ANOVA (1 x 5) of each of the alpha properties by the 5 age groups will be conducted.

Chapter 3

3 The relationship between AEP-age, alpha resting-state oscillations, and language ability in young children

3.1 Introduction

3.1.1 Auditory Evoked Potentials and Language Development

The auditory cortex does not reach full maturity until late adolescence or adulthood (Bender et al., 2006; Bishop et al., 2011; Fox et al., 2010; Moore, 2002; Pang & Taylor, 2000; Ponton et al., 2000; Sussman et al., 2008). In order to understand the possible contributions of auditory cortical maturation to spoken language development, a number of studies have used auditory evoked potentials (AEP), measured using electroencephalography (EEG), as an index of auditory maturation (Choudhury & Benasich, 2011; Espy et al., 2004; Leppänen et al., 2010; Ponton et al., 2000; Tonnquist-Uhlen et al., 2003). The most significant waveform components of the AEP appear between 50 and 250 ms after the onset of an auditory stimulus, including P1, N1, P2, and N2 (Ponton et al., 2000). The latency and amplitude of these components vary as children grow (Bender et al., 2006; Fox et al., 2010; Ponton et al., 2000; Sussman et al., 2008). Some AEP components (e.g., N1) appear late in childhood (Ponton et al., 2000), and in neurodevelopmental disorders, they can be delayed or absent (Edgar et al., 2014; Shafer et al., 2011).

Auditory cortex maturation has been explored using conventional EEG analysis of peak amplitude and latency, independent component source identification, and time-frequency analysis. However, Bishop et al. (2011) found an ICC-based analysis of AEPs to be the most reliable index of auditory cortical maturation. In the ICC analysis, AEPs from all participants of the same age group are averaged to generate a grand average for that age group (e.g., all 7 year old participants' AEPs were averaged to form a 7-year-old grand average waveform). This is repeated for participants in different age groups to create different normative grand averages for different ages. Then an individual's waveform is compared to these normative grand averages in order to find the one grand average that has the strongest ICC value (i.e., most similar) with that participant's AEP. The age

associated with the grand average AEP with the highest correlation is chosen as the participant's "brain age" or their *AEP-age*, which is an estimate of the maturity of that participant's auditory cortical response (Bishop et al., 2011; Kwok et al., 2018).

Using ICC, Bishop et al. (2007) demonstrated that AEP-age is sensitive to developmental changes, distinguishing between participants who were 5-12 years old, from those who were 13-16 years old, versus adult participants (Bishop et al., 2007). However, this ICC metric was not sensitive enough to discriminate within smaller age band (e.g., 5 vs. 6 vs. 7 years). They conducted another study with a greater sample size and the findings from this study revealed that the AEP-age index could detect maturational changes in the auditory ERP and was able to distinguish between children aged 7, versus 9, versus 11 years old (Bishop et al., 2011). However, differences within these age bands were not explored (i.e., the difference between 7 vs. 8 vs. 9 vs. 10 vs. 11).

Kwok et al. (2018) attempted to reproduce the AEP-age as a marker of age-related developmental changes in AEPs and to further investigated if AEP-age could explain variances in cognitive and language ability. They recorded AEPs in response to simple tones in typically developed 7-, 8-, 9- and 10-year old subjects and used ICC to estimate the AEP-age for each participant. This study demonstrated that while ICC could distinguish 7-8-year-olds from 9-10-year-olds, it could not differentiate within these age groups (7 vs. 8, and 9 vs. 10 years). In addition, AEP-age predicted chronological age and language ability in this cohort, but not nonverbal IQ. One possible limitation in this study was the possibility of overestimation of AEP-age for the youngest age (e.g., 7 years old) and underestimation for the highest age (e.g., 10 years old) due to the limitations in normative grand averages. In other words, children who are 7 years old can only have an AEP-age as low as 7 years because there was no AEP grand average from a younger age group to compare them to, and children who are 10 years old can only have an AEP-age as high as 10 years since there was no AEP grand average from an older age to compare them to. As a result, it remained unclear in this study whether AEP-age has sufficient resolution to differentiate between school-aged children who are one year apart. The authors recommended that future studies include AEP grand averages that are both younger and older than the age groups under study to address this issue.

Results of the studies conducted to date suggest that AEP-age measured using ICC could be a potential index to predict language development trajectory. Previous research has shown that ICC is the best method for measuring maturation in AEPs of school-aged children (Bishop et al., 2011) and that AEP-age can predict language ability in this age range (Kwok et al., 2018). AEP-age could be an excellent tool for pediatric research and clinical needs in the future. While some studies have found AEP-age sensitivity to chronological age and its relationship to linguistic skills in school-aged children, these relations are unknown in younger children.

3.1.2   Alpha Oscillations and Language Development

Alpha frequency is the most salient oscillation in resting-state EEG recordings, which has a peak in the power spectrum in the 8–12 Hz range in adults (Srinivasan, 1999) and 6-10 Hz in children (Marshall et al., 2002). Previous research considered the inhibitory functions for alpha frequency (Jensen & Mazaheri, 2010a; Weisz et al., 2011) as well as possible active roles for alpha rhythms in attentional, executive, and contextual functions (Palva & Palva, 2007). Alpha frequency has been widely studied in order to better understand cognitive functions, mainly cortical inhibition and attention, in both individuals with typical development (Klimesch, 2012; Palva & Palva, 2007) and those with neurodevelopmental disorders such as ADHD (Barry et al., 2003) and dyslexia (Babiloni et al., 2012; Colon et al., 1979). The role of alpha frequency power in reading ability (Babiloni et al., 2012; Colon et al., 1979; Duffy et al., 1980; Sklar et al., 1972), as well as written and spoken language skills, has been investigated (Duffy et al., 1980; Hulme & Snowling, 2014; Kwok et al., 2019).

Although promising, power spectral analysis assumes that EEG signals are sinusoidal. However, recent research found evidence that brain oscillation may be non-sinusoidal (Cole & Voytek, 2017; Jones, 2016) and these non-sinusoidal features may play crucial roles in neural communication and cognition (Cole & Voytek, 2017). In continuous EEG recordings, non-sinusoidal oscillations appear as short bursts of energy (Jones, 2016; Lundqvist et al., 2016). These neural activity bursts can appear regularly and at a fixed or irregular frequencies, depending on the flexibility of the underlying neural oscillator.

Estimation of the oscillator's frequency range can provide information on the oscillator's flexibility, which Kwok et al. (2019) call *frequency flexibility*.

Furthermore, previous research has also shown that amplitude fluctuations of ongoing oscillations in EEG brain signals exhibit autocorrelations that decay slowly in time (Linkenkaer-Hansen et al., 2007; Smit et al., 2011). These autocorrelations' behavior is best characterized by power-law spectra $P(f) \propto 1/f^{\beta}$, where β is the power-law scaling exponent reflecting the decay in temporal correlations (Smit et al., 2011). These correlates are called *long-range temporal correlations* (LRTC), and it measures how rhythmic neural activity propagates through time (Thiery et al., 2018).

In their investigation of the association between resting-state alpha oscillation and spoken language ability in children aged 4-6 year olds, Kwok et al. (2019) calculated not only power but also alpha frequency flexibility and LRTC. Their results revealed that higher language scores correlated with lower alpha power, higher alpha flexibility, and higher LRTC in 4-6 year old children. The mechanisms behind the relationships between these features of the alpha oscillator and language development, however, have yet to be discovered.

3.1.3   Relationship between AEPs and Alpha Oscillations

Previous research has looked into the role of event-related alpha activity in auditory processing (Haegens et al., 2015; Keller et al., 2017; Lehtelä et al., 1997; Yordanova & Kolev, 1997), revealing that alpha oscillation has both excitatory and inhibitory functions during auditory processing (Haegens et al., 2015; Keller et al., 2017; Yordanova & Kolev, 1997). Lehtelä et al. (1997) provided evidence for this statement that neurons in the human auditory cortex show alpha-like spontaneous oscillations around 10 Hz. However, they found that this alpha-like activity was attenuated after exposing the subjects to 500 ms bursts of white noise. Frey et al. (2014) also provided evidence that a distinct auditory cortex alpha generator exists and can be measured noninvasively (Frey et al., 2014). Keller et al. (2017) found that alpha oscillation was present throughout the posterior regions of the brain while subjects were attending to auditory sequences. Haegens et al. (2015) identified that alpha power was high in the infragranular (deep)

layers of the A1 (as in V1, S1) in macaques during both spontaneous activity and passive sensory stimulation. This indicates that alpha is likely involved in excitability as well as inhibitory functions in the auditory cortex.

Furthermore, in response to repeated auditory stimulation, those with Parkinson's disease (PD) had considerably higher oscillatory power in the alpha, delta, and theta frequency ranges than healthy controls (Güdücü et al., 2019). Similarly, during a sentence-in-noise identification task, those with PD had considerably higher alpha power than controls, implying that bottom-up inhibitory processing of irrelevant auditory information is hindered in PD (de Groote et al., 2021). Even though the role of alpha power during auditory processing has been examined in the literature, the relationship between spontaneous alpha oscillation and AEPs has not, to my knowledge, been addressed.

3.1.4   The Present Study

In the prior literature, the association between resting-state alpha oscillation and language abilities (Kwok et al., 2019; Roehm et al., 2001) as well as AEP and language skills (Cruz et al., 2022; Kwok et al., 2019; Picton, 2013; Woodruff Carr et al., 2021) has been investigated separately. However, to my knowledge, no prior research has looked at the relationship between AEP-age and language abilities in children younger than 7 years. In addition, no prior studies have examined the relationship between the AEP-age and spontaneous alpha oscillations, nor between AEP-age, alpha oscillations, and language abilities in children. Given that both AEP-age and alpha oscillations have been found to be related to children's language abilities, one possibility is that auditory cortical maturation plays a role in the relationship between alpha oscillation and language abilities, and is related to alpha oscillations in general.

Both resting-state EEG and AEP data have been collected from the same children in our lab. For example, the 4-6 year old children who participated in the Kwok et al. (2019) alpha oscillation study were also presented with a task during which AEPs were recorded. These AEP data had not yet been submitted to AEP-age analysis or related to our previously reported data on alpha power, alpha frequency flexibility, alpha LRTC, and spoken language abilities in this sample (Kwok et al. 2019).

This dataset provided a unique opportunity to fill in gaps in the literature and expand our knowledge about how the AEP-age index relates to spontaneous alpha oscillations and linguistic ability in younger children that previously studied. To close this gap, the present study aimed to determine whether: (a) the AEP-age index can differentiate between 5 and 6 year old children, (b) AEP-age can predict language ability and non-verbal IQ in 5-6 year olds, (c) AEP-age correlates with alpha oscillation properties including alpha power, alpha temporal correlation, and alpha frequency flexibility in the same sample, and (d) AEP-age, alpha oscillations, and language abilities are related. Using AEP recordings for children aged 4-7 years old, we were able to examine whether AEP-age could discriminate between 5- vs. 6-year-old children. To address limitations in previous AEP-age studies, we included grand average AEP data from 4 and 7-year-olds to avoid under- or over-estimation of AEP-age in the 5 and 6-year-old children. We predicted that 5-year-olds would have a younger AEP-age than 6-year-olds, and that AEP-age would predict language ability but not nonverbal IQ in this cohort. We then compared the AEP-age estimates we generated for these 5-6 year-olds to their alpha oscillation properties and language abilities that were previously reported in Kwok et al. (2019) in order to examine whether AEP-age is related to the alpha oscillation properties, and whether both of these were related to language ability.

3.2 Method

3.2.1 Participants

For resting-state analysis, we had data from 29 participants aged 5-6 years old from Kwok et el. (2019): 5 (n=14) and 6 (n=15) years. For AEP-age analysis, we had AEP data from these same 29 participants, as well as 36 additional participants aged 4 (n=16) and 7 (n=20) years. AEP-age were not calculated for 4- and 7-year-olds and their data were only used for comparison reasons (i.e., obtaining AEP grand averages) in AEP-age calculation for the 5- and 6-year-old participants.

Participants were recruited partially as a part of an epidemiological investigation of language, reading, and arithmetic skills of 4- to 10-year-old children in a local school district (Archibald et al., 2013) and partially through personal contacts. According to

parental reports, the participants had no neurological, hearing, or visual difficulties. Children had to score within the normal range (i.e., no more than 1SD below the mean) on the Performance IQ (PIQ) of the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, D. 1999) and the Core Language Score (CLS) of the Clinical Evaluation of Language Fundamentals–Preschool - 2 (CELF-P2; Wiig et al., 2004) ($M = 105.1$, $SD = 9.4$) to be included in the study. We employed standard scores from the PIQ and CLS for our analyses because they are norm-referenced and age-corrected and estimate the relative strength of each participant's abilities compared to a group of same-age peers.

Resting-state EEG data for the 5- and 6-year-olds included in the present study were previously reported in Kwok et al. (2019). AEP data for these same participants, along with those of the 4-year-olds from Kwok et al. (2019), were recorded during the same session but have not been previously published. AEP data from the 7-year-olds was previously published in Kwok et al. (2018).

3.2.2   Procedures

EEG data were recorded using a 128-channel DenseArray EEG system with HydroCel Geodesic Sensor Nets (Electrical Geodesics, Inc., Eugene, OR, USA) while children were seated in a soundproof booth. Two tasks were completed: the first to generate resting state data for alpha oscillation analyses and the second to generate AEPs for use in calculation of each child's AEP-age.

In the first task, resting state recordings were made during eyes open and eyes closed conditions (Kwok et al., 2019). More specifically, participants were instructed to stay still and open or close their eyes for one minute at a time. There were three repeats of alternating eyes-open and eyes-closed trials, totaling three minutes of EEG recording for each condition. The resting state EEGs were recorded at a 500-Hz sampling frequency.

Prior to beginning the second task, each child's hearing threshold (dB SL) for a 50ms, 490 Hz pure tone was measured using a 2-up/1-down approach. Then AEPs were recorded at 250 Hz while participants were presented with 225 repetitions of the tone for about 5 minutes (Kwok et al., 2018), with tone amplitude set at 50 decibels above the

child's hearing threshold. Participants sat calmly in a comfortable chair while auditory stimuli were passively presented binaurally via a digital-to-analogue conversion device (UA-25, Edirol Inc., Japan), an amplification system (Series III, Tucker Davis Technologies Inc., Florida, USA), and insert earphones (ER3A, Etymotic Research, Illinois, USA) (Kwok et al., 2018). To help children stay still during recording, they watched a silent movie. E-PRIME software was used to control presentation of the tones (Psychology Software Tools Inc., Pittsburgh, PA).

Following the EEG recordings, children participated in standardized testing, including administration of the CELF-P2 for oral language assessment, and the WASI PIQ scale for non-verbal IQ assessment.

3.2.3   Analysis

3.2.3.1   AEP-age analysis

3.2.3.1.1   AEP data preparation

EEG data recorded during the second task were passed through a 0.1–100 Hz online bandpass filter and a 60-Hz notch filter. Channels with impedances greater than 75 k were excluded from further analysis. Average referenced data were time-locked to the onset of the tone and divided into 1200-ms epochs (containing 200 ms pre-stimulus baseline). AEPs were calculated by averaging segments that were free of artifacts (movement artifacts, eye blinks, and eye motions). In addition, AEPs from all children of the same age (4 years, n=16; 5 years, n=14; and 6 years, n=15, 7 years, n=20) were used to produce four grand average waveforms.

3.2.3.1.2   AEP-age analysis

Fisher-transformed intraclass correlation (ICC) statistic was used to compare the similarity of each child's waveform from 0 to 500 ms to grand average waveforms obtained at nine electrodes (F3, Fz, F4, C3, Cz, C4, T7, Pz, T8) for each of the four age groups (Kwok et al., 2018). For each 500 ms AEP waveform, 125 data points were acquired (500 ms x 250 Hz sampling rate = 125 data points). Each participant's 125 data

points were compared to the 125 data points acquired for the 4 grand averages of each age group using the formula:

$$(Mean\ Square_{between} - Mean\ Square_{within})/$$
$$(Mean\ Square_{between} + Mean\ Square_{within}),$$

Where

1 $Mean\ Square_{between} = \{[\sum X^2 + \sum Y^2 + 2 \times \sum(X.Y)] / 2 - (\sum X + \sum Y)^2 \ 2N\}/(N-1),$

2 $Mean\ square_{within} = [0.5 \times (\sum X^2 + \sum Y^2) - \sum(X.Y)]/N,$

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

4 $X, Y = the\ two\ AEP\ waveforms\ under\ comparison$

This process results in ICC values for each channel of each participant's waveform. These ICC values present estimations of how similar the participant's AEP waveform is to the grand average waveform. The highest value ICC was selected for each participant, and the age group of that ICC was allocated to that participant as the channel's age equivalent. Finally, the age equivalents for each of the nine channels were averaged to determine the participant's overall age equivalent. We call this age equivalent *AEP-age,* which is an estimate of AEP maturity for each participant (See Figure 1 for an example).

AEP-age was not calculated for children in the 4 and 7 year age groups. Their AEPs were only used for the purpose of having 4 and 7 year grand average AEPs for comparison purposes. Having grand average AEPs representing chronological ages both younger and older than the youngest (5 years old) and oldest (6 years old) participant groups in the sample provides the opportunity to identify immaturity in the youngest children (e.g., a 5-year-old's AEP best correlates with that of 4-year-old children) or advanced development in the oldest children (e.g., a 6-year-old's AEP waveform best correlates with that of children aged 7 years old), to not artificially inflate or deflate their AEP-age estimate.
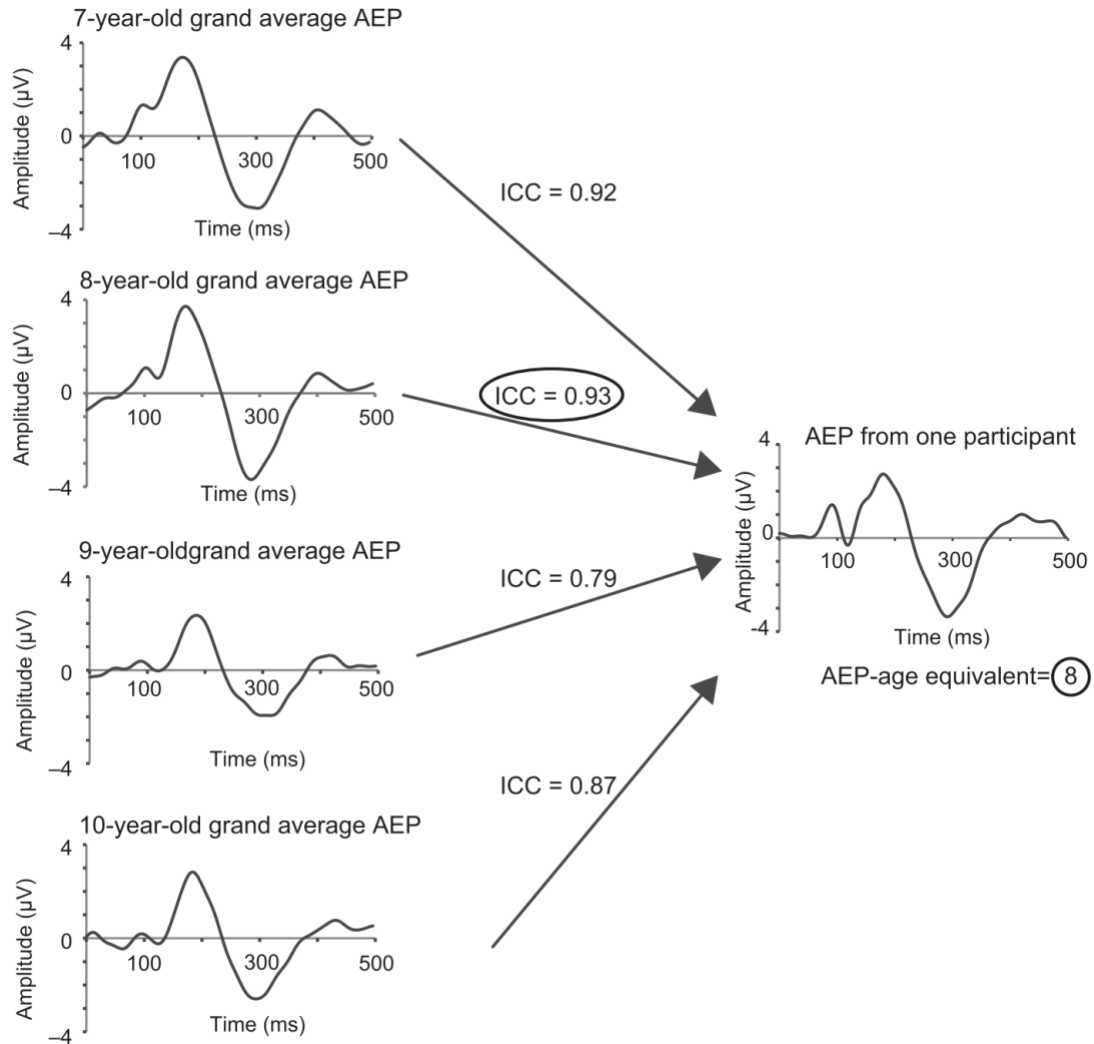
Figure 4. Example of ICC calculation. ICC calculations in children aged 7-10 from Kwok et al (2018). In this example, the grand average AEP waveforms of a single channel for each of the four age groups were compared to the AEP from the participant. The highest ICC value, which is the 8-year-old grand average, was selected as the age equivalent of that AEP waveform for that channel. This process was repeated for each channel and then averaged together to give an overall AEP-age index for that participant.

3.2.3.2   Statistical analysis

To reduce the load of data analysis, we selected 9 channels out of 128 including frontal, central, and temporal electrodes (Fz, F3, F4, Cz, C3, C4, T7, T8, and Pz), which shows a good representation of the scalp. It has been indicated that differences in ICC values are smaller in temporal and parietal electrodes rather than central and frontal (Bishop et al., 2007). Also, in other studies, it has been demonstrated that AEP maturation is most robust at frontal and central channels (Bishop et al., 2011; Kwok et al., 2018; Ponton et al., 2000). So, it is possible that ICC calculation may not be sensitive across all channels. To find out which channels provide AEP-age equivalents that correlate with chronological age, we used Spearman correlation with Bonferroni correction ($\alpha = 0.05/9$) on channel's AEP-age equivalents and chronological age. The Spearman correlation was used because the results of Shapiro-Wilk test showed that the distribution departed significantly from normality for chronological age ($W = 0.9$, $p < 0.05$), and AEP-age in all 9 channels ($p < 0.001$). Based on this outcome, Spearman correlation, which is a non-parametric test, was used. Based on the results of this analysis, we revised the averaged AEP-age index and defined AEP-ageR based on the only channels that correlate with chronological age.

Potential mean differences in AEP-age, CELF-P2 Core Language, and WASI Performance IQ scores by chronological age group were explored with t-test analysis.

Hierarchical regressions were used to examine whether AEP-age predicted language ability and non-verbal IQ. We used language scores as dependent and chronological age as independent variables in the first step, and used language scores as dependent and both AEP-age and chronological age as independent variables in the second step. In another regression analysis, we used PIQ scores as dependent and chronological age as independent variables in the first step, and PIQ scores as dependent and AEP-age, and chronological age as independent variables in the second step.

To examine the possible relationship between AEP-age and alpha frequency measures (alpha power, alpha frequency flexibility, and alpha long-range temporal correlation), which were available from the Kwok et al. (2019) study, Spearman correlation was used.

Again, Spearman correlation was used because the results of Shapiro-Wilk test showed that the distribution departed significantly from normality for chronological age (W = 0.88, p-value < 0.05), AEP-ageR (W=0.91, p-value < 0.05), CELF-P2 (W=0.91, p-value < 0.05), alpha power (W=0.78, p-value < 0.001), and LRTC (W=0.9, p-value < 0.05).

Finally, we ran another hierarchical regression analysis to examine possible relationships between alpha oscillation measures, AEP-ageR, and language scores in our participants. We used language scores as dependent and alpha LRTC as independent variables in the first step, and language scores as dependent and both AEP-ageR and alpha LRTC as independent variables in the second step.

3.3 Results

The results of the Spearman correlation showed that AEP-age in 4 out of the 9 channels (T7, Cz, F4, Fz) in central, frontal, and left temporal parts of the brain correlated with chronological age ($p < 0.001$) (Table 1). The average of these four channels together was used to define AEP-ageR for further analysis.

Table 1. Correlations between AEP-age in 9 channels and chronological age

Channel	Chronological Age
F3_AEP_Age	.061
Fz_AEP_Age	<.001***
F4_AEP_Age	<.001***
C3_AEP_Age	.039
Cz_AEP_Age	<.001***
C4_AEP_Age	.024
T7_AEP_Age	<.001***
Pz_AEP_Age	.125
T8_AEP_Age	.013

***$p < .001$

The results of independent t-tests revealed no significant difference between language abilities ($p = 0.35$), PIQ ($p = 0.67$), and AEP-ageR ($p = 0.89$) in 5- and 6-year-olds (see Table 2).

Table 2. Means, Standard Deviations, and independent t-test in Language ability, PIQ, and AEP-age by chronological age

	5-year-olds		6-year-olds		t	p	Cohen's d
	M	SD	M	SD			
Language ability	107.36	8.57	102.86	9.94	1.28	0.35	9.28
AEP-ageR	5.59	1.02	5.88	0.98	-0.79	0.89	1.00
PIQ	108.64	11.89	104.27	11.29	1.02	0.67	11.58

***$p < .05$

Hierarchical regressions investigated the ability of AEP-ageR to predict language ability and nonverbal IQ. No significant model was found when AEP-ageR derived from the four channels was entered as a predictor of language, $F(2,25) = 0.66$, $p = 0.52$, or Performance IQ, $F(2,26) = 2.8$, $p = 0.08$ (see Table 3).

The results of correlational analysis revealed no significant correlation between AEP-ageR and spontaneous alpha oscillation power ($p = 0.75$) and alpha frequency flexibility ($p = 0.58$). However, AEP-ageR and alpha long-range temporal correlation were significantly correlated ($p = 0.024$) in these participants (Table 4).

Hierarchical regressions explored the ability of AEP-ageR to predict language ability beyond what was explained by alpha LRTCs. When alpha LRTC was used as the only predictor of language ability, a significant model was observed, $F(1,23)=6.39$, $p=0.019$. However, When AEP-ageR obtained from the four channels was added to the model as the second predictor of language, no significant model was discovered, $F(2,22) = 5.39$, $p = 0.069$ (see Table 5).

Table 3. Predicting language ability and nonverbal IQ using chronological age and AEP-ageR

	t	p	$ß$	F	df	Adj R^2	ΔR^2
Language ability							
Step 1				1.3	1		
Chronological age	-1.14	0.26	-0.21		26	0.011	0.048
Step 2							
Chronological age	-1.15	0.26	-0.23	0.66	2		
AEP-ageR	0.27	0.52	0.05		25	-0.026	0.003
Nonverbal IQ							
Step 1					1		
Chronological Age	-1.1	0.28	-0.21	1.204	27	0.007	0.043
Step 2							
Chronological Age	-.56	0.58	-0.104		2		
AEP-ageR	-2.06	0.08	-0.38	2.8	26	0.134	0.11

$p < 0.05$ (two-tailed).

Table 4. Correlation between AEP-ageR and Properties of Alpha Oscillation

	$\Delta alpha\_power$	alpha-frequency dynamics	alpha temporal correlation
AEP-ageR	r = 0.06	r = 0.107	r = 0.45*
	p = 0.48	p =0.59	p = 0.024

*$p < 0.05$

Table 5. Predicting language ability using alpha LRTC and AEP-ageR

	t	p	β	F	df	Adj R^2	ΔR^2
Language ability							
Step 1				6.39	1		
Alpha LRTC	2.53	0.019*	0.47		23	0.18	0.22
Step 2							
Alpha LRTC	3.24		0.63	5.39	2		
AEP-ageR	-1.91	0.069	-0.37		22	0.27	0.11

*$p < 0.05$ (two-tailed).

3.4 Discussion

In this study, we first attempted to determine whether the AEP-age index is a reliable predictor of oral language abilities in typically developing children aged 5–6 years, and then we investigated the relationship between AEP-age and resting-state alpha frequency oscillation properties, which were available from Kwok et al. (2019).

Based on the results of Kwok et al. (2018), we expected to detect a difference in AEP-age between 5- and 6-year-olds, in which 5-year-olds would have younger "brain ages" than 6-year-olds. However, this prediction was not supported: AEP-age was similar in both age groups. As expected, the 5- and 6-year-olds did not differ in their language and performance IQ scores, because these scores are normalized and not dependent on age.

Our AEP-age findings for 5-6-year-olds are not consistent with those of Kwok et al. (2018), who found that AEP-age distinguished typically developing 8-year-old children from 9-year-olds. According to Kwok et al. (2018), this suggested that AEP-age had a 1-year resolution at least for the two ages (8 vs. 9 years). However, Kwok et al. also found that AEP-age did not differentiate 7-year-olds from 8-year-olds, nor 9-year-olds from 10-year-olds. The issue of inflation and underestimation of AEP-age was not addressed by Kwok et al. (2018) for the 7- and 10-year-old groups, but the 8- and 9-year-olds in their study had lower and higher ages to compare against. We addressed this problem of inflation and underestimation in our study by including grand averages for both 4- and 7-

year-olds in our AEP-age calculations for the 5- and 6-year-old groups. Despite this, our results revealed that AEP-age did not have 1-year resolution to discriminate 5- vs. 6-year-olds. According to Kwok et al. (2018) and Bishop et al. (2011), one possible explanation for the absence of difference between our two age groups is that AEP-age only has sensitivity to 2-year changes in auditory maturation.

Another possibility is maturational changes between the ages of 5 and 6 years are subtle and not detectable by a measure like AEP-age. Moore (2002) reported that children's performance in perceiving complicated speech improves dramatically between the ages of 4 and 5 years and 11 and 12 years. Axonal maturation in the auditory cortex's superficial layers occurs in late childhood, between the ages of six and twelve, and is the last stage in the auditory cortex's structural maturation (Moore & Linthicum Jr, 2007). A small number of filament-stained axons can be seen in layers 2 and 3 of the brain by the age of five, which are the first indicators of this process (Moore & Linthicum, 2007). This suggests that the difference in AEP maturation between 5- and 6-year-olds may be minor and undetectable in this experiment. Our sample size may also have been insufficient to identify slight differences in AEP-age between these age groups.

In contrast to Kwok et al. (2018), our regression analysis revealed that AEP-age did not explain any variance in language ability in our study. However, our regression analysis confirmed that AEP-age is unrelated to performance IQ, as Kwok et al. (2018) found. Our findings imply that AEP-age does not predict linguistic ability in children aged 5-6 years. It is possible that we did not have a sufficiently broad age range for our study to detect language skills and AEP-age, which might be more apparent when the age range is extensive enough. Furthermore, given that the relationship between AEP-age and language ability has only been investigated in one study (Kwok et al., 2018), it is possible that AEP-age is not a strong predictor of children's language ability.

Although all three alpha measures (alpha power, alpha frequency flexibility, and alpha LRTC) were related to language ability in 4-6-year-old children (Kwok et al., 2019), and AEP-age has also been previously related to language ability, we did not find any relationship between AEP-age and resting-state alpha power and alpha frequency

flexibility. However, there was a positive correlation between alpha LRTC and AEP-age: 5-6-year-old children with more mature AEPs had a higher temporal correlation in their resting-state alpha activity.

LRTC is thought to indicate criticality, meaning the extent to which the brain is operating at ideal capacity. This may be connected to better or ideal cognitive function. AEP-age reflects auditory cortex maturity, which may be regarded as the auditory cortex performing at a more advanced or developed state. The correlation between alpha LRTC and AEP-age might be related to the idea that, when the brain is running at ideal capacity (i.e., higher LRTCs), this may positively affect the auditory cortex, allowing it to be more functional. This aligns with Smit et al. (2011), who found that higher alpha LRTC was connected to fewer behavioral errors in a finger-tapping task (Smit et al., 2011).

Although there was a correlation between alpha LRTC and AEP-age, we found no correlation between alpha power and AEP-age. Power and LRTC have been shown to be unrelated (Kwok et al., 2019; Linkenkaer-Hansen et al., 2007). The independence and robustness of LRTC in EEG oscillations suggest that LRTC and oscillation power are driven by different biophysical mechanisms and serve different roles in the brain (Linkenkaer-Hansen et al., 2007). LRTC measures the frequency's rhythm, but the frequency's energy is represented by power. As such, it may not be surprising that we did not see correlations between AEP-age and alpha power while seeing in LRTCs and AEP-age. This finding further supports the need for future EEG research to focus on non-sinusoidal features of EEG signals.

Even though frequency flexibility represents another aspect of self-organized criticality (Garrett et al., 2013; Wainio-Theberge et al., 2022), we found no link between alpha frequency flexibility and AEP-age in our study. One possible reason may be that LRTCs represent a more robust, reliable measure. Past studies support this assertion. Hartley et al. (2012) found LRTCs even in the very immature human brain (i.e., the preterm human brain) when the cerebral cortical structure is not fully developed. Similarly, prior studies identified scale-free properties in asphyxic neonates (Iyer et al., 2014) and preterm infants (gestational age 22–28 weeks) (Iyer et al., 2015) in the hours immediately

following birth. They also demonstrated that the distributions of burst area and duration in these data predict later clinical outcomes (Iyer et al., 2014) and correlate significantly with later mental development (Iyer et al., 2015).

According to our regression analysis AEP-age did not predict language ability in 5-6-year-old children beyond what was explained by alpha LRTC. The purpose of examining the relationship between AEP-age and resting-state alpha oscillation was to see if any neural mechanisms could account for the previously discovered links between AEP-age and oral language abilities (Kwok et al., 2018), as well as between resting-state alpha oscillation and oral language abilities (Kwok et al., 2019). The current study found no evidence that auditory processing maturation has a role in the relationship between resting-state alpha oscillation and oral language ability. One possibility is that the links between auditory maturation and language abilities, as well as spontaneous alpha oscillation features and language abilities, are driven by two separate brain mechanisms.

One critical challenge for understanding the relations between AEP-age, alpha LRTC, and language abilities is that, in the present study, AEP-age did not predict language ability in our study, which is not consistent with Kwok et al. (2018) and Bishop et al. (2011). One possibility is that the number of trials (maximum of 225) utilized in this study for AEP recording from young children were inadequate. The trial numbers used in this study were based on previous studies of school-aged children (Bishop et al., 2011), but it is possible that EEG data recorded from younger children requires more trials. First, younger children may have more trials rejected due to artifacts. Second, the AEPs of children change more rapidly with age in earlier ages, resulting in a higher amount of trial-to-trial variability in this population. The subsequent study was designed to investigate this possibility (see Chapter 4).

Chapter 4

4   Trial number optimization using standardized measurement error

4.1   Introduction

ERPs are very small signals, so to amplify them, many trials are presented to participants, and their brain responses in these trials are averaged together. Averaging removes the effects of the voltage variations, which are not time-locked to the event of interest, thus increasing the signal-to-noise ratio. As a result of this process, the ERPs become more significant than the noise. Therefore, more trials lead to an improved signal-to-noise ratio (Luck, 2014)

The number of trials in ERP experiments has been found to be crucial in obtaining reliable findings. Huffmeijer et al. (2014) proposed that acquiring valid ERP data necessitates a large number of trials (Huffmeijer et al., 2014). Baker et al. (2021) have shown the importance of a large number of trials in order to achieve strong statistical power (Baker et al., 2020). According to Button et al. (2013), low statistical power diminishes the chances of discovering a statistically significant result that reflects a true effect (Button et al., 2013). They also asserted that research in the neuroscience field has relatively poor median statistical power, which leads to an overestimation of effect size and low repeatability of results. Furthermore, according to Clayson and Miller (2017), many contextual elements can influence the reliability of ERP results (Clayson & Miller, 2017). Consequently, they advocated for a formal assessment of ERP scores on a study-by-study basis in order to obtain accurate results. However, many ERP experiments are built on tradition, using rules of thumb or evidence from past research (Baker et al., 2020; Boudewyn et al., 2018).

The importance of trial number selection based on quantification methods has recently received increased attention in the literature. According to Fischer et al. (2017), specific suggestions based on ERP stability tests may not be useful as guidelines for spotting differences across groups (Fischer et al., 2017). They demonstrated that, compared to number-of-trial estimations obtained from a simple examination of stability, more trials

are required to obtain adequate statistical power to detect significant differences between groups. Thigpen et al. (2017) revealed how to assess the internal consistency of three often-studied elements in ERP investigations (Thigpen et al., 2017). They demonstrated how to calculate the effect size for several indices obtained from the ERP to measure the robustness of experimental condition differences. Luck et al. (2021) proposed standardized measurement error (SME) as a universally applicable metric to compare ERP study outcomes across diverse conditions, such as trials. Using this metric, the results from different ERP experiments could be compared together. The lower the SME's mean, the better ERP data quality. Baker et al. (2021) also suggested that the limitations on statistical power in ERP experiments can depend on both sample size and the number of trials. They provided an online tool for creating power contours, which may be used to calculate the best combination of trials and sample size for future investigations.

The amount of within-subjects variability may be a particularly significant issue at younger ages. It is more difficult to get younger children to comply with the necessary requirement for high-quality recordings, so younger children may have more trials rejected due to artifacts. ERP studies involving children can provide additional hurdles, resulting in lower data quality (Brooker et al., 2020). According to Brooker et al. (2020), from 1% to more than 36% of children in ERP studies were excluded due to severe artifacts. It is also worth noting that the amplitude of various ERP components changes with age (Bishop et al., 2011; Johnstone et al., 1996), which could be confused with and perceived as methodological and experimental differences. Additionally, age-related changes may include a higher tolerance for experimental procedures (Brooker et al., 2020).

In our prior work, we were unable to replicate findings of a relation between AEP-age and language ability in 7-10-year-olds found by Kwok et al. (2018) in our study of 4-7-year-olds (see Chapter 3), which let us to question the adequacy of trial numbers in our study of younger children. The metric proposed by Luck et al. (2021) allowed us to assess the quality of data we used. We aimed to address this question in the present study.

4.2   The Present Study

As outlined previously, the quality of the EEG data impacts the ability to detect a statistically significant result. The present study aimed to investigate within-subjects variabilities in AEP waveforms across 4-7 year old participants. If trial-by-trial variation (e.g., noise) is substantially higher in younger years than in older years, younger-age data may be less reliable than older-age data. As a result, more trials for lower ages may be required to account for the difference in trial-to-trial noise between age groups. SME could thus assist us in determining whether trial-to-trial noise varies significantly by age groups between 4-7 years old and whether more trials for younger children are required.

The data set used in this study is the same as our prior work. We used the same AEP data collected from 4-7-year-olds in our lab (i.e., 4-6 year old data reported in Chapter 3 and 7 year-old data reported in Kwok et al., 2018). The findings of this study may provide insight about the impact of trial numbers on previous and future EEG studies of children. It may assist us in optimizing the necessary trial numbers for various age groups and validate or raise concerns about the results of earlier studies. The same reasoning would apply to studies of children with atypical cognitive functions, in that understanding different trial number requirements for different populations would aid us reinterpreting prior findings and ensuring appropriate trial numbers in future research.

4.3 Method

4.3.1   Participants

We had access to AEP data collected in our lab from 74 participants aged 4 (n=14), 5 (n=21), 6 (n=19), and 7 (n=20) years. Participants were recruited partially as a part of an epidemiological investigation of language, reading, and arithmetic skills of 4- to 10-year-old children in a local school district (Archibald et al., 2013) and partially through personal contacts. According to parental reports, the participants had no neurological, hearing, or visual difficulties. Children had to score within the normal range (i.e., no more than 1SD below the mean) on the Performance IQ (PIQ) of the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999) to be included in the study.

4.3.2   Procedure

EEG data were recorded using a 128-channel DenseArray EEG system with HydroCel Geodesic Sensor Nets (Electrical Geodesics, Inc., Eugene, OR, USA) while children were seated in a soundproof booth.

Prior to beginning the ERP recording task, each child's hearing threshold (dB SL) for a 50ms, 490 Hz pure tone was measured using a 2-up/1-down approach. Then AEPs were recorded at 250 Hz while participants were presented with 225 repetitions of the tone for about 5 minutes (Kwok et al., 2018), with tone amplitude set at 50 decibels above the child's hearing threshold. Participants sat calmly in a comfortable chair while auditory stimuli were passively presented binaurally via a digital-to-analogue conversion device (UA-25, Edirol Inc., Japan), an amplification system (Series III, Tucker Davis Technologies Inc., Florida, USA), and insert earphones (ER3A, Etymotic Research, Illinois, USA) (Kwok et al., 2018). To help children stay still during recording, they watched a silent movie. E-PRIME software was used to control presentation of the tones (Psychology Software Tools Inc., Pittsburgh, PA).

Following the EEG recordings, children were administered the WASI PIQ scale for non-verbal IQ assessment.

4.4   Analysis

4.4.1   Standardized measurement Error (SME) analysis

4.4.1.1   Standardized Measurement Error (SME) vs Standard Error of Measurement (SEM) vs Standard Deviation (SD):

The standard deviation (SD) measures the dispersion of data from the mean. In contrast, the standard error of measurement (SEM) estimates how repeated measures of a subject at the same task and under the same condition tend to be distributed around their true score. The standard error of the mean (SME) is a case of the standard error of measurement where the "measurement" is the mean (Luck et al., 2021).

Analytically, the SEM can be expressed as

$$SEM = \frac{SD}{\sqrt{N}}$$

where SD is the standard deviation of the infinite population from which the sample is chosen, and N is the number of observations in the sample. Practically, we do not have access to this population, but instead, we can use the estimate of the SEM ($SEM^{\wedge}$) by taking the standard deviation of the sample (SD^) and dividing it by the square root of the number of observations:

$$SEM^{\wedge} = \left(\frac{SD^{\wedge}}{\sqrt{N}}\right) \qquad\qquad (1)$$

Theoretically, we may estimate the SEM empirically by repeating an experiment multiple times and observing how much the sample mean fluctuates among these repeats. This is referred to as empirical SEM. However, it is not feasible. Instead, we can do a single experiment and use equation (1) to calculate the SEM. This equation allows us to predict the result we would get if we repeated an experiment unlimited times using data from a single experiment.

To put it another way, Equation 1 gives us an estimate of the SD of the sample distribution we would acquire if we performed the experiment several times. Even though the two methods for calculating the SEM are fundamentally different, the SEM obtained by applying Equation 1 to data from a single experiment is substantially identical to the SEM obtained by repeating the experiment and calculating the SEM of the sampling distribution. We call this the analytic SEM when Equation 1 is employed to calculate the SEM (Luck et al., 2021).

SEM can be used in two ways: single-point single-participant SEM and single-point group SEM. The single-participant SEM is determined at each time point throughout all trials of each participant. In contrast, the group SEM is calculated at each time point in a grand average ERP waveform across all subjects. In other words, the number of subjects will be the nominator for the group SEM. In contrast, the number of trials run for each

subject will be the nominator for the single-participant SEM, according to equation (1) (Luck et al., 2021).

4.4.1.2   Applying the SEM to the Time-Window Mean Amplitude Score:

For example, suppose we want to estimate SEM for time-window mean amplitude from 300 to 500 ms in the EEG waveform shown in Figure 5. In that case, we should first obtain time-window mean amplitude scores from 300 to 500 ms on each individual trial, then take the SD of these scores, and finally divide it by the square root of the number of trials (see Figure 5).
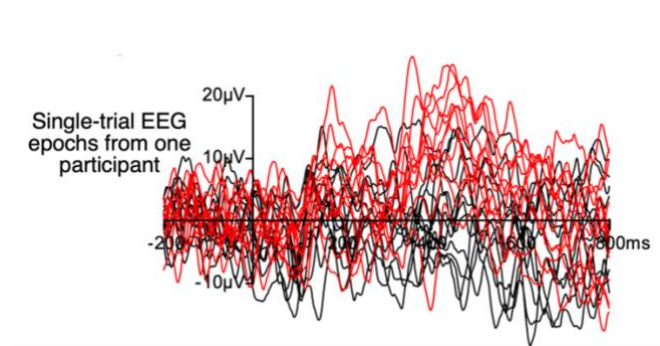
Figure 5. Single-Point Single-Participant SEM from Luck et al., 2021, Supplemental Materials Figure S1

4.4.1.3   Standardized Measurement Error (SME):

SEM is a criterion that can quantify our uncertainty about a subject's true value. A smaller SEM gives us more confidence in the score we get from a subject's averaged ERP waveform. When the SEM is used to quantify single-participant data quality, we call it the *standardized measurement error* or *SME* because it is a metric of measurement error that uses standardized units (units of SD) (Luck et al., 2021).

SME = SEM

4.4.1.4 SME vs. Traditional Analysis:

The traditional method of data analysis is depicted in the bottom graph of Figure 6. As a result, we have a mean grand average (the red line) for each time point and the standard error at each data point (the shaded area). The following section explains how it was calculated.
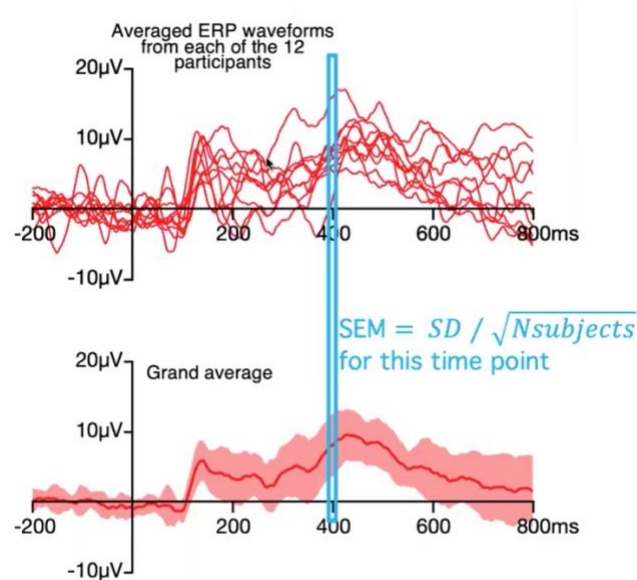
Figure 6. SME vs. Traditional Analysis from Luck et al. (2020). The upper graph shows the averaged ERP waveforms from each participant (e.g., 12), and the bottom graph shows the traditional analysis of 12 participants by calculating the Grand average over all participants.

The averaged ERP waveform for each subject is shown Figure 6, the upper graph (in this example, 12 subjects). At every point in time, we take the voltage for each subject, take the standard deviation of that, and divide it by the square root of the number of subjects. Then, we will have the standard error at that point. This standard error represents both measurement errors (data noise) and fundamental subject differences. However, it provides no information on the precision of our score, which was a time-window mean amplitude of 300–500 ms. So, we can take this concept and apply it in one participant.

Figure 7 depicts all of the trials conducted for a single subject (i.e., single trials, not averaged). The averaged ERPs will be the average of voltages at that time point over the trials. The standard error will be the standard deviation of the voltages at that time point over trials divided by the square root of the number of trials at each point in time (the blue part). This standard error is slightly better because it only represents measurement error (as we excluded the variability between subjects here). However, it only tells us the standard error at each time point and does not tell us about the precision of our score, which was the time-window mean amplitude from 300 to 500 ms.

$$SEM = \frac{SD}{\sqrt{Ntrials}}$$
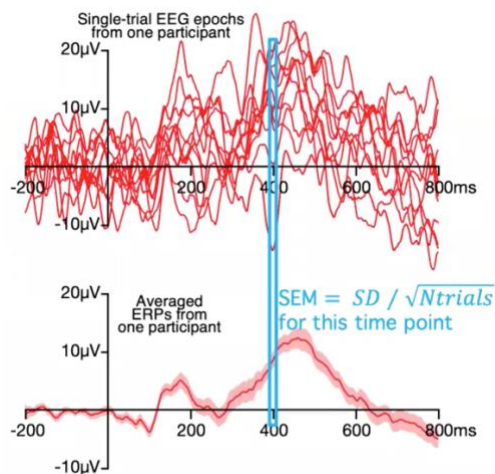
Figure 7. Single-trial EEG epochs from one participant from Luck et al. (2020)

For evaluating standardized measurement error (SME), we must measure the time-window mean amplitude from 300 – 500 ms on each trial before computing. So, the SME reflects the measurement error and gives us precision of our score, which was time-window mean amplitude from 300 – 500 ms (see Figure 8).
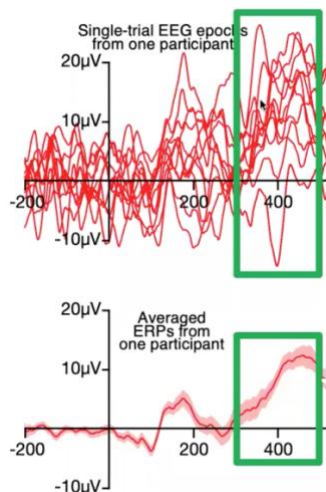
Figure 8. Single-trial EEG epochs from one participant from Luck et al. (2020)

4.4.2   Statistical analysis

By taking the approach Luck et al. (2021) proposed, we used ERPlab toolbox to analyze the SME of typical children for time windows 0-150 ms (P1 component) and 150-300 ms (N2 component) (Ponton et al., 2000) over 9 channels (Fz, F3, C3, T7, Pz, C4, T8, F4, Cz) for four different age groups (4, 5, 6, and 7 years). We considered nine channels out of 128 to reduce the computational analysis load, and because these 9 channels provide an excellent representation of the scalp. These nine channels were the same ones we used in our prior study (see Chapter 3). We analyzed SMEs only on components P1 and N2 of the ERP waveform because components P2 and N1 are not reliably visible at 4 and 5 years (Ponton et al., 2000).

Using two-way ANOVA (4 age groups x 9 channels), we explored whether there was a statistically significant difference between SMEs of different ages in different channels. We ran two separate two-way ANOVA analyses, one for the P1 component (*SME_P1*) and one for the N2 component (*SME_N2*). We conducted post hoc analyses using Tukey HSD.

We also defined two categories: lower age and higher age. We combined the ages 4 and 5 years into the younger group and 6 and 7 years into the older group. Then we ran two separate two-way ANOVA (2 age groups x 9 channels) for SMEs of component P1 and

SMEs of component N2 to investigate the difference in SMEs in these two age categories, and conducted post hoc comparisons using Tukey HSD.

4.5 Results

The two-way (4x9) ANOVA revealed no statistically significant interaction between the effects of age and channels on SME values from the P1 component, $F(24, 618) = .361$, $p = .998$. Figure 9 shows the SME value of each age group in component P1. However, main effects analysis showed that age did have a statistically significant effect on SME_P1 ($p < .001$). Also, simple main effects analysis showed that channels had a statistically significant effect on SME_P1 ($p < .001$) (see Table 6).
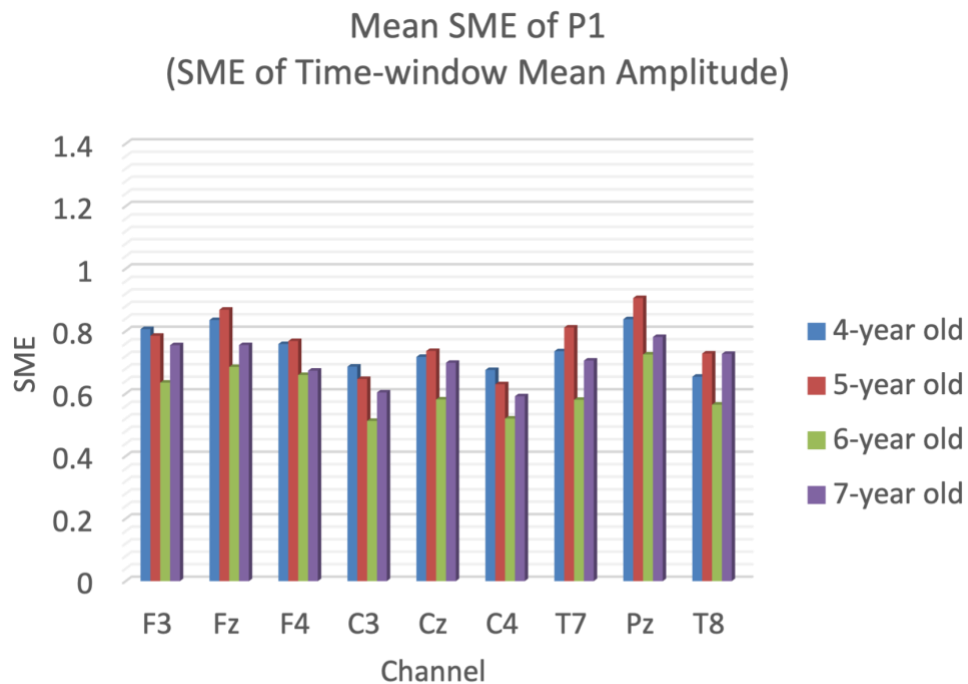
Figure 9. The SME values for component P1 for each age group

Table 6. Two-way ANOVA for SME_P1 across 4 age groups

Source of variation	Sum of Square	df	Mean Square	F	p
Intercept	313.6	1	313.7	6710.99	.000
Age	2.46	3	0.82	17.55	.000
Channel	2.81	8	0.35	7.51	.000
Age * Channel	0.405	24	0.017	0.36	.998
Error	28.88	618	0.047		
Total	356.86	654			

The post hoc comparisons using Tukey HSD showed that there was no significant difference between SME_P1s for ages 4 and 5 years (p = 0.88) and ages 4 and 7 years (p = 0.3), but the SME_P1s for age 4 were significantly greater than age 6 (p < 0.000). The post hoc tests also revealed that the SME_P1s for age 5 were significantly greater than both age 6 (p < 0.000) and age 7 (p < 0.05). However, SME_P1s for age 6 were significantly smaller than SME_P1s for age 7 (p < 0.000) (see Tables 7 and 8).

Because the pattern of SME_P1 differences between age groups (see Table 7) was difficult to interpret, we elected to simplify the analysis by combining the two younger and two older age groups. The two-way (2x9) ANOVA revealed no statistically significant interaction between the effects of age (younger and older) and channels on SME_P1, F(8, 636) = .27, p = .97. However, simple main effects analysis showed that age did have a statistically significant effect on SME_P1 (p < .001). Figure 10 shows how the SME values in component P1 change between the higher-age and lower-age groups. Also, simple main effects analysis showed that channels had a statistically significant effect on SME_P1 (p < .001) (see Table 9).

Table 7. Comparison of SME_P1 between the 4 age groups

Age (I)	Age (J)	Mean difference (I-J)	p
Age 4	Age 5	-0.019	0.45
	Age 6	0.138*	< 0.001
	Age 7	0.046	0.07
Age 5	Age 6	0.157*	< 0.001
	Age 7	0.065*	0.004
Age 6	Age 7	-0.092*	< 0.001

* $p < 0.5$

Table 8. Mean SME_P1 averaged across 9 channels for each age group

Age	Mean	Lower bound	Upper bound
Age 4	0.745	0.707	0.784
Age 5	0.765	0.734	0.796
Age 6	0.607	0.574	0.64
Age 7	0.699	0.668	0.731
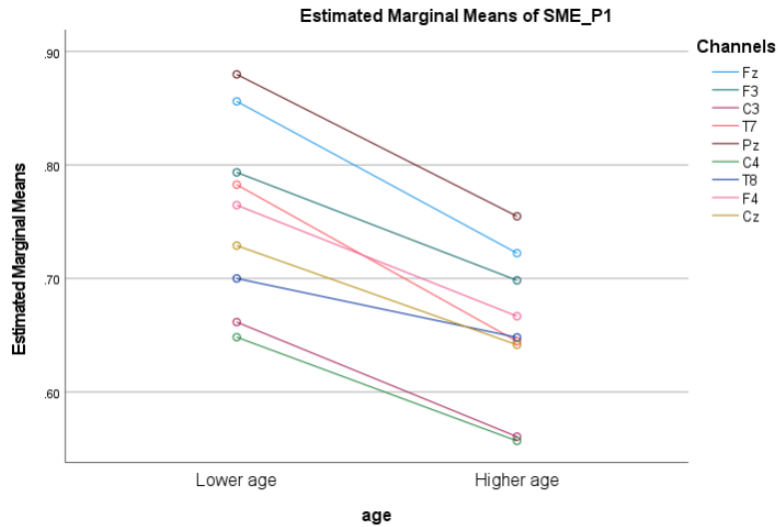
Figure 10. SME values for component P1 in each channel between higher-age and lower age groups

Table 9. Two-way ANOVA for SME_P1 across younger and older age groups

Source of variation	Sum of Square	*df*	Mean Square	*F*	*p*
Intercept	324.58	1	324.58	6895.67	.000
Age	1.705	1	1.705	36.232	< .001
Channel	3.018	8	0.37	8.015	< .001
Age * Channel	0.103	8	0.013	0.27	.97
Error	29.94	636	0.047		
Total	356.86	654			

The post hoc comparisons using Tuckey HSD showed that SME_P1 for the younger group was significantly higher than the older group (p < 0.001) (see Table 10).

Table 10. Mean SME_P1 averaged across 9 channels and comparison of younger and older age groups

Age	Mean	Mean difference (I – J)	p
Lower-age (I)	0.757	0.102*	< 0.001
Higher-age (J)	0.655		

* $p < 0.5$

Two-way (4x9) ANOVA for SME_N2 showed no significant interaction between age and channel, $F(24, 618)=.313$, p=.999, but significant main effects for both age (p < .000) and channel (p < .000) (see Table 11). Figure 11 shows the SME value of each age group in component N2.

Table 11. Two-way ANOVA for SME_N2 across the 4 age groups

Source of variation	Sum of Square	df	Mean Square	F	p
Intercept	573.83	1	573.83	4168.54	.000
Age	6.05	3	2.018	14.66	.000
Channel	5.021	8	0.63	4.56	.000
Age * Channel	1.034	24	0.043	0.313	.999
Error	85.072	618	0.138		
Total	690.29	654			
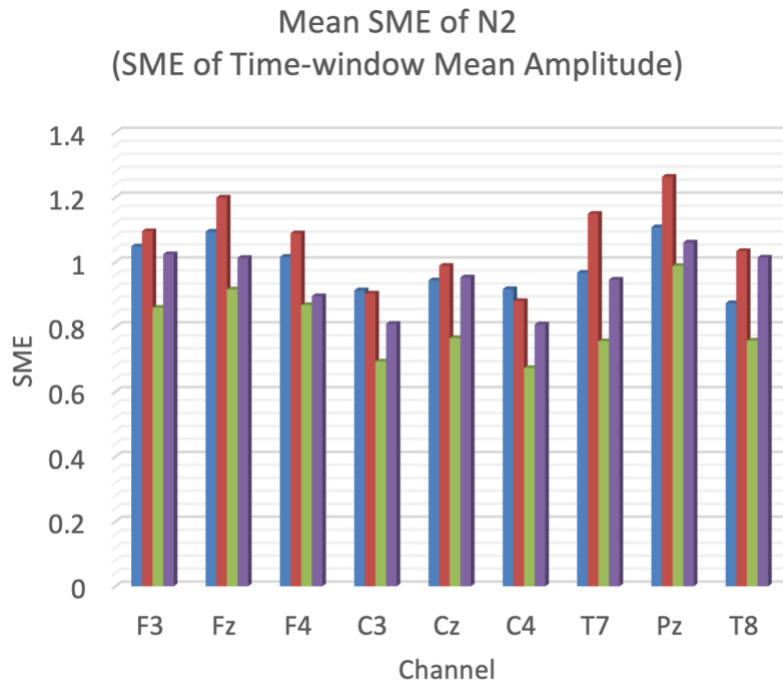
Figure 11. The SME values for component N2 for each age group

Post hoc comparisons using Tukey HSD showed that there is no significant difference between SME_N2 for ages 4 and 5 (p = 0.31) and ages 4 and 7 (p = 0.78), but the SME_N2s for age 4 were significantly greater than age 6 (p < 0.001). In addition, SME_N2s for age 5 were significantly greater than both age 6 (p<0.001) and age 7 (p = 0.014). However, SME_N2 for age 6 were significantly smaller than SME_N2 for age 7 (p = 0.003) (see Tables 12 and 13).

The two-way (2x9) ANOVA revealed no statistically significant interaction between the effects of age (younger and older) and channels on SME_N2, F(8, 635) = .25, p = .98. However, main effects analysis showed that age did have a statistically significant effect on SME_N2 (p < .001). Figure 12 shows how the SME values in component N2 change between the higher-age and lower-age groups. Also, main effects analysis showed that channel had a statistically significant effect on SME_N2 (p < .001) (see Table 14).

Table 12. Post-hoc comparison of SME_N2 between the 4 age groups

Age (I)	Age (J)	Mean difference	p
Age 4	Age 5	-0.076	0.31
	Age 6	0.18*	< 0.001
	Age 7	0.041	0.78
Age 5	Age 6	0.26*	< 0.001
	Age 7	0.12*	0.014
Age 6	Age 7	-0.14*	0.003

* $p < 0.5$

Table 13. Mean SME_P1 averaged across 9 channels for each age group

Age	Mean	Lower bound	Upper bound
Age 4	0.99	0.92	1.06
Age 5	1.07	1.01	1.12
Age 6	0.81	0.75	0.86
Age 7	0.95	0.89	1.002
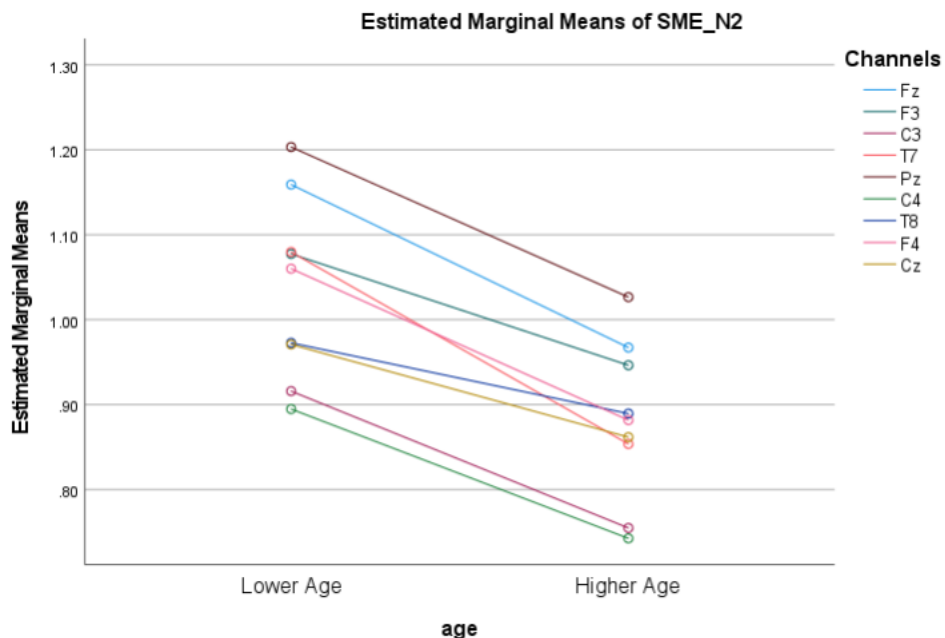
Figure 12. SME values for component N2 in each channel between higher-age and lower age groups

Table 14. Two-way ANOVA for SME_N2 across younger and older age groups

Source of variation	Sum of Square	df	Mean Square	F	p
Intercept	597.51	1	597.51	4318.96	< .001
Age	3.99	1	3.99	28.83	< .001
Channel	5.39	8	0.67	4.87	< .001
Age * Channel	0.28	8	0.035	0.25	.98
Error	87.85	635	0.138		
Total	689.93	653			

The post hoc comparison using Tuckey HSD showed that younger children had a significantly higher SME_N2 than older children (p < 0.001) (see Table 15).

Table 15. Mean SME_P1 averaged across 9 channels and comparison of younger and older age groups

Age	Mean	Mean difference (I – J)	*p*
Lower-age (I)	1.037	0.157*	< 0.001
Higher-age (J)	0.88		

* *p* < 0.5

4.6 Discussion

In this study, we first attempted to determine whether trial-by-trial variation (i.e., noise) decreases between 4 to 7 years. Then we investigated whether the trial-by-trial noise is higher in younger (4-5 years old) than in older children (6-7 years old). To do so, we examined the quality of the data from our previous work using the standardized measurement error (SME) approach that Luck et al. (2021) recently proposed.

Given our hypothesis that trial-by-trial noise would decrease with age, we expected to detect a difference in SME for both P1 and N2 across all four age groups. However, our results did not entirely support this hypothesis. Consistent with our predictions, the SME of P1 and N2 were significantly higher in 4-year-olds compared to 6-year-olds, and higher in 5-year-olds compared to 6- and 7-years-olds. However, we found no significant differences in P1 and N2 SME between children aged 4 and 5 years or 4 and 7 years, which does not align with our predictions. Moreover, the SME of components P1 and N2 were actually significantly smaller (less noisy) in 6-year-olds compared to children one year older, the direct opposite of what we predicted. The pattern of these findings is difficult to explain and in general, do not align with our overall hypothesis. Since it is difficult to predict whether the noise will diminish with age, it is essential that all ERP research report SME values, as Luck et al. (2021) have advised.

When we merged children aged 4 and 5 years into a single younger age group and children aged 6 and 7 years into an older age group, we found a significant difference in SME of both components P1 and N2. The SME of younger children was significantly higher than the older children, which is consistent with our expectations. These results are not in line with the findings of Isbell and Grammer (2022). They used SME to assess the data quality of mean ERP amplitude for error-related negativity (ERN) and the error positivity (Pe) in typically developing 5-6 years old children during a Go-No-go task. Their study found no correlation between SME and age in these participants. However, these findings suggest that the level of trial-by-trial noise may be of greater concern at younger ages. In this case, younger children may need to participate in more trials to acquire high-quality recordings, which may need to be addressed in future studies.

In our first analysis, the SMEs on components P1 and N2 were significantly higher at age 5 than at age 6. The AEPs in these two age groups were of interest in our prior study (see Chapter 3). If we consider these findings in isolation, they may suggest that trial-by-trial noise during the recording of AEPs in response to a pure tone may be of concern when comparing 5- and 6-year-old children. In this case, it is possible that the AEP-age paradigm used in our prior study may require modification, namely more trials.

The comparison of SME across different channels was not the focus of the present study, and all of our reported SME values were averaged over the nine selected channels (Fz, F3, C3, T7, Pz, C4, T8, F4, Cz). Main effects for channel were identified in both of our analysis. We did not examine them further because the effects of channel did not interact with the effects of our variable of interest, age. Although we did not have any hypotheses regarding why and how particular channels would provide more accurate ERP data than others, further research in this area could yield valuable information about brain activity.

Even though we did not compare the SME in AEPs acquired from children with neurodevelopmental conditions to those acquired from typically developed children in our study, it would be important to do so in future investigations. The SME analysis presented here could be a valuable starting point for evaluating the quality of ERP data and optimizing trial numbers in children who might be predicted to have greater sources

of noise (e.g., associated with movement or attentional fluctuations) that can affect data quality.

Chapter 5

5 General Discussion

The links between brain activity and language acquisition have been explored from different perspectives. The relationship between EEG signals and language development has been suggested as one of the best approaches to use in the early stages of development because it is possible to acquire these signals without active participation. Recently, the links between spontaneous alpha frequency oscillation and language skills in young children have been investigated (Kwok et al., 2019). This study demonstrated that three metrics of resting-state alpha oscillation, namely alpha power, alpha frequency flexibility, and alpha long-range temporal correlation, significantly correlated with language abilities in children aged 4-6 years. From another perspective, the role of auditory cortical response maturity in linguistic skills has been investigated. In this area, one metric called AEP-age has been defined to capture the maturity of the auditory cortex (Bishop et al., 2011). This measure has been shown in several studies to be sensitive to developmental level (Bishop et al., 2011; Kwok et al., 2018), and in one study, it has been shown to be able to predict language abilities in school-aged children, as well (Kwok et al., 2018).

This thesis aimed to refine and broaden our understanding of the potential connections of the above spontaneous and evoked neural measures with spoken language during the earliest stages of development. The first study proposed a method to examine potential links between spontaneous alpha power, alpha frequency flexibility, and alpha long-range temporal correlation and language development in infants and toddlers between the ages of 18 and 48 months. The second study investigated (a) the utility of the AEP-age index to capture auditory cortex maturation in 5- and 6-year-old children, (b) the ability of AEP-age to predict language skills in these participants, and (c) potential links between AEP-age, spontaneous alpha frequency properties, and language abilities in the same population. Finally, the third study was designed to explore whether (a) the AEP trial numbers we employed in the first study were adequate and (b) age should be taken into account when designing an ERP experiment with children. In this chapter, I summarize

each of the three studies undertaken for this thesis and discussed future directions and general implications for this line of research.

5.1 Study 1: The Role of Alpha Oscillations in Early Language Acquisition. A stage 1 registered report

Previous research has established a relationship between spontaneous brain activity and children's language development and ability. A previous study in our lab showed that spontaneous alpha oscillations during resting-state related to language development in 4-6-year-old children. Because language development, as well as brain growth, proceeds rapidly in the early stages of development, investigating this association in younger pre-school children would be informative. The study pre-registration outlined in Chapter 2 aims to add evidence to the literature for this purpose. In this study, we will recruit 120 typically developing children between the ages of 18 and 48 months. While children sit comfortably on their parents' laps viewing a silent animation, we will record their brain signals using EEG. Three minutes of resting-state EEG data will be captured. We will assess participants' oral language skills using a standardized test. To investigate the moment-to-moment fluctuations of resting-state alpha oscillations, we will apply the methodologies defined by Kwok et al. (2019) including alpha frequency flexibility and alpha long-range temporal correlation analysis, as well as alpha power. We will then examine potential correlations between these alpha frequency features and oral language ability. Findings of this study will build our understanding of whether spontaneous brain activity connects with oral language development in young children and will support future research of whether EEG resting-state neural activity during these developmental periods can predict early language acquisition difficulties.

5.2 Study 2: The relationship between AEP-age, alpha resting-state oscillations, and language ability in young children

Previous research has indicated that auditory cortical response maturation and children's linguistic abilities are related. A previous study in our lab revealed that an index of AEP maturity, named *AEP-age*, is related to the strength of language skills in children aged 7-

10 years, and Kwok et al. (2019) showed that spontaneous alpha oscillations during resting-state related to language maturity in 4-6 year old children. These findings raise questions about possible relationships between AEP-age, spontaneous alpha oscillation, and language abilities in children, which has yet to be investigated and was the focus of the study outlined in Chapter 3. We were able to examine these questions in 5-6 year old children using AEP and resting-state data previously gathered as a part of several studies in our lab. Participants' resting-state EEG was recorded while sitting comfortably in a soundproof room, and their AEP was recorded during presentation of pure tone stimuli during the same lab visit. Children's spoken language abilities and nonverbal IQ were assessed using standardized tests. Results revealed that AEP-age was not sensitive enough to discriminate between 5- and 6-year-olds, and did not predict chronological age or language ability in these children. No significant correlation was found between the AEP-age index and two of the alpha oscillation measures, alpha power and flexibility. However, results demonstrated a correlation between AEP-age and alpha oscillation long-range temporal correlation. This study added to our understanding of how the auditory cortex may be associated with and contribute to spontaneous brain activity, and whether these measures are related to and could predict language abilities in young children.

5.3 Study 3: Trial number optimization using standardized measurement error

The study outlined in Chapter 4 aimed to examine whether trial-by-trial noise diminishes with age using a new universal metric of ERP data quality called *standardized measurement error* (SME) (Luck et al., 2021). If noise decreases with age, this may mean that we would need more ERP trials for younger children compared to older children in order to gather reliable data. We wondered if past research in this area had been limited by a lack of consideration for the number of trials required for different age groups. If this is the case, previous data may need to be re-analyzed, and future studies may need to account for this in their design. We used the technique recently proposed by Luck et al. (2021) to quantify SME for two EEG components, P1 and N2, in 9 channels from 4 different age groups ranging from 4 to 7 years old. Then, using two-way ANOVA, we

investigated potential differences in the SMEs of these four age groups in the nine chosen channels. Even though there was not a steady decrease in SMEs between each of these four age groups, the results suggested that SME decreases with age in these participants. This study supported the notion that the trial numbers utilized in our prior study (see Study 2) may not be adequate, and we may need more trial numbers in younger participants to find more reliable results.

5.4 Future Directions and Implications

The next step for Study 1 is to submit it as a Stage 1 registered report in order to receive helpful feedback from reviewers, receive in-principle acceptance that the study will be published regardless of the findings once completed, then publicly register the study. Data collection will then follow.

The majority of findings from Study 2 were unanticipated and inconsistent with prior research. Moving forward, it would be advisable to broaden the age ranges and sample sizes for this type of analysis to ensure reliable results. This study only included two ages (5 and 6 years), whereas previous related research had more age groups. In addition, given the findings of Study 3, it is possible that altering the experimental design for younger age groups (i.e., increasing the number of trials) would be necessary to obtain results that are as reliable as those reported for older children.

The results of Study 3 suggest that future AEP studies of young children may benefit from using recently proposed programs to justify the choice of trial numbers and to find a better fit of these for each age range. Baker et al. (2021) has offered one online tool for this purpose, which may have the potential to be considered in future experimental designs. It would also be informative to conduct a data quality assessment of AEP studies of children with neurodevelopmental difficulties compared to typically-developing children using the SEM approach.

One other avenue for this line of research may be using state-of-the-art technology, such as artificial intelligence. These methods have been vastly employed in numerous studies, and they may be able to aid in our investigation of the neuromarkers of interest in this

thesis. These approaches have begun to be used in the diagnosis of neurodevelopmental disorders, particularly autism spectrum disorder (Anagnostopoulou et al., 2020; Chen et al., 2020; Megerian et al., 2022), and may have potential to predict future language trajectories based on the EEG data from the very early stages of the development.

As highlight at the first chapter of this thesis, identifying early indications of future persistent language difficulties could greatly benefit clinical interventions. The significance of early interventions in neurodevelopmental disorders has been underscored extensively in prior research (Cioni et al., 2016; Hadders-Algra, 2021). Finding early, robust, and reliable neuromarkers to detect the first signs of language disorders would open new avenues for improving health and rehabilitation outcomes. In addition to future clinical implications, this thesis also has important implications for research. The application of SME analysis to data quality assessment offers new perspectives on ERP studies of young children and toddlers. The accuracy of the data from all ERP experiments conducted to date may be impacted by the uniform design used for participants of all ages. The age sensitivity of AEP studies and the possibility that younger children may require greater trial numbers in order to obtain reliable outcomes was a novel contribution to the scientific literature. However, further research in this area is needed.

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Curriculum Vitae

Name: Tahereh Karami Shoar

Post-secondary Amirkabir University of Technology
Education and   Tehran, Iran
Degrees: 2008-2013 B.Sc., Electrical Engineering

         University of Tehran
         Tehran, Iran
         2013-2016 M.Sc., Clinical Psychology

         Western University
         London, Ontario, Canada
         2019-2022 M.Sc., Neuroscience

Related Work   Autism Spectrum and Language Disorder Lab
Experience   Western University
         Supervisor: Dr. Janis Oram Cardy
         2019-Present

         Graduate Teaching Assistant
         Western University
         2019-2022