

DEVELOPMENT AND PLASTICITY OF THE MISMATCH NEGATIVITY IN
TYPICALLY DEVELOPING CHILDREN, CHILDREN WITH LANGUAGE
IMPAIRMENTS, AND ADULTS

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Abstract

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The processing of human speech requires the integration of brief auditory stimuli that enter the central nervous system in rapid succession. This ability has been termed rapid auditory processing (RAP). RAP skills are believed to underlie successful language acquisition, and deficits in RAP have been consistently observed in individuals with developmental language impairments (LI). These disorders and the role of RAP in language development have been the focus of much research over the past several decades. However, many questions remain regarding the etiology and remediation of developmental LIs, as well as the normal maturational mechanisms involved in language acquisition, including the role of attention in the modification of neural sound representations. The series of experiments described here investigate the relations among RAP, attention, and language ability in several populations: normal adults, children diagnosed with an LI, and children with typical language development (TLD) using the mismatch negativity response (MMN), a component of the auditory ERP waveform that reflects an automatic auditory change detection process. The impact of an auditory discrimination training program (Fast ForWord-Language®) was also investigated.

Results show that in TLD children, developmental MMN components (early and late MMN) are modulated by rate and attention in a manner similar to adults. Attention enhances auditory discrimination in TLD children, increasing auditory processing to a level that is similar to adults. The MMN components in LI children differ from TLD children, particularly in the latency of the responses, consistent with the idea of a RAP deficit underlying developmental LI. In the LI children who completed FFWD, immediate and significant gains in oral language and auditory temporal processing abilities, as well as changes in MMN responses were observed. Further, significant associations are found between behavioral and MMN measures, with the most robust and persistent relations found between behavior and MMN components elicited by paired complex tones presented at a rate in the time range that is essential for accurate speech processing (70 ms). Together, these findings facilitate a better understanding of the role of RAP in language processing, specifically with regard to maturation, attentional mechanisms, and neural plasticity.

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Figure 6.2.2.1: TLD eMMN Amplitude in the Ignore vs. Attend Conditions. eMMN amplitudes are significantly larger in the Attend condition as compared to the Ignore condition for the 300 and 70 ms ISIs only. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Amplitudes shown are 300 ms ISI: Ignore -2.16 (SE 0.47) (Ch. 4), Attend -3.21 (SE 0.47) (Ch. 4); 70 ms ISI: Ignore -1.73 (SE 0.35) (Ch. 53), Attend -2.83 (SE 0.46) (Ch. 53); 10 ms ISI: Ignore -1.18 (SE 0.64) (Cz), Attend -1.63 (SE 1.19) (Cz) (p. 118).

Figure 7.2.1a: MMN Amplitude in Adults and TLD Children in the Ignore Condition. MMN amplitude elicited by the 10 ms ISI stimuli is significantly larger for Adults as compared to TLD children. Values

shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Amplitudes shown are 300 ms ISI: Adults -2.22 (SE 0.37) (Cz), TLD -2.16 (SE 0.47) (Ch. 4); 70 ms ISI: Adults -2.59 (SE 0.26) (Cz), TLD -1.73 (SE 0.35) (Ch. 53); 10 ms ISI: Adults -2.81 (SE 0.34) (Cz), TLD -1.18 (SE 0.64) (Cz) (p. 125).

Figure 7.2.1b: MMN Amplitude in Adults and TLD Children in the Attend Condition. There are no significant differences in MMN amplitude between Adults and TLD children elicited by the three rates of presentation. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Amplitudes shown are 300 ms ISI: Adults -3.33 (SE 0.58) (Cz), TLD -3.21 (SE 0.47) (Ch. 4); 70 ms ISI: Adults -3.73 (SE 0.47) (Ch. 4), TLD -3.08 (SE 0.45) (Ch. 4); 10 ms ISI: Adults -2.18 (SE 0.69) (Cz), TLD -1.63 (SE 1.19) (Cz) (p. 125).

Figure 8.1.1.1a: LI Ignore 300 ms ISI grand averaged waveforms (n = 15). Channel Fcz (Channel 4) is outlined. The standard wave is shown in blue, the deviant wave in red, and the difference wave (Deviant – Standard) in green (p. 136).

Figure 8.1.1.1b: LI Ignore 300 ms ISI grand averaged waveform at Fcz (Channel 4). The standard wave is shown in blue, the deviant wave in red, and the difference wave (Deviant – Standard) in green. In the difference wave, the eMMN occurs at a latency of at 508 ms (138 ms after the second tone in the deviant stimulus) and is -1.3 uV in amplitude. The IMM/LDN occurs at a latency of 844 ms (474 ms after the second tone in the deviant stimulus) and is -1.5 uV in amplitude (p. 136).

Figure 8.1.1.2a: LI Ignore 70 ms ISI grand averaged waveforms (n = 29). Channel Fcz (Channel 4) is outlined (p. 138).

Figure 8.1.1.2b: LI Ignore 70 ms ISI grand averaged waveform at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 396 ms (256 ms after the second tone in the deviant stimulus) and is -0.8 uV in amplitude, and the IMM/LDN occurs at a latency of 560 ms (420 ms after the second tone in the deviant stimulus) and is -0.9 uV in amplitude (p. 138).

Figure 8.1.1.3a: LI Ignore 10 ms ISI grand averaged waveforms (n = 14). Channel Fcz (Channel 4) is outlined (p. 138).

Figure 8.1.1.3b: LI Ignore 10 ms ISI grand averaged waveform at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 369 ms (289 ms after the second tone in the deviant stimulus) and is -0.8 uV in amplitude. The IMM/LDN occurs at a latency of 560 ms (480 ms after the second tone in the deviant stimulus) and is -0.9 uV in amplitude (p. 138).

Figure 8.1.2.1a: LI Attend 300 ms ISI grand averaged waveforms (n = 4). Channel Fcz (Channel 4) is outlined (p. 140).

Figure 8.1.2.1b: LI Attend 300 ms ISI grand averaged waveform at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 512 ms (142 ms after the second tone in the deviant stimulus) and is -3.0 uV in amplitude. The IMM/LDN occurs at a latency of 960 ms (590 ms after the second tone in the deviant stimulus) and is -1.8 uV in amplitude (p. 140).

Figure 8.1.2.2a: LI Attend 70 ms ISI grand averaged waveforms (n = 24). Channel Fcz (Channel 4) is outlined (p. 140).

Figure 8.1.2.2b: LI Attend 70 ms ISI grand averaged waveform at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 464 ms (324 ms after the second tone in the deviant stimulus) and is -0.9 uV in amplitude. The IMM/LDN occurs at a latency of 656 ms (516 ms after the second tone in the deviant stimulus) and is -1.1 uV in amplitude (p. 140).

Figure 8.1.2.3a: LI Attend 300 ms ISI grand averaged waveforms (n = 6). Channel Fcz (Channel 4) is outlined (p. 141).

Figure 8.1.2.3b: LI Attend 10 ms ISI grand averaged waveform at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 456 ms (376 ms after the second tone in the deviant stimulus) and is -1.5 uV in amplitude. The IMMN/LDN occurs at a latency of 568 ms (488 ms after the second tone in the deviant stimulus) and is -0.7 uV in amplitude (p. 141).

Figure 8.2.3.1: eMMN Latency in the Ignore Condition for TLD vs. LI Children. TLD children exhibit significantly shorter eMMN latencies as compared to LI children in the 300 and 70 ms ISIs. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Latencies shown are 300 ms ISI: TLD 116.4 (SE 2.04) (Cz), LI 184.2 (SE 29.9) (Cz, Ch. 4); 70 ms ISI: TLD 205.2 (SE 22.3) (Cz), LI 254 (SE 23) (Cz); 10 ms ISI: TLD 224.8 (SE 19.4) (Cz), LI 226 (SE 16.5) (Cz) (p. 147).

Figure 8.3a: eMMN Latency in TLD and LI Children in the Ignore Condition. TLD children have significantly shorter eMMN latencies at the 300 ms ISI as compared to the 70 and 10 ms ISIs, while for the LI children there are no significant differences in eMMN latency among any of the three ISIs. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Latencies shown are 300 ms ISI: TLD 116.4 (SE 2.04) (Cz), LI 184.2 (SE 29.9) (Cz, Ch. 4); 70 ms ISI: TLD 205.2 (SE 22.3) (Cz), LI 254 (SE 23) (Cz); 10 ms ISI: TLD 224.8 (SE 19.4) (Cz), LI 226 (SE 16.5) (Cz) (p. 155).

Figure 8.3b: eMMN Latency in TLD and LI Children in the Attend Condition. In the Attend condition, TLD children show the same pattern of rate-related differences in eMMN latency as they do in the Ignore condition (300 ms ISI > 70 and 10 ms ISI), while LI children continue to show no differences in eMMN latency among the rates compared. For LI children, only the Attend 300 vs. 10 ms ISIs were available for comparison in these analyses. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Latencies shown are 300 ms ISI: TLD 114 (SE 9.4) (Ch. 4), LI 187 (SE 44.1) (Ch. 4); 70 ms ISI: TLD 276.8 (SE 22.2) (Ch. 4); 10 ms ISI: TLD 234.7 (SE 13.1) (Ch. 4), LI 156 (SE 30.2) (Ch. 4) (p. 155).

Figure 8.3c: IMMN/LDN Latency in TLD and LI Children in the Ignore Condition. Both TLD and LI children exhibit longer IMMN/LDN latencies at the 300 ms ISI as compared to the 70 and 10 ms ISIs in the Ignore condition. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Latencies shown are 300 ms ISI: TLD 467.8 (SE 18.1) (Ch. 54, 4), LI 471 (SE 12.5) (Cz); 70 ms ISI: TLD 441.1 (SE 15.7) (Ch. 54, 4), LI 439.8 (SE 12.6) (Ch. 4); 10 ms ISI: TLD 443.8 (SE 15.5) (Ch. 4), LI 436.4 (SE 18.4) (Ch. 4, Cz) (p. 156).

Figure 8.3d: IMMN/LDN Latency in TLD and LI Children in the Attend Condition. In the TLD children, there are no significant differences in IMMN/LDN latencies elicited by the different rates of presentation in the Attend condition. However, LI children have significantly longer IMMN/LDN latencies elicited by the 300 ms ISI as compared to the 10 ms ISI stimuli. Values shown in this figure are from representative channels demonstrating the overall effects found in the statistical analyses. Latencies shown are 300 ms ISI: TLD 422.2 (SE 59.8) (Ch. 4), LI 541 (SE 39.5) (Cz); 70 ms ISI: TLD 441.1 (SE 15.7) (Ch. 54, 4); 10 ms ISI: TLD 451.6 (SE 52.5) (Ch. 4), LI 424.7 (SE 28.4) (Cz) (p. 156).

Figure 9.1.1.1a: TLD Ignore 300 ms ISI grand averaged waveforms at Visit 2 (n = 7). Channel Fcz (Channel 4) is outlined (p. 160).

Figure 9.1.1.1b: TLD Ignore 300 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). The standard wave is shown in blue, the deviant wave in red, and the difference wave (Deviant – Standard) in green. In the difference wave, the eMMN occurs at a latency of at 488 ms (118 ms after the second tone in the deviant stimulus) and is -1.7 uV in amplitude. The IMMN/LDN occurs at a latency of 788 ms (418 ms after the second tone in the deviant stimulus) and is -2.2 uV in amplitude (p. 160).

Figure 9.1.1.2a: TLD Ignore 70 ms ISI grand averaged waveforms at Visit 2 (n = 12). Channel Fcz (Channel 4) is outlined (p. 161).

Figure 9.1.1.2b: TLD Ignore 70 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the eMMN (observed as a negative-going “notch”) occurs at a latency of at 400 ms (260 ms after the second tone in the deviant stimulus) and is -0.3 uV in amplitude, and the IMM/LDN occurs at a latency of 532 ms (392 ms after the second tone in the deviant stimulus) and is -1.5 uV in amplitude (p. 161).

Figure 9.1.1.3a: TLD Ignore 10 ms ISI grand averaged waveforms at Visit 2 (n = 5). Channel Fcz (Channel 4) is outlined (p. 161).

Figure 9.1.1.3b: TLD Ignore 10 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the only peak of interest is a large, broad negativity (-1.1 uV) at 448 ms (368 ms after the second tone in the deviant stimulus) that is the child IMM/LDN. There is no eMMN identified in the waveform (p. 161).

Figure 9.1.2.1a: LI Ignore 300 ms ISI grand averaged waveforms at Visit 2 (n = 11). Channel Fcz (Channel 4) is outlined (p. 162).

Figure 9.1.2.1b: LI Ignore 300 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 500 ms (130 ms after the second tone in the deviant stimulus) and is -1.5 uV in amplitude. The IMM/LDN occurs at a latency of 796 ms (426 ms after the second tone in the deviant stimulus) and is -1.6 uV in amplitude (p. 162).

Figure 9.1.2.2a: LI Ignore 70 ms ISI grand averaged waveforms at Visit 2 (n = 22). Channel Fcz (Channel 4) is outlined. (p. 163).

Figure 9.1.2.2b: LI Ignore 70 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). The IMM/LDN occurs at a latency of 564 ms (424 ms after the second tone in the deviant stimulus) and is -2.1 uV in amplitude. An eMMN is not present in the difference wave. This is likely due to the large positive component (P3) following the N2 in the deviant wave (p. 163).

Figure 9.1.2.3a: LI Ignore 10 ms ISI grand averaged waveforms at Visit 2 (n = 11). Channel Fcz (Channel 4) is outlined (p. 164).

Figure 9.1.2.3b: LI Ignore 10 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). The IMM/LDN occurs at a latency of 456 ms (376 ms after the second tone in the deviant stimulus) and is -1.3 uV in amplitude. An eMMN is not present in the difference wave. This is likely due to the large positive component (P3) following the N2 in the deviant wave (p. 164).

Figure 9.1.3.2a: TLD Attend 70 ms ISI grand averaged waveforms at Visit 2 (n = 12). Channel Fcz (Channel 4) is outlined (p. 165).

Figure 9.1.3.2b: TLD Attend 70 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 408 ms (268 ms after the second tone in the deviant stimulus) and is -0.7 uV in amplitude. The IMM/LDN occurs at a latency of 696 ms (556 ms after the second tone in the deviant stimulus) and is -1.2 uV in amplitude (p. 165).

Figure 9.1.3.3a: TLD Attend 10 ms ISI grand averaged waveforms at Visit 2 (n = 4). Channel Fcz (Channel 4) is outlined (p. 166).

Figure 9.1.3.3b: TLD Attend 10 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). The IMM/LDN occurs at a latency of 616 ms (536 ms after the second tone in the deviant stimulus) and is -0.8 uV in amplitude. An eMMN was not identified in the waveform (p. 166).

Figure 9.1.4.2a: LI Attend 70 ms ISI grand averaged waveforms at Visit 2 (n = 17). Channel Fcz (Channel 4) is outlined (p. 168).

Figure 9.1.4.2b: LI Attend 70 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 448 ms (308 ms after the second tone in the deviant stimulus) and is -0.2 uV in amplitude. The last negativity in the difference wave is not identified as the IMM/LDN because there is no inversion of polarity at the mastoids (p. 168).

Figure 9.1.4.3a: LI Attend 10 ms ISI grand averaged waveforms at Visit 2 (n = 5). Channel Fcz (Channel 4) is outlined (p. 169).

Figure 9.1.4.3b: LI Attend 10 ms ISI grand averaged waveform at Visit 2 at Fcz (Channel 4). In the difference wave, the eMMN occurs at a latency of at 408 ms (328 ms after the second tone in the deviant stimulus) and is -1.8 uV in amplitude. The IMM/LDN occurs at a latency of at 576 ms (496 ms after the second tone in the deviant stimulus) and is -1.8 uV in amplitude (p. 169).

Figure 9.2.5: Changes in eMMN Latency from Visit 1 to Visit 2 in LI Children. From Visit 1 to Visit 2, LI children exhibit a significant increase in eMMN latency in the Ignore condition, and a significant decrease in eMMN latency in the Attend condition. Each line represents a frontocentral channel (p. 188).

Figure 9.3.1a: CELF-4 standard scores are plotted for TLD and LI children for Visit 1 (solid bars) and Visit 2 (shaded bars). There were no significant changes in CELF-4 scores in the TLD group, but in the LI group, all CELF-4 scores increased significantly from Visit 1 to Visit 2 (p. 192).

Figure 9.3.1b: CELF-4 Standard scores at Visit 1 and Visit 2 are shown for TLD and LI children. In TLD children there is very little change (*ns*) in (a) CELF-Core, (b) Receptive, or (c) Expressive Language standard scores from Visit 1 to Visit 2. However, in LI children significant increases ($p \leq .01$) in (d) CELF-Core, (e) Receptive, and (f) Expressive Language standard scores are observed from Visit 1 to Visit 2. Note that there are different scales for TLD and LI children (p. 192).

Figure 9.3.4.2a: ART-C Performance for 2-tone sequences at Visit 1 and Visit 2 (all subjects). This figure illustrates improvements in performance from Visit 1 to Visit 2 for the three shortest ISIs of the 2-tone sequences (ISI x Visit: $F = 4.76$, $p = .01$) for all participants. The smallest increase in Percent of Correct Trials was seen for the 150 ms ISI, followed by a greater increase for the 70 ms, and the largest increase occurred for the 10 ms ISI (p. 202).

Figure 9.3.4.2b: ART-C Performance for 3-tone sequences at Visit 1 and Visit 2 (all subjects). Over all participants, performance for 3-Slow is better than for 3-Fast (Rate: $F=54.59$, $p=.00$) and performance improves from Visit 1 to Visit 2 (Visit: $F=13.42$, $p=.001$). There are no significant interactions among the variables (p. 202).

Figure 9.5.1: CELF-4 Core Language Standard Scores are plotted against eMMN Amplitude in the Attend 70 ms ISI condition at channel 62 for (a) TLD children at Visit 1, (b) TLD children at Visit 2, (c) LI children at Visit 1 and (d) LI children at Visit 2. TLD children exhibit a decrease in eMMN amplitude from Visit 1 to Visit 2, but no significant change in language performance. LI children do not exhibit a change in eMMN amplitude, but rather have a notable increase in language scores from Visit 1 to Visit 2. The changes in both groups result in a significant association at Visit 2 where better language performance is associated with lower eMMN amplitudes. There are no significant associations at Visit 1 (p. 222).

1.0 General Introduction and Literature Review

Understanding how language is processed in the brain, elucidating the neural mechanisms that allow translation of the sounds that make up speech into meaningful communication, has been the subject of study for many years. Focused research, intense debate, and the continued refinement of theories of language processing and the techniques used to study them have contributed much insight into neural pathways critical for acoustic signal processing. However, many questions remain. Here, we are interested in studying language by examining acoustic signal processing in the human brain. Spoken language can be broken down into sounds that are coded by the auditory system as frequency patterns as a function of time. Many of these cues are brief, rapid (only tens of milliseconds in duration), and successive. Thus, signal analysis must be fast and accurate in order for such cues to be decoded within the ongoing speech stream. We refer to the processing of two or more brief, successive acoustic cues that are rapidly presented to the central nervous system as rapid auditory processing (RAP).

In the studies described below, we address three broad research questions: (i) what happens when the auditory system functions normally over the course of development and RAP is efficient, (ii) what happens when the system functions abnormally and RAP is impaired, and (iii) how can the system be altered to improve RAP abilities, and what are the measurable results of such changes? In the literature, various approaches have been utilized to study these issues, including psychophysical behavioral studies, electrophysiological investigations (EEG/ERPs), neuroimaging techniques, and neuroanatomical inspection. In the following experiments, we will employ the converging methodologies of behavioral psychophysical and electrophysiological (ERP)

assessments in adults and children in order to investigate the neural bases of RAP and its relation to language. We hypothesized that in the normally functioning system, RAP changes over the course of development, between childhood and adulthood, as evidenced by both behavioral and electrophysiological assessments. Improvements in RAP may be due to an increased efficiency of neural networks that represent and process sounds of a child's ambient language. This increased efficiency may reflect the establishment and refinement of categorical phonemic representations during development as normal 'pruning' of lesser-used neural synapses progresses, and remaining connections are strengthened. Selective attention is also hypothesized to play a role in the establishment and tuning of phonological categories, both over the course of normal development, and in an intense training setting designed to drive neural plasticity (Tallal & Gaab, 2006; Näätänen et al., 1993b). Attention, defined in the present experiments as focusing on events in one sensory modality, may influence auditory processing by recruiting more neurons, inducing greater synchrony among neural coalitions, or both (Gomes et al., 2000). Further, we anticipated finding differences in RAP, as indexed by ERPs, between children diagnosed with a LI and children with typical language development (TLD). Additionally, attention may modulate RAP differently in LI and TLD children. Finally, as a consequence of receiving the intervention program Fast ForWord-Language®, designed to improve auditory processing rates, sequencing, memory and attention (Merzenich et al. 1996; Tallal et al., 1996; Temple et al, 2003; Gaab et al., 2007), we hypothesize that changes in both RAP and language processing will occur and be evident in post-training behavioral assessments as well as in the mismatch negativity components of the ERP waveforms.

1.1 Language Development and Rapid Auditory Processing

Rapid auditory processing (RAP) skills are believed to be critical to the timely mounting of early language. RAP is defined as the ability to process two or more brief, successive auditory stimuli that are rapidly presented to the central nervous system. Such skills are essential for decoding the acoustic cues contained within the speech stream, such as formant transitions of stop consonants and voice onset times (VOTs), which are brief periods of silence between laryngeal pulsing and the onset of consonant release by the articulators. Words are comprised of phonemes, defined as the smallest unit of sound that alone can differentiate meaning, and phonemes are characterized by formants, which are frequency patterns created by sound resonating in the vocal tract. Formants of vowels are generally steady state over time, whereas stop consonants (/p,b,t,d,k,g/) are characterized by formant transitions. During a formant transition, frequency position changes rapidly as the stop consonant occlusion is released and the vocal tract shape changes to form the subsequent vowel. In order to accurately discriminate and perceive stop consonants, the rapid formant transitions must be correctly processed by the auditory system. For example, critical information for differentiating the consonant-vowel syllables /ba/ from /da/ occurs within the first 40 milliseconds of formants 1 and 2 (F1 and F2); thereafter the frequency bands of the steady state vowel are nearly identical (see Figure 1 - /ba/ and /da/ spectrographs). The auditory system must accurately discriminate changes in the position frequency of formants in a matter of milliseconds, as these cues are transient and occur in rapid succession during spoken language. Slowed or inaccurate auditory processing may cause essential information to be missed, resulting in difficulty deciphering the speech stream.

Individuals with RAP difficulties may exhibit deficits in phonological, syntactic and/or grammatical processing, and indeed, there is accumulating evidence that impaired RAP skills are characteristic of developmental language delays and impairments (for reviews, see Tallal, 2004; Tallal et al., 1998; Farmer & Klein, 1995). Intact RAP skills in infancy are important for constructing the framework upon which future language skills will be built. In particular, the proper development of categorical phonemic representations appears critical for later language learning success.

From birth, and even before birth, human infants are exposed to speech. A newborn can discriminate phonemes contained in all languages (Eimas, Miller, & Jusczyk, 1987), but during the first year of life, infants quickly ‘tune in’ to their native language and rapidly lose the ability to discriminate phonemes in other tongues. Research has demonstrated that infants born into Japanese and American (English speaking) families up to the age of 6 months can discriminate between /r/ and /l/, a contrast that is very difficult for Japanese adults to discern as there is no /r/ vs. /l/ distinction in the Japanese language (Strange, 1995; Best, 1993). However, by the time these children are 12 months old, Japanese babies have difficulty making the /r/ vs. /l/ distinction while American 12 month olds have improved in their ability to discriminate this contrast (Kuhl et al., 1997). Thus, the perception of phonemes is influenced by one’s ambient language during the first year of life. During this period, speech sound representations in the brain are being assembled and refined, and RAP appears to play a critical role in the accurate construction of phonemic categories, which provide the basis for higher level language acquisition, from semantics (word meaning) to syntax (grammatical rules).

Degraded auditory input resulting from poor hearing (chronic ear infections: Friel-Patti & Finitzo 1990; Lonigan, Fischel, Whitehurst, Arnold, Valdez-Menchaca, 1992; Menyuk 1986; Wallace, Gravel, McCarton, & Ruben, 1988) or inefficient RAP (Choudhury & Benasich, 2003; Benasich & Tallal, 1996; 2002) during infancy and early childhood may result in delayed or impaired language development. Poor resolution of auditory input may lead to ‘blurred’ or overlapping neural maps that result in poorly specified representations of phonemes (Godfrey et al., 1981; Werker & Tees, 1987, Elbro, 1998). These inefficient phonological representations may lead to expressive and/or receptive language delays or impairments in early childhood, and subsequent reading, writing, and spelling deficits due to poor phonographic (spoken) to orthographic (visual/written) mapping (Fitch & Tallal, 2003; Tallal, 2000; Benasich & Read, 1998). Such deficits comprise the diagnostic criteria for developmental language disorders, such as dyslexia and Specific Language Impairment (SLI). There is accumulating evidence to support the hypothesis that a RAP deficit is a basic impairment in many individuals with developmental language disorders (for reviews, see Fitch & Tallal, 2003, Tallal & Benasich, 2002, and Leonard, 1998), and that intact RAP skills are required for normal language acquisition (Benasich et al., 2006; Choudhury et al., 2007; Benasich & Tallal, 2002). The large and ever-growing relevant literature contains behavioral and brain imaging studies of both normally developing children, and children and adults with developmental language disorders.

1.2 Developmental Disorders of Language and RAP

A developmental language disorder is characterized by a significant limitation¹ in expressive and/or receptive language skills in the context of otherwise normal development. Specific Language Impairment (SLI), previously termed developmental dysphasia (Benton, 1964), is a developmental language disorder diagnosed on the basis of exclusion, meaning there are no apparent factors to account for a significant delay or impairment in language acquisition, such as hearing impairment, mental retardation, childhood schizophrenia, infantile autism, severe environmental deprivation, or frank neurological damage (APA: DSM-IV, 1994). It is estimated that 6 to 8 percent (girls and boys, respectively) of all children beginning school can be classified as specifically language impaired, though most have never been identified as having a language learning problem (Tomblin et al., 1997). Children with SLI, who have normal non-verbal intelligence, often go on to develop reading problems like those seen in dyslexia (Tallal, Curtiss, & Kaplan, 1988; Catts, 1993), and many children with reading difficulties often exhibit oral language problems (for a review, see Snow, Burns, & Griffin, 1998). Dyslexia is also considered to be a developmental disorder of language, although dyslexia is classically defined as the failure to develop age-appropriate reading skills in the absence of a known cause. Research has shown that approximately 50 % of children classified as SLI go on to develop dyslexia (Catts 1993; Bishop and Snowling 2004), providing support for the view that developmental language and reading disorders may share a common etiology and represent a continuum between oral and written language impairments (Tallal & Benasich, 2002; APA: DSM-IV, 1994).

¹ The diagnostic requirement for a developmental language disorder includes a standardized language score usually ≥ 1.25 SD below the mean (Fitch & Tallal, 2003).

Further, individuals with SLI and dyslexia often exhibit similar behavioral deficits in rapid sensory processing (for reviews, see Fitch & Tallal, 2003, and Leonard, 1998) and neuroimaging studies have revealed alterations in neuroanatomical substrates common to these two disorders (discussed in more detail in the following section: 1.4 Neuroanatomical Anomalies in Developmental Language Disorders) (Leonard et al., 1993; Larsen, Höien, Lundberg, & Ödegaard, 1990; Jancke, Schlaug, Huang, & Steinmetz, 1994; Schultz et al., 1994; Hynd, Marshall, & Semrud-Clikeman, 1991; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Jernigan, Hesselink, Sowell, & Tallal, 1991; Plante, Swisher, Vance, & Rapcsak, 1991; Gauger, Lombardino, & Leonard, 1997, but see ²). In addition, EEG/ERP studies of SLI and dyslexic individuals report similar findings (Uwer, Albrecht, & von Suchodoletz, 1998; Kujala et al., 2000). Thus, it is likely that children with SLI and dyslexia comprise an overlapping, though not identical, population. More recently, the term Language Learning Impairment of unknown cause (here referred to as LI) has begun to be adopted by researchers (Tallal, 2002), and will be used in the following discussion, taking into account the findings that many of the deficits exhibited by children with SLI lead to more general learning problems, including spelling, reading and writing, and are not specific to language per se (for reviews, see Fitch & Tallal, 2003, Tallal & Benasich, 2002, and Leonard, 1998). On a more basic acoustic processing level, RAP difficulties have been found to be a hallmark of LI.

² There are some exceptions and inconsistencies in this area of research, such that some children with SLI do not exhibit abnormal asymmetry (Plante et al., 1991) and some individuals with atypical asymmetry exhibit no language problems (Jernigan et al., 1991). Further, in individuals with SLI and dyslexia, abnormalities have been found in brain areas outside language centers. Such findings underscore the idea that SLI and dyslexia are disorders characterized by heterogeneous behavioral profiles, with potentially variable underlying neurobiological substrates as well.

Individuals with LI exhibit RAP difficulties with linguistic stimuli, such as stop consonants (Kraus et al., 1996; Tallal & Piercy 1974, 1975; Tallal et al., 1980a, 1980b; Werker & Tees, 1987), as well as non-linguistic stimuli, such as tone pairs (McCroskey & Kidder, 1980; Tallal & Piercy 1973a, 1973b; Witton et al., 1998), click trains (Hari & Kiesila, 1996), and frequency modulated tones (Wright, Bowen, & Zecker, 2000). Early suggestions of an auditory perceptual deficit in LI included hypotheses regarding temporal ordering difficulties, and generalized sequencing and memory impairments (Efron, 1963; Poppen, Stark, Eisenson, Forrest, & Wertheim, 1969). Subsequent research identified and characterized a RAP impairment in LI.

In 1973, Tallal and Piercy assessed non-verbal auditory processing in a group of LI (aphasic) children (ages 6.8 to 9 years) using a two-tone identification and sequencing task (Tallal & Piercy, 1973a). One tone was 100 Hz and the other was 305 Hz, and the time between the two tones (inter-stimulus interval, ISI) was varied between 400 and 8 milliseconds. Children were asked to repeat the sequence of tones they heard by pressing two buttons mounted on a box, one corresponding to each tone. Children with LI were significantly impaired relative to controls when the ISI was less than 305 milliseconds. Controls performed above chance levels at all ISIs. In a related “same-different” discrimination task, children were asked to indicate whether two tones they heard were the same or different from each other. The pattern of results was similar, with LI children performing significantly worse than controls at ISIs less than 305 ms. Based on these results, the authors suggested that discrimination of sounds may be the fundamental deficit of LI, with sequencing and memory problems explicable in terms of a basic auditory processing dysfunction.

Furthermore, Tallal and Piercy (1973b) found significant group differences in RAP of tone sequences of variable length and ISI. They observed that the performance of the LI children was significantly affected by tone duration, as well as the overall stimulus duration (tones + ISI), while controls were not. The authors concluded that the amount of *time* available for auditory processing is critical for children with LI, affecting performance on tasks of auditory discrimination and identification. Continuing this line of investigation, Tallal and Piercy (1974) observed that LI children were also impaired in discriminating the consonant vowel syllables /ba/ and /da/. The computer generated speech stimuli were 250 ms in duration, and differed only in the first 43 ms (in the formant transitions of the second and third formants). Neither LI children nor controls had any difficulty discriminating 250 ms steady state vowels /ε/ and /ae/. These findings suggested that LI children have difficulty discriminating consonant stimuli due to the brief duration of the formant transitions (Tallal & Piercy, 1974). Vowel-vowel combination stimuli that differed only in the first 43 ms were then created (e.g. /ε/ for 43 ms and /I/ for 207 ms) and it was again demonstrated that the performance of LI children was significantly impaired relative to controls (Tallal & Piercy, 1975). Finally, the /ba/ and /da/ stimuli were altered so the formant transitions were extended from 43 ms to 95 ms. Under these conditions, the performance of LI children and controls did not significantly differ (Tallal & Piercy, 1975).

These results led to the idea that the ability to process the brief discriminable characteristics of a stimulus, like the rapid formant transitions of a consonant-vowel syllable in human speech, is impaired in children with LI. This series of studies, and subsequent replication of the results across laboratories, tasks, and stimulus variations

(for reviews, see Leonard, 1998, and Tallal & Gaab, 2006), spawned and strengthened the hypothesis that a RAP deficit is a basic impairment in LI. It is this deficit that appears to underlie an LI individual's inability to integrate sensory information that enters the central nervous system in rapid succession over a short period of time (Tallal, Miller, & Fitch, 1993).

1.3 Multimodal Processing in Developmental Language Disorders

Rapid processing deficits do not appear to be restricted to the auditory domain in individuals diagnosed with a Language Learning Impairment (LI). Research has shown that individuals with developmental language disorders exhibit processing deficits in other modalities, including motor coordination (Wolff, Michel, Ovrut & Drake, 1990; Bishop and Edmundson, 1987, Stark & Tallal, 1981), automatization of skills (Nicolson, Fawcett, & Dean, 2001.), and tactile and visual perception (Talcott, Witton, Hebb, Stoodley, Westwood, France, Hansen, & Stein, 2002; Stoodley, Talcott, Carter, Witton, & Stein, 2000; Stein, 1999; Stein & Talcott, 1999; Talcott, Hansen, Assoku, & Stein, 2000; Witton et al., 1998; Livingstone, Rosen, Drislane, & Galaburda, 1991)³ suggesting the existence of a more general neural mechanism accounting for slowed sensory processing, rather than one specific to language per se.

Nicolson and colleagues propose a generalized cerebellar deficit that accounts for the reading and writing difficulties experienced by individuals with dyslexia (Nicolson, Fawcett, & Dean, 2001; Nicolson, Daum, Schugens, Fawcett, & Schultz, 2001). The

³ In SLI children it has been proposed that some of these deficits may be the result of poor attention span (not explicitly assessed by traditional IQ tests), and indeed a relatively high proportion of SLI children meet the criteria for attention deficit disorder (Beitchman et al., 1986). This issue is addressed in the studies reported here.

ability to perform skills automatically, such as eye-blink conditioning and speech articulation, is believed to be dependent upon the cerebellum. It has been found that articulation is slowed in dyslexic children, suggesting that they require more time to plan motor actions and access phonological representations (Fawcett & Nicolson, 2002). Also, young adults with dyslexia show abnormal acquisition of the conditioned response in simple eye blink conditioning as compared to controls. These findings support the idea that cerebellar dysfunction may be a causal factor in developmental dyslexia. Other studies have examined processing in the visual modality of individuals with dyslexia. These investigations have revealed that the ability to process fast, low contrast visual stimuli is impaired in individuals with dyslexia relative to controls (Witton et al., 1998). This apparent deficit in the magnocellular visual pathway is evident in behavioral as well as neurophysiological measurements. Dyslexic subjects' ERPs to rapidly presented visual stimuli have longer latencies than controls, reflecting a slower neural response (Livingstone et al., 1991; Lehmkuhle, Garzia, Turner, Hash, & Baro, 1993). In addition, post-mortem analyses of the brains of individuals with dyslexia revealed that in the lateral geniculate nucleus (LGN), the visual nucleus of the thalamus, magnocellular neurons (magno-cells) were abnormally small in comparison to controls (Livingstone et al., 1991). This convergence of behavioral and anatomical evidence led to suggestions of visual processing disturbances in dyslexia in the magnocellular system. Further convergence of behavioral multi-modal processing deficits in LIs and results of neuroanatomical studies are discussed below.

1.4 Neuroanatomical Anomalies in Developmental Language Disorders

Consistent with the findings of abnormal cell densities in the LGN of individuals with dyslexia, anatomical analyses of the brains of dyslexic individuals revealed that the size of cells in the auditory nucleus of the thalamus, the medial geniculate nucleus (MGN), were altered in dyslexic subjects as compared to controls. There were more small and fewer large neurons in the left MGN of dyslexics, whereas in controls there were no differences between right and left MGN cell measurements (Galaburda, Menard, & Rosen, 1994). The function of magno-cells in the MGN is not well understood. However, it has been suggested that these cells, like magnocellular neurons found in the visual thalamic region, large cells in the dorsal column somaesthetic nuclei and the dense magnocellular input to the cerebellum, may be involved in the rapid transmission of neural information due to their large size and consequent faster conduction velocities (Stein, 2001). Thus, disturbances in RAP may result, at least in part, from an abnormal ratio of magno-cells in the thalamic nuclei of individuals with a LI.

In addition to such reported subcortical abnormalities, analyses of the brains of humans with dyslexia have revealed focal neocortical malformations, including microgyria and ectopias, which result from errors in neuronal migration (Drake, 1968; Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Cohen, Trehub, Thorpe, & Morrongiello, 1989; Humphreys, Kaufmann, & Galaburda, 1990). Recently, genetic variants of four different genes involved in early brain development have been proposed to associate with an elevated incidence of developmental dyslexia in humans. Three of these, *DYX1C1*, *DCDC2*, and *KIAA0319*, have been shown to play a role in neuronal migration in the developing neocortex. (Galaburda et al., 2006; Threlkeld et al., 2007; Burbridge et al., 2008). In anatomical

studies, Galaburda and colleagues (1979, 1985), and Humphreys et al. (1990) describe neuronal ectopias often found in Layer 1, and four layered polymicrogyria distributed throughout the cortex. The consistent discovery of these cortical abnormalities led the authors to posit that the language disabilities of dyslexic individuals may be explicable in terms of these neuropathological changes. The direct relation between the neuroanatomical malformations found in the brains of dyslexics and deficient RAP skills cannot be easily assessed in humans. Therefore, researchers have exploited an animal model to investigate this association.

The neuroanatomical abnormalities characteristic of the brains of human dyslexics can be reproduced in animals. A strain of autoimmune mice (BXSB) spontaneously develops ectopias, and it has been shown that ectopic mice display auditory processing deficits similar to children with dyslexia (gap detection: Clark, Sherman, Bimonte, & Fitch, 2000). Also, auditory event related potentials recorded from ectopic mice reveal a reduced response to the second auditory event of a pair, only when a very short interstimulus interval (36 and 72 ms) precedes the second stimulus (Frenkel, Sherman, Bashan, Galaburda, & LoTurco, 2000). In rats, cortical microgyria can be induced via a focal freezing lesion applied to the developing cortical plate on postnatal day one (P1)⁴. Disrupting normal cellular migration on P0 or P1 in the rat causes microgyria to develop that are histologically similar to those found in the brains of dyslexics (Ferrer, 1993; Rosen, Press, Sherman, & Galaburda, 1992; Humphreys, Rosen, Press, Sherman, & Galaburda, 1991). Additionally, like the brains of individuals with dyslexia, the brains of animals with induced microgyria also show differences in medial

⁴ In the rat, neuronal migration continues for two to three days following birth, roughly corresponding to gestational weeks 18 through 24 in the developing human brain.

geniculate nucleus (MGN) cell size and number (more small and fewer large neurons). These animals also exhibit RAP deficits analogous to those exhibited by individuals with LI (Herman, Galaburda, Fitch, Carter, & Rosen, 1997; Rosen, Herman, & Galaburda, 1999).

Fitch and colleagues have demonstrated that adult microgyric rats are significantly impaired in rapid auditory discrimination as compared to sham subjects using an operant task (go/no-go, two tone identification) (Fitch, Tallal, Brown, Galaburda, & Rosen, 1994; Herman et al., 1997; Clark, Rosen, Tallal, & Fitch, 2000a). Also, using a reflex modification paradigm (prepulse inhibition), it has been shown that adult microgyric rats performed as well as shams in a simple gap detection task (Friedman, et al., 2004; Peiffer, Friedman, Rosen, & Fitch, 2004; Clark et al., 2000b). This finding is consistent with the human literature reporting that adults with developmental dyslexia perform as well as controls in tasks of gap detection (McAnally & Stein, 1996; Protopapas, Ahissar, & Merzenich, 1997), suggesting the existence of a developmental progression in the ability to perceive gaps in otherwise continuous auditory stimuli. With the reflex-modification paradigm, Clark et al. (2000b) also demonstrated that microgyric subjects were significantly impaired relative to shams in discriminating tone-pairs of short duration in the more complex tone-pair discrimination task, extending the findings of Fitch and colleagues (for a review, see Fitch et al., 2008).

In addition to the focal anomalies described above, more global differences in brain structure have been identified in individuals with a developmental LI as compared to controls. For example, in the majority of the population, it is well established that the planum temporale, a structure located on the superior surface of the temporal lobe in the

posterior perisylvian region (which includes a portion of Wernicke's area), is larger in the left hemisphere as compared to the right. However, in individuals with SLI and dyslexia, reversed asymmetry (right larger than left) of the planum temporale has been consistently reported, both in post-mortem (Geschwind & Levitsky, 1968, Humphreys et al., 1990; Galaburda, 1991) and neuroimaging (Leonard et al., 1993; Larsen et al., 1990; Jancke et al., 1994, Schultz et al., 1994; Hynd et al, 1991; Hynd et al., 1990) investigations. More recently, magnetoencephalography (MEG) studies have shown that right hemisphere organization is altered in dyslexic children, adolescents, and adults, revealed by a lack of asymmetry of the sources underlying the obligatory cortical evoked response to a change in the auditory environment. This component is identified as the P100 in children and adolescents (Heim, Eulitz, & Elbert, 2003a), and the N100 in adults (Heim, Eulitz, & Elbert, 2003b). Because this result was consistently obtained across development, it is suggested that this is a stable characteristic of dyslexia, rather than an issue of maturation. The authors speculate that the decreased lateralization of the P100/N100 in dyslexic subjects may reflect altered morphology of structures in the posterior perisylvian region, and that such alterations interfere with auditory processing (Heim et al., 2003b). Consequently, other, less efficient areas might then be recruited for auditory processing, contributing to the RAP deficits consistently observed in individuals with developmental language disorders.

Utilizing ERPs, Shafer and colleagues (Shafer, Schwartz, Morr, Kessler, & Kurtzberg 2000; Shafer et al., 2001) also found abnormal asymmetrical responses in children with SLI. In these studies, the word "the" (117 ms in duration) was presented in three contexts: in a story, within strings of nonsense syllables, and repeated. The ERP

response to “the” in the story and nonsense contexts were not significantly different, suggesting that the processing measured was not dependent on semantic capabilities, but rather reflected lower level auditory processing. In SLI children, the researchers observed an attenuated response in the temporal cortex of the left hemisphere, and an elevated response in the right hemisphere. This reversed asymmetry, as compared to controls who showed a greater response in the left versus the right temporal cortex, is consistent with anatomical and MEG findings of reversed hemispheric asymmetry in individuals with developmental LIs. Shafer and colleagues (2000, 2001) suggest that in SLI children, increased activity in the right hemisphere may reflect a compensatory mechanism to make up for reduced activation in the left hemisphere, where this type of brief stimulus would normally be processed. Additionally, these studies analyzed the sources of the scalp recorded activity and found that, in contrast to controls, children with SLI appear to lack activity of a deep-lying generator, possibly localized in the hippocampus or basal ganglia.

At this point, the relations between focal cellular abnormalities and anatomical and/or functional reversed asymmetry remain unclear. However, the incidence of abnormal RAP in individuals with LIs who have such anomalies is well documented. Investigations into the etiology of RAP deficits and later language outcome are ongoing in an effort to gain scientific knowledge to elucidate the neurobiological bases of developmental LIs, and to make clinical advances in the early identification and treatment of LIs. Prospective longitudinal studies linking pre- or peri-natal neural circumstances to later language outcome in children comprise a powerful and promising arm of the research effort exploring these issues.

1.5 Early Rapid Auditory Processing Abilities and Language Outcome

Since ectopias and microgyria found in the brains of dyslexics result from errors in cell migration, it is believed that the mechanism responsible for causing these malformations occurs during prenatal development, approximately between 18 and 24 weeks of gestation (Barth, 1987; Njikiktjen, 1994) ⁵. Such a mechanisms could involve a prenatal brain insult (i.e. due to a viral infection), and/or genetic factors which initiate a cascade of events as the brain develops, ultimately resulting in the behavioral profile characteristic of a developmental LI with underlying abnormal neurobiological substrates (Benasich & Read, 1998; Galaburda et al., 2006). A similar scenario may be useful to explain alterations in structural and functional hemispheric asymmetry in individuals with developmental LIs. The widely reported finding of an alteration or absence of the normal left greater than right hemispheric asymmetry in individuals with dyslexia (Heim, Eulitz, & Elbert, 2003a, 2003b) and SLI (Shafer et al., 2000; Shafer et al., 2001) may be due to an interaction between environmental stimuli (i.e. speech requiring RAP) and altered underlying neural morphology over the course of development. In this scenario, the posterior perisylvian regions that typically support RAP function abnormally, and other brain regions are recruited to perform this function. However, these alternate areas are less efficient processors, leading to a deficit in RAP, and possible phonological processing difficulties.

Based on the idea that the abnormal neural substrates underlying LIs may be present from birth, either in the form of focal neocortical anomalies and/or whole brain alterations, it has been hypothesized that RAP deficits should be observable in pre-verbal

⁵ A full-term pregnancy is 40 weeks long.

infants, and that these infants may develop subsequent language delays or impairments (Fitch, Read, & Benasich, 2001). The relation between early RAP skills and later language development has been investigated by two groups. Benasich & Tallal (1996) examined a sample of infants with a family history of language impairment (FH+), thus at an elevated risk of developing a language impairment themselves (Choudhury & Benasich, 2003; Tallal, Ross, & Curtiss, 1989; Tomblin, 1996). They found that infants in the FH+ group performed more poorly on measures of RAP as compared to a control group. However, an even more striking finding was that RAP thresholds measured in infancy were significantly related to later language comprehension and production at 16, 24, and 36 months of age in *all* subjects (Benasich & Tallal, 2002, 2000, 1998). In fact, discriminate function analyses show that RAP alone predicts language outcome (impaired vs. normal development) with approximately 90% accuracy (Benasich & Tallal, 2002). Thus, an infant's RAP threshold to non-verbal auditory stimuli in infancy, regardless of family history, has been shown to be the single best predictor of language ability up to 3 years of age. Similarly, but in a retrospective study, Trehub and Henderson (1996) found that infants who performed above the median on an auditory gap detection⁶ task had more sophisticated language skills at 16 to 29 months of age. These studies provide support for the use of infant RAP measures to predict later language development in both at-risk and normally developing populations.

In addition, recent neurophysiological studies have shown that newborn infants at-risk for developmental dyslexia have different patterns of event related potential (ERP)

⁶ Gap detection is one of the most widely used paradigms in the study of auditory temporal acuity. Gap detection is classically defined as the ability to detect a brief silent period within otherwise continuous background noise. Trehub and Henderson (1996), though, used Gaussian enveloped tones as the leading and trailing gap stimuli.

responses to speech stimuli as compared to controls (Leppänen et al., 2002; Guttorm, Leppänen, Richardson, & Lyytinen, 2001; Leppänen, Pihko, Eklund & Lyytinen, 1999; Pihko et al., 1999; Leppänen & Lyytinen, 1997). For example, Leppänen and colleagues (2002; 1999) found that the ERPs of infants at-risk for dyslexia lacked a specific component called the mismatch negativity (MMN), which reflects the pre-attentive detection of a change in the auditory environment (a more detailed explanation of the MMN is presented in Section 1.6 below; for a recent review, see Näätänen et al., 2007), when the stimulus was short in duration. The same stimulus elicited a MMN response in control infants. Moreover, in the left hemisphere, ERPs showed more differentiation between frequent and rarely occurring stimuli in the control group as compared to at-risk infants (more overlap of the waveforms). The authors suggest that at-risk children are deficient in discriminating the temporal cues (e.g. duration) of the linguistic stimuli used in the study. Furthermore, it has been found that ERP responses to speech and non-speech stimuli in infancy predict language ability up to 8 years later (Molfese 2000; Molfese & Molfese 1997, 1985). These results provide additional evidence that the processing deficits that may underlie LI are present and measurable early in life, well before the development of spoken language.

In addition to investigations of impaired RAP systems, studies of gap detection abilities in normally developing infants have shown that infants have higher thresholds than adults (Trehub, Schneider, & Henderson, 1995; Werner, Marean, Halpin, Spetner, & Gillenwater, 1992), and young children diagnosed with LI have higher gap detection thresholds as compared to controls (Ludlow, Cudahy, Bassich, & Brown, 1983). This is notable since adults with developmental dyslexia perform as well as controls in gap

detection tasks (McAnally & Stein, 1996; Protopapas et al., 1997), suggesting the existence of a developmental progression in the ability to perceive gaps in otherwise continuous auditory stimuli. Indeed, across species, adult gap detection thresholds are in the range of 2 to 6 ms (rats: Ison, 1982; Leitner et al., 1993; humans: Ison & Pinckney, 1983), while for infants and children thresholds are significantly higher. Werner and colleagues (1992) found that 3 to 6 month old human infants have gap detection thresholds considerably higher than adults (means of 36 and 16 ms, respectively). Trehub et al. (1995) also determined that 6.5 to 12 month old infants have higher gap detection thresholds than adults, but by using modified stimulus parameters they were able to show that infants' auditory processing thresholds are significantly lower (i.e., better) than previously indicated by Werner and colleagues (11 ms). Additionally, in studies with juvenile rats, it has been found that acuity for detecting silent gaps is dependent on maturation, as well as repeated daily testing (age P15 and greater: Friedman et al., 2004; age P35 and greater: Dean, Sheets, Crofton, & Reiter 1990). Together, these results support the idea of a developmental progression in the ability to perceive and discriminate brief, and/or rapidly presented stimuli (silent gaps surrounded by tones or background noise) across species, and such changes in auditory acuity may be important for the development of language skills.

It should be noted that the aforementioned studies utilized the classic gap detection paradigm in which the leading and trailing stimuli surrounding a silent gap are similar, if not identical. Such gap detection stimuli have been termed 'within-channel', and are usually of relatively long durations (Phillips, 1999; Phillips, Taylor, Hall, Carr, & Mossop, 1997). Though this is an accepted and reliable measure of auditory acuity,

within-channel gap stimuli do not closely mimic ‘gaps’ found in speech. To this end, ‘between-channel’ gap stimuli, comprised of short leading and longer trailing markers with different center frequencies, have been exploited. These stimuli more closely resemble gaps found in speech (e.g. voice onset times, VOTs), and gap thresholds for between-channel stimuli have been shown to be dependent on the duration of the leading marker (less than 30 ms, Phillips et al., 1997) and frequency disparity between leading and trailing markers (Phillips & Hall, 2002; Fitzgibbons, Pollatsek, & Thomas, 1974; Formby, Sherlock, & Forrest, 1996; Phillips et al., 1997). The central neural processes required for these two types of gap detection are thought to be distinct. Within-channel gap detection requires the perception of discontinuity, such that a single neuronal population detects the offset and onset of a particular stimulus (Phillips et al., 1997). In contrast, between-channel gap stimuli are believed to elicit a temporal cross-correlation operation in which the timing of the activation of distinct neural ensembles is compared.

This between-channel relative timing operation may be impaired in systems with RAP deficits, affecting the accurate perception of stop consonants (Phillips et al., 1997) and more complex non-verbal stimuli (Wright et al., 1997), while discontinuity detection is less or not at all disturbed. This would explain the failure to find within-channel gap detection deficits in mature animal and human systems with impaired RAP. This has been addressed in experiments using between-channel non-verbal (tone sequences) and verbal (consonant-vowel syllables) stimuli with the rat model of impaired RAP (Fitch et al., 1994; Clark, et al., 2000a, 2000b) as well as in language impaired children and adults (for reviews see Fitch & Tallal, 2003; Leonard, 1998; Benasich & Tallal, 1996). In all of these studies, controls performed significantly better than the LI groups when between-

channel gaps were relatively short in duration. Taken together, the results suggest that there is a normal developmental progression in RAP, with thresholds decreasing with age, and that this maturational process may be altered or disrupted in individuals with RAP impairments. Such RAP deficits, that are present and measurable early in life, may lead to speech processing problems due to poorly specified phonological representations at the neural level, and other language related difficulties (e.g. spelling, reading) that eventually become manifest in a LI diagnosis. This scenario underscores the need for the early identification of individuals with RAP deficits, and intervention programs to improve RAP functioning in such children. It is well known that the developing brain possesses a great capacity for neural plasticity, and it has been recognized that the most effective tools in ameliorating RAP deficits may be those that tap into this potential. Identifying RAP deficits in individuals at risk for language impairments, and thus candidates for intervention tools, is a major step forward toward these goals. Although behavioral measures of auditory processing have been very fruitful in these efforts (e.g. Benasich & Tallal, 2002), another converging method for detecting subtle differences in RAP or auditory discrimination are auditory Event Related Potentials (ERPs), specifically the Mismatch Negativity component (MMN).

1.6 Event Related Potentials – The Mismatch Negativity

Auditory event-related potentials (ERPs) are voltage deflections of scalp-recorded electroencephalography (EEG) that are time locked to external stimuli. Although the biophysical events that give rise to ERPs are not fully understood, ERPs are believed to result mainly from brain activation related to summated postsynaptic potentials in

vertically oriented cortical pyramidal neurons, with contributions from other cortical and sub-cortical neuronal events including inhibitory postsynaptic potentials (IPSPs), and are thought to reflect specific neural responses linked to particular cognitive processes (Luck, 2005). By averaging time-locked EEG-epochs to a stimulus event (often over many trials), it is possible to separate the ERP signal from background EEG activity (“noise”) (see e.g., (Regan, 1989). The averaged ERP waveform is deconstructed into components that are major positive or negative deflections of the wave that have been named according to polarity, latency, amplitude, topography, and/or the parameters of the task (Coles, Gratton, & Fabiani, 1990; Donchin, Karis, Bashore, & Coles, 1986; Donchin, Ritter, & McCallum, 1978; Gevins & Cuttillio, 1986). ERPs are believed to reflect "higher" cognitive processes, involving memory, expectation, attention, or changes in mental state (Luck, 2005). A component that has been widely studied in relation to auditory and language processing is the mismatch negativity (MMN).

The auditory mismatch negativity response (MMN) is an ERP component which is elicited by a deviant or rarely occurring stimulus presented within an otherwise homogeneous stream of standard stimuli (Näätänen, Gaillard, & Mäntysalo, 1978). It is calculated by subtracting the averaged deviant wave from the averaged standard wave, resulting in a “difference wave”. The MMN is thought to precede conscious awareness since it occurs approximately 150 - 300 ms after the onset of a deviant stimulus, and it can be elicited passively, even with a subject under anesthesia. The MMN is very sensitive to acoustic stimulus properties, and thus this response is apparent when changes occur in frequency, intensity, duration, location, or pattern, even when the acoustic difference is near the psychophysical threshold (Näätänen, 1992) or stimulus differences

are consciously imperceptible (Allen, Kraus, & Bradlow, 2000). These properties of the MMN make it well suited for the study of auditory processing mechanisms underlying speech perception. Data suggests that the MMN originates in the primary auditory cortex, with contributions from auditory association areas, medial geniculate nucleus of the thalamus, and hippocampus (Shafer et al., 2001; Kraus et al., 1994a; Kraus, McGee, Littman, Nicol, & King, 1994b). The MMN has been widely studied in adults over the past several decades and the mature MMN is well characterized, however the literature describing the MMN's developmental progression throughout childhood is not as extensive.

1.6.1 Developmental Changes in the MMN

Auditory evoked ERPs exhibit developmental changes in which latencies generally decrease and amplitudes typically increase (Thomas and Crow, 1994), and these maturational changes are thought to result from increases in synaptic density in the auditory cortex, increases in myelination, as well as differences in the location and orientation of MMN generators (Martin et al., 2003; Gomot et al., 2000; Eggermont 1998, 1992, 1988; Huttenlocher et al., 1982). Various studies have reported maturational changes in the latency and amplitude of the MMN specifically. Using a typical oddball paradigm with **tone stimuli**, it has been shown that the *latency* of an MMN-like response in young children decreases between the ages of 3 to 44 months (Morr, et al., 2002) and between the ages of 4 to 10 years (Shafer et al., 2000), but no changes in *amplitude* were observed in these studies. These findings are consistent with previous reports of latency differences in the MMN of adults as compared to children (i.e. 5 – 10 yrs old, Korpilahti, & Lang, 1994). In comparison to the MMN response to non-verbal stimuli, the MMN

elicited by **speech stimuli** in school-age children and adults has been found to be similar in *latency* and morphology (i.e. 5 – 10 yrs old, Korpilahti, & Lang, 1994: just perceptibly different variants of /da/; Kraus, McGee, Carrell, Sharma, & Nicol, 1995b: variants of /da/ and /ga/; Kraus, McGee, Sharma, Carrell, & Nicol, 1992). Despite these apparent similarities, Cheour and colleagues (2000) caution that the adult MMN and child MMN do not appear to be equivalent. Indeed, differences in the *amplitude* of the mature and developing MMN have been documented, with the MMN being larger in children as compared to adults (Cespe et al., 1995; Kraus, McGee, Micco, Carrell, & Nicol, 1993b; Kraus et al., 1995b). Maturational differences in the MMN may be modulated by the type of stimuli used (non-speech vs. speech; simple vs. complex), as well as the perceived difficulty of the discrimination. In both adults and children, the difficulty of the standard-deviant discrimination has been shown to affect the amplitude of the MMN, such that the MMN exhibits a shorter latency and greater amplitude if the difference between standard and deviant stimuli is large (e.g. stimuli are easily discriminable) (Kraus et al., 1993b; Sams et al., 1985; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989, Paavilainen, Karlsson, Reinikainen, & Näätänen, 1989)⁷.

In addition to correlates of the adult-like MMN, sometimes called the early MMN (eMMN) in children (Korpilahti et al., 2001), an additional MMN component, also with a frontocentral topography, has been more recently identified in children called the late MMN or Late Discriminative Negativity (IMMN/LDN) (for a review, see Cheour et al., 2001; Korpilahti et al., 2001; Ceponiene et al., 2004, 2002). The eMMN exhibits a latency range of c.a. 150 – 400 ms after the onset of a deviant stimulus, whereas the

⁷ For more complex stimuli, however, this relation between latency/amplitude and stimulus difference magnitude may not be monotonic (Sams & Näätänen, 1991).

IMMN/LDN has a latency range of c.a. 400 – 600 ms (Ceponiene et al., 1998; Korpilahti et al., 1998, 2001; Bitz et al., 2007). The eMMN is thought to reflect pre-attentive, automatic change detection processes associated with the mature MMN, while the IMMN/LDN may index further processing of the deviant stimulus, especially when the stimuli are complex, and be dependent on the development of attention mechanisms linked to the general maturation of the central nervous system (Hämäläinen et al., 2008; Ceponiene et al., 2002; Cheour et al., 2001). A IMMN/LDN-like component has been described in adults (with complex stimuli; Aaltonen, 1997; Alho et al., 1992; Trejo et al., 1995), but in general, IMMN/LDN amplitude has been found to decrease rapidly with age (Cheour et al., 2001), making it unsuitable for study in adults, but a potentially interesting component for investigations with young children, in both normally developing and impaired populations.

In studies of children with language and reading difficulties, abnormal or absent mismatch responses have been reported for both the eMMN and IMMN/LDN (Hämäläinen et al., 2008; Rinker et al., 2007; Alonso-Bua et al., 2006; Uwer et al., 2002; Shafer et al., 2005; Kraus et al., 1996), supporting the idea that these two MMN components are sensitive measures of auditory discrimination. In addition to eliciting the eMMN and IMMN/LDN under conditions of passive listening, it has been shown that the MMN may be modulated by attention.

1.6.2 MMN and Attention

Although the MMN is generally thought to reflect a pre-attentive process, it has also been demonstrated that the MMN can be modulated by selective attention⁸. Several

⁸ All of the studies described here refer to the mature MMN or child eMMN. To date, there are no studies of which we are aware that directly examine attention modulation of the IMMN/LDN.

investigations with normally developing populations have shown that the amplitude of the MMN is greater when a subject actively attends to auditory stimuli, especially when the discrimination between standard and deviant stimuli is difficult (Alho, Woods, Algazi, & Näätänen, 1992; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993a). It has also been shown that the MMN to an easily discriminated deviant stimulus is not modulated by attention (Alho et al., 1992; Woods, Alho, & Algazi, 1992.). This may be due to the fact that automatic processing, reflected in the MMN response, may be less efficient or effective for difficult discriminations as compared to easy ones. Thus, active attention may be required or advantageous when the discrimination is perceived as hard. Consistent with this proposal, differences in attention related enhancements of the MMN have been found between adults and children (8 to 12 years of age) in a frequency discrimination task in a study conducted by Gomes and colleagues (2000).

Gomes and colleagues (2000) compared the amplitude of the MMN elicited by three different deviants⁹ in children (8 to 12 yrs old) and adults. During the neurophysiological assessment, the subjects were instructed to attend to the stimuli in some blocks of trials, and ignore the sounds in other blocks. In this way, the authors were able to examine the modulatory effects of attention on the MMN. In adults, the MMN elicited by all three deviants were not significantly altered by attention, and children's MMN to the two 'easier' deviants were also impervious to attention. Behavioral discrimination data revealed that adults were able to detect all three deviants, while the children were only reliably able to detect the easiest deviant. For the middle deviant, children were performing close to chance with a correct detection level of 56% (standard deviation of 33.8), and performance was poor for the hardest deviant, with detection only at 36% (SD

⁹ The standard tone was 1000 Hz, and the deviants were 1050, 1200, or 1500 Hz.

38.5). These data indicate that pre-attentive acoustic processing, reflected by the presence of an MMN, enabled the children to detect the medium and hard deviants, even though behaviorally this discrimination was poor. Further, attention enhanced the MMN to the hardest deviant only in children. Based on the adult data, the authors suggest that with maturation the ability to discriminate all three deviants, both actively and automatically, will be acquired. The authors hypothesize that over the course of development, the ability to make fine auditory discriminations improves due to practice or experience effects, and as this improvement occurs, discrimination becomes automatic, not requiring focused attention. In such a scenario, it may be suggested that attention functions to recruit more neural resources, increase synchrony among neural ensembles, or both. Such a mechanism, even in the short term, may drive plasticity, or learning, so that the neural response to a sensory event that is initially voluntary (requires attention to induce increased synchrony and/or recruit additional neural coalitions) eventually becomes automatic and observable in the MMN component of the ERP waveform.

Amplification of ERPs elicited while a participant is attending to auditory stimuli has been documented in adults (Hillyard et al., 1973, 1987) and normally developing children (Gomes et al., 2000; Coch et al., 2005; Sanders et al., 2006), but in language impaired populations this attention enhancement is not evident (Stevens et al., 2006). Children with language deficits may have difficulty automatically allocating their potentially limited auditory attentional resources as compared to children with normally developing language (Shafer et al., 2005, 2007). Recently, Stevens and colleagues (2008) showed that this attention effect can be ‘restored’ after language impaired children participated in an intense intervention program designed to drive neural plasticity and

improve rapid auditory processing (Stevens et al., 2008). This is one example of neural plasticity and how it has been applied to learning impairments.

1.7 Neural Plasticity and LI Intervention

In addition to age-related changes in RAP, the enhancing effects of practice on sensory thresholds, indicative of brain plasticity, are well documented (for review see Karni & Bertini, 1997). Practice and/or experience-induced changes in threshold have been observed in various sensory modalities, including low-level auditory processing tasks. In the rat, two groups have shown that experience, as well as development, influences gap detection thresholds (Friedman et al., 2004; Dean et al., 1990). Further, the effects of learning dependent plasticity have been documented in a number of studies using various intervention programs with children diagnosed with a LI.

Utilizing magnetic source imaging (MSI), Simos and colleagues (Simos et al., 2002a) found that following successful remediation with intervention programs that focused on phonemic awareness, the brain activation profiles of individuals with dyslexia were drastically altered. Before intervention, children with dyslexia (Simos et al., 2002a) and those at-risk for reading difficulties (Simos et al., 2002b) exhibited brain activation patterns that differed radically from controls during a phonological processing task. This aberrant profile was characterized by activation in the posterior portion of the right superior temporal gyrus (STGp) and inferior parietal regions (supramarginal and angular gyrus), and a lack activation in left homologous regions. In contrast, in normal children, the phonological processing task engaged left STGp and inferior parietal areas, with little activity seen in right homologous regions. After completing the remediation program, all

children with dyslexia had improved reading performance such that their scores were in the normal range, and striking changes in their brain activation profiles were observed. Activation in the left STGp and inferior parietal areas increased dramatically, and the profiles of children with dyslexia appeared normalized.

A similar pattern of normalization was found in a study of German-speaking children with LI who participated in a syllabic training intervention for 4 weeks (Heim, Eulitz, & Elbert, in press). Following training, improvements in reading, spelling, and phonological processing skills were observed. Additionally, magnetoencephalography (MEG) measurements to syllables /ba/ and /da/ pre- and post- training revealed a change in the mismatch response, which indicates the detection of a change in the auditory environment. In the pre-training MEG, LI children had a greater mismatch response in the right hemisphere, whereas normal children showed a larger left hemispheric response. After training, LI children showed a greater left hemisphere mismatch response that was statistically indistinguishable from that of controls. The authors posit that this normalization of the mismatch response may reflect changes in the functional organization of brain areas supporting the cognitive processes underlying spelling and reading. Other investigations have sought to more specifically drive changes in RAP, a skill believed to underlie phonological processing, to affect bottom-up processing of speech.

As reported in studies by Merzenich et al. (1996) and Tallal et al. (1996), an adaptive training program for children with LI was developed and implemented to improve RAP, and therefore enable gains to be made in both receptive and expressive language skills. The computer ‘games’ used in the intervention program included both

verbal and non-verbal stimuli that had certain fast and transient components altered so as to make these critical acoustic cues easier for LI children to process. For linguistic stimuli, the intensity and duration of formant transitions of syllables containing stop consonants were altered (formant transitions were slowed by 50%, and the intensity of consonants were increased by up to 20dB), and the time between two consonant-vowel stimuli (interstimulus interval, ISI) was varied. The non-linguistic stimuli consisted of two upward or downward gliding frequency modulated (FM) tones that had speeds and frequency ranges similar to consonants in normal speech. The time between the FM tones (ISI) and the FM frequencies were varied. The studies showed that the performance of children with LI improved significantly on measures of language and RAP following training, often equivalent to gains of 1 to 2 years, and many participants' post-training scores were in the normal range. This work suggests that altering low-level RAP, achieved by providing modified detectable signals for processing and practice exercises, significantly improves the ability to decode normal, unaltered speech. More recently, Gaab et al. (2007) and Temple et al. (2003) found that after completing the training program described by Merzenich, Tallal and colleagues, children with dyslexia showed changes in brain activity, visualized with fMRI, both with linguistic and non-linguistic stimuli. In normal readers, it has been observed that phonological processing activates left temporoparietal cortex and inferior frontal gyrus. In the study by Temple and colleagues (2003), prior to remediation, dyslexic children showed reduced activity in these regions during a letter rhyming task. After completing the 8-week intervention program, the scores of children with dyslexia significantly improved (were in the normal range) on reading, oral language, and rapid naming measures, and these changes were

reflected in fMRI measures indexing increased neural activity in the left inferior frontal gyrus during a phonological task. In addition, a compensatory increase was observed in areas not normally active during reading: right inferior, middle, and superior gyri, and middle temporal gyrus. Gaab and colleagues (2007) also investigated a group of 10 year old children with dyslexia before and after completing the FFWD program. They confirmed improvements in language and reading abilities, as well as changes in patterns of brain activation as measured by fMRI in response to nonlinguistic stimuli with rapid or slow transitions. Children with dyslexia showed increased brain activity following FFWD in left pre-frontal regions¹⁰ to stimuli with rapid as compared to slow transitions. These findings suggest that the adaptive training intervention protocol used in this study drives normalizing, as well as compensatory mechanisms in individuals with LI.

Another study reports changes in behavioral performance and electrophysiological measures following a more narrowly defined intervention protocol. Kujala and colleagues (Kujala, Kallio, Tervaniemi, & Näätänen, 2001) found that audio-visual training with dyslexic children, using only non-verbal stimuli, improves reading accuracy and speed, and reaction time. Also, the amplitude of the mismatch negativity response (MMN), the ERP component indicative of auditory change detection (Näätänen et al., 2007), is significantly increased in amplitude following intervention. It appears that perceptual training with non-linguistic stimuli results in plastic changes in the neural substrates supporting bottom-up processing (sound discrimination). These results support the view that phonological difficulties encountered by individuals with dyslexia are due,

¹⁰ Following FFWD, increased brain activation was observed in several brain regions in children with dyslexia to rapid vs. slow frequency transitions, including bilateral insula, left operculum, right inferior frontal sulcus, left superior frontal regions, right precuneus, cingulate gyrus, and bilateral thalamic regions. These areas showed also increased activation for rapid vs. slow frequency transitions in typical-reading children.

at least in part, to a general sensory discrimination dysfunction rather than a specific language impairment, *per se*¹¹. These studies provide insight into the types of training that drive plastic changes in classically defined language areas of the brain and MMN generators, but questions remain as to the relations between the consequent changes in neural substrates, changes in behavior, and the role of attention in these processes.

1.8 Selective Attention and Plasticity

In developing organisms very early on, exposure to sensory events may be sufficient to stimulate changes in neural networks and drive the construction and organization of initial representations of stimuli (Zhang, Bao, Merzenich, 2002). Though the potential for cortical self-organization persists across the lifespan (Kaas, 1999), for systems outside of the early developmental time window (critical period), it is generally understood that mere exposure is not adequate to drive learning, and in this case, attention is necessary. Though defining the term “attention” has been the subject of volumes of work, in the present discussion, attention is defined here as *selectively focusing on events in one sensory modality*. Attention may function to (i) recruit more neural resources during the processing of a stimulus or event, or (ii) increases synchrony among neural ensembles responding to the stimuli, or (iii) both (Näätänen et al., 1993b; Gomes et al., 2000). This drives plasticity so that a neural response to a sensory event that is initially voluntary (requires attention to induce synchrony and/or recruit additional neural coalitions) eventually becomes automatic or involuntary. At the physiological

¹¹ The authors suggest that this is even a more general dysfunction than RAP impairment since no stimuli in this paradigm were rapidly presented.

level, it has been demonstrated that paired cortical and neuromodulatory mechanisms appear necessary for such plastic changes to occur.

The basal forebrain, a group of structures that lie close to the medial and ventral surfaces of the cerebral hemispheres and include the nucleus basalis, diagonal band, medial septum and substantia innominata, has been implicated in this type of plasticity. This highly complex brain region appears to play a role in attention, motivation, and memory as well as in related neuropsychiatric disorders including schizophrenia, Alzheimer's disease, and Parkinson's disease. Within the basal forebrain, which contains many different types of neurons (Zaborszky & Duque, 2000), there are scattered clusters of cholinergic cells that are collectively referred to as the nucleus basalis (of Meynert; NB). The NB receives inputs from limbic and paralimbic structures and projects to the hippocampus, amygdala, and the entire cortex (Mesulam, Mufson, Wainer, & Levey, 1983). It has been shown that basal forebrain neurons are activated by sustained attention during learning (Muir, Page, Sirinathsinghji, Robbins, & Everitt, 1993; Sarter, Givens, & Bruno, 2001; Arnold, Burk, Hodgson, Sarter, Bruno, 2002), and NB lesions disrupt learning and cortical plasticity (McGaughy, Everitt, Robbins, & Sarter, 2000; Juliano, Ma, & Eslin, 1991). Further, Kilgard and Merzenich (1998) found that pairing the presentation of a specific tone with NB stimulation, which results in the release of acetylcholine in the cortex, resulted in the reorganization of primary auditory cortex (A1) in the rat, such that the number of neurons responding to the relevant tone greatly increased. Recently, Bao and colleagues (Bao, Chang, Davis, Gobeske, & Merzenich, 2003) found that pairing NB stimulation with broadband noise disrupted A1 organization and tonotopy, but subsequent pairing of NB stimulation with tones of discrete frequencies

restored the tonotopic organization of primary auditory cortex. This evidence suggests that the basal forebrain, and in particular, the nucleus basalis, may be critical to inducing plastic changes in the auditory cortex. The coincidence of a sensory event and NB activation appears necessary to drive cortical changes, and so it may be that attention serves to facilitate NB activation in the presence of behaviorally relevant stimuli, telling the brain what stimuli are “important”.

The role of attention in auditory learning is unclear. It has been documented that LI and attention difficulties often co-occur, but this relation is not well understood (Shafer et al., 2007; Stevens et al., 2006). A better understanding of how attention affects the modification of neural representations will be beneficial in the development and revision of useful intervention strategies that maximize gains in rapid processing and language skills, as well as help elucidate the mechanisms of normal language learning across development. These questions will be investigated in the following experiments.

1.9 Summary and Specific Aims

To summarize, in the present dissertation, there are three specific aims with respect to the overall goal of investigating rapid auditory processing and language ability: The first aim (1) is to compare RAP, using both electrophysiological and behavioral indices, in the mature adult and the developing system in order to characterize potential changes in RAP. Using the same methodology, the second aim (2) is to compare RAP and language skills in control children to children with a diagnosed language impairment (LI). In this way, we intend to characterize RAP deficits in children with a diagnosed LI and describe distinguishing features of ERPs in children with poor RAP. The third aim

(3) is to examine effects of auditory discrimination training with the intervention program Fast ForWord-Language® with LI children, and index any resulting neurophysiological changes through ERP analyses and assess behavioral changes with standardized tests of language. Gaining a better understanding of what drives changes and improvements in RAP and language processing will help in the future development of intervention strategies for children with LIs. The experiments designed to address these aims and our working hypotheses are detailed in the following section.

2.0 General Methods

The processing of human speech requires the integration of brief auditory stimuli that enter the central nervous system in rapid succession. This ability has been termed rapid auditory processing (RAP). RAP skills are believed to underlie successful language acquisition, and deficits in RAP have been linked to developmental language learning impairments (LI). Although a significant literature exists examining the role of RAP in language development and LI, many questions remain regarding the etiology and remediation of developmental LIs as well as the normal maturational mechanisms involved in language acquisition, including the role of attention in the modification of neural sound representations. The dissertation experiments described here were designed to investigate the relations between rapid auditory processing (RAP), attention, and language ability, and specifically address three main questions: (1). How are these factors (RAP, attention and language) are related when development proceeds normally and language is *intact*? (2). How are these factors are related when development is abnormal and language is *impaired*? (3) How are these factors are related when the abnormally developing system is *intervened* and language and the underlying auditory system are altered?

To address these questions, a series of five experiments were conducted which all utilize the same converging electrophysiological and behavioral techniques:

Experiment 1: Modulation of the Mismatch Negativity Elicited by Tone Doublets with Variable Interstimulus Intervals in Normal Adults. This study examines the modulatory effects of attention and rate of presentation on the auditory-evoked mismatch negativity response (MMN), a component of the auditory ERP

waveform that reflects a pre-attentive auditory change detection mechanism, in normal adults. These findings provide information about potential differences in RAP when listening is passive (ignoring auditory signals) and active (attending), and lay the foundation for a developmental comparison of ERPs between adults and children by providing an understanding of auditory processing in the intact mature brain. A behavioral task of RAP was also included in this experiment so relations between behavioral and electrophysiological responses could be explored.

Experiment 2: Modulation of the Mismatch Negativity Elicited by Tone Doublets with Variable Interstimulus Intervals in 6 – 9 year old Children with Typical Language Development. This study parallels Experiment 1, examining the modulatory effects of attention and rate of presentation on long latency ERPs elicited by compound auditory stimuli in young school-age children between the ages of 6 and 9 years. The electrophysiological techniques and behavioral assessment of RAP in this experiment are identical to those in Experiment 1. Additionally, children in this experiment received a comprehensive behavioral battery consisting of standardized tests of language, reading and non-verbal cognitive ability. These assessments were included to insure that all children in this study had normally developing skills, and to allow for detailed comparisons with children with abnormally developing language skills (Experiment 4).

Experiment 3: Developmental Changes in the Mismatch Negativity Elicited by Tone Doublets with Variable Interstimulus Intervals: Adults and 6 – 9 year old Children. This experiment comprises a series of analyses examining maturational differences in the Mismatch Negativity (MMN) response in adults as compared to

typically developing 6 to 9 year old children, specifically looking at how attention may modulate the MMN differently in the mature and developing brain as a function of the rate of presentation of the auditory stimuli. Potential hemispheric differences in the MMN in adults and TLD children are also explored.

Experiment 4: Modulation of Mismatch Negativity Components Elicited by Tone Doublets with Variable Interstimulus Intervals in Children with a Language Impairment and Controls. This experiment examines relations between RAP, attention and language in children age 6 to 9 years when development is abnormal and a language learning impairment (LI) has been diagnosed. Children with normally developing language skills who participated in Experiment 2 served as controls. All electrophysiological and behavioral methodology here is identical to that of Experiment 2. The effects of rate of presentation and attention on long latency ERPs were compared between LI and control children.

Experiment 5: Changes in Rapid Auditory Processing and Language Skills Following a Computerized Auditory Training Program: An ERP Study. In this experiment, a subgroup of the LI children who participated in Experiment 4 completed the intervention protocol Fast ForWord-Language® aimed at improving RAP via adaptive sound discrimination training. The electrophysiological and behavioral procedures common to Experiments 2 and 4 were administered to assess changes in long latency ERPs and language abilities in (i) LI children following the intervention, and (ii) a subgroup of the normally developing children who participated in Experiment 2 after a time interval equivalent to the intervention (but no intervention was received). In this way intervention effects and short-term developmental changes were assessed. The results

address the question of what changes may occur in RAP that are then reflected in improvements in language skills.

In all five experiments, the electrophysiological techniques and auditory stimuli were identical. This allowed for rigorous inspection of how the brain responds to rapidly presented compound auditory stimuli across several populations: adults who experienced normal language development, 6 to 9 year old children with typically developing language skills, and 6 to 9 year old children diagnosed with a LI both before and after completing a language intervention program. Age appropriate behavioral assessments of RAP and language ability provide converging information to facilitate a better understanding of relations between ERPs and language skills. All participant information and electrophysiological and behavioral methods are described in detail below.

2.1 Participant Recruitment and Inclusion Criteria

2.1.1 Adult Participants (Experiments 1 and 3)

Adult participants were recruited locally through posters and flyers displayed around the Rutgers – Newark campus in Newark, New Jersey, and also within the Rutgers – Newark Neuroscience department through word of mouth. To be included in this study, participants were required to have no hearing, language, or neurological problems. Each participant was paid \$15 for his or her time.

2.1.2 Children with Typical Language Development (TLD) (Experiments 2, 3, 4, 5)

Experiments 2, 3, 4: Children between the ages 6 and 9 years were recruited through local New Jersey schools by distributing brochures about the study. With written

permission from the school, brochures were given to all children in first, second and third grades. Additionally, 6 to 9 year old children and siblings of children involved in a longitudinal study at the Infancy Studies Laboratory, Rutgers University, were invited to participate. The children in the longitudinal study were originally recruited through local pediatric practices in Northern New Jersey. Participants visited the lab previously at ages 6, 9, 12, 16, 24, 36, 48 and 60 months, and some children also had completed 84 month visits.

To be included in the present studies, children must have had unremarkable pre- and peri-natal circumstances, been born full-term and of normal birth weight, have no history of hearing problems or other neurological or psychiatric disorders (e.g. brain damage, autism, learning problems, attention deficit disorder), have no known family history of a language-based learning impairment (LI), and be monolingual English speakers.

Experiment 5: TLD children who participated in Experiments 2, 3 and 4 were invited to take part in Experiment 5. Participation involved returning to the laboratory after an interval of approximately 3 months to repeat the ERP session and behavioral battery to examine short-term developmental effects on ERPs and to assess potential practice effects on standardized language and reading measures.

2.1.3 Children with Language Based Learning Impairment (LI) (Experiments 4, 5)

Experiments 4 and 5: Children between the ages of 6 and 9 years with language-based learning impairments (LI) were recruited through private speech and language therapists in the metropolitan New York area and throughout New Jersey. In order to be

included in the study, children had to meet one of the following LI criteria based on the administered behavioral battery (described in the following section – 3.2. Standardized Behavioral Testing): (1) Overall standardized language score 1 or more SD below the mean (CELF-4 Core Language score ≤ 85), or two or more language area scores (CELF-4 Receptive Language, Expressive Language, Language Content, Language Structure) ≤ 85 ; (2) Three or more standard subtest scores $\leq 25^{\text{th}}$ percentile in language (CELF-4 subtest standard score ≤ 8) with a history of language therapy or intervention within the last 6 months or ongoing; or (3) Three or more standard subtest scores $\leq 25^{\text{th}}$ percentile in language (CELF-4 subtest standard score ≤ 8) and reading (Woodcock Word ID, Word Attack, Passage Comprehension standard score ≤ 85) with a history of language therapy or intervention within the last 6 months or ongoing.

Criteria #2 and #3 were designed to allow children into the study who may have significant disparities in various language areas, with very low performance in some areas and average performance in others. Using overall language scores (CELF-4 core or area scores) alone would obscure such weaknesses because multiple subtests are used to generate area scores and can “average out” to a standard score in the normal range.

For all LI participants, non-verbal cognitive score (performance IQ of the Wechsler Abbreviated Scale of Intelligence, WASI) had to fall within the normal range (≥ 85) and could not be lower than overall language score (CELF-4 Core). Children with autism, hearing loss, frank neurological damage, apraxia, dyspraxia, oral facial abnormality or disorder, psychiatric disorder (obsessive compulsive disorder, bipolar disorder) and epilepsy were excluded. English had to be the primary language for all children. Multi-lingual children were excluded.

All LI children included in Experiment 4 were invited to participate in Experiment 5 in which LI children completed the Fast ForWord-Language® (FFWD) intervention program (described below in section 3.3. Auditory Training procedure – Fast ForWord-Language®) and then returned to the lab for post-intervention testing. These children completed FFWD under the guidance of a certified provider who was a licensed speech and language pathologist. After completing FFWD, the children returned to the lab for post-intervention behavioral and ERP sessions.

2.2 Event-Related Potential (ERP) Recording Session (Experiments 1, 2, 3, 4, 5)

2.2.1. Procedure

In all experiments (1, 2, 3, 4, and 5), when a participant arrived in the laboratory, the experimental procedures were explained and the adult participant or parent(s) of child participants provided informed consent (children provided verbal assent). For the ERP recording, participants were seated in an acoustically shielded room in a comfortable chair. In preparation for the ERP recording session, head circumference at the glabella (brow ridge) and occipital protuberance, inion-nasion¹² distance, and distance between preauricular points¹³ of the participant were measured using a tape measure. The midpoint between the inion and nasion centered between the preauricular points is the *vertex*. The vertex of a participant was marked with a small “x” using a washable marker, and this point served as a guide when applying the apparatus used for recording ERPs, the Geodesics Sensor Net.

¹² Inion is the nape of the neck, a point located on the external occipital protuberance at the intersection of the midline. Nasion is the point on the skull that is middle point of the nasio-frontal structure (the forehead and nose) (Stedman’s Medical Dictionary, 26th Edition. Ed. M. Spraycar, 1995)

¹³ preauricular points are anterior to the auricle of the ear (Stedman’s Medical Dictionary, 26th Edition. Ed. M. Spraycar, 1995).

The Geodesic Sensor Nets (GSN; Electrical Geodesics, Inc.) used in these experiments each consists of 64 molded plastic sensor housings interconnected by polyurethane elastomer threads (see Figure 1). Each sensor housing contains a silver-silver chloride (Ag/AgCl) electrode embedded in an electrolytic sponge. This plastic housing, sponge and embedded electrode together is referred to as a *channel*. The construction of the GSN is such that a single inter-channel distance is approximated between all pairs of channels. This network structure allows channels to spatially adjust simultaneously when the net is placed on the head so that a single distance, a geodesic (the shortest distance between two points on the surface of a sphere) spans all pairs.

Fourteen different size GSNs were available in the lab. For each participant, the appropriate size net was chosen based on the aforementioned head measurements and sizing guidelines from Electrical Geodesics, Inc. (see Figure 2 – Size chart for GSN). The elastic construction of the GSN allows for a good fit across a range of head sizes and thus insures good contact between the sensors and scalps of all participants.

Before placing the GSN on the head, the net was soaked for at least one minute in an electrolyte solution¹⁴ to increase conductance of the EEG from the scalp. When applying the net, the vertex channel was aligned with the marked vertex point on the scalp and correct positioning of the net was further aided by color-coded mastoid channels (without electrodes). Once placed on a participant, the infraorbital channels (63 and 64) were positioned directly below the participant's pupils and roughly over the

¹⁴ The electrolyte solution was made by combining 1 liter of distilled water with 8.5 grams of powdered potassium chloride crystals and 3 cc of Johnson's Baby Shampoo (GSN Technical Manual, 2000. Electrical Geodesics, Inc.).

infraorbital foramen¹⁵. The position of the net was checked for lateral symmetry using the ear markers and a straight line of channels proceeding from nasion toinion was visually verified. Then all 64 channels were serially positioned perpendicular to the head with hair underlying the sensor gently moved aside to attain the best possible contact with the scalp. During positioning of individual sensors, a few drops of the electrolyte solution were added to each sensor using a plastic pipette. After applying the net, the GSN was connected to the amplifier and impedance, the resistance to current flow from the brain to the electrode, was measured using a 10 Hz sine wave for each electrode. If the impedance of a channel was above 50 k Ω , the scalp at that location was gently scrubbed with the tip of the plastic pipette and a few more drops of the electrolyte solution were added. This process continued until the impedances of all channels were below 50 k Ω . The entire net application process typically lasted about 20 minutes.

After net application was complete, the lights in the room were dimmed, the participant was given instructions to remain quietly seated, and the ERP recording session was initiated.

2.2.2 Stimuli

In all experiments (1, 2, 3, 4, 5), the stimuli were complex tones with a fundamental frequency of 100 or 300 Hz with 15 harmonics (6 dB roll-off per octave). Each tone was 70 ms in duration. The tones were presented in pairs with varying interstimulus intervals (ISIs) of 300, 70, or 10 ms (see Figure 2.2.2). These ISIs were selected based upon consideration of the time ranges that are important for natural speech perception. The 300 ms ISI is outside of the range of RAP, but is included based on the

¹⁵ The external opening of the infraorbital canal on the anterior surface of the upper jaw bone (Spraycar, M. (Ed.) 1995).

range of impaired RAP skills demonstrated in children with LI (Tallal & Piercy, 1973). The 70 ms ISI falls within the “tens of milliseconds” range that is critical for discrimination of rapid formant transitions found in stop consonants (maximum c.a. 80 ms) and voice onset times (VOT; discrimination range c.a. 25 – 70, phonetic boundary c.a. 30 ms) (Kewley-Port, 1982; Borden & Harris, 1980; Phillips, 1999). Further, a series of studies examining RAP abilities in infants and toddlers suggests that the ability to resolve a 70ms ISI predicts normal language acquisition at later ages (Benasich et al., 2006; Benasich & Tallal, 2002; Benasich, Thomas, Choudhury & Leppänen, 2002). On the other hand, the 10 ms ISI is close to the highest adult threshold of auditory acuity in terms of gap detection (Phillips, 1999) and represents the upper limits of RAP as defined in the present set of studies. There is also some evidence that higher acoustic modulatory rates and/or signals that differ in temporal structure (i.e, very short ISIs) may be processed differently by the same neurons (Marsat & Pollack, 2004).

Tone pairs were presented at 75 dB SPL free field via speakers to the left and right of the participant. The presentation of one tone pair was a trial. Blocks of 833 trials with a fixed ISI were presented in a typical Oddball paradigm. In Experiment 1 with adults, the repeating standard stimulus occurred with a probability of 85% (708 trials), and the deviant stimulus occurred with a probability of 15% (125 trials). In Experiments 2, 4 and 5 with children, the repeating standard stimulus occurred with a probability of 80% (667 trials), and the deviant stimulus occurred with a probability of 20% (166 trials)¹⁶. The standard tone pair was 100 Hz – 100 Hz, and the deviant tone pair was 100 Hz – 300 Hz. Deviant tone-pairs were presented in a pseudo-random order with at least 3

¹⁶ The Oddball presentation for all child participants (20% deviant trials) was modified slightly from Experiment 1 (15% deviant trials) in order to include more deviant trials because children tend to have more trials contaminated with artifacts due to eye or muscle movement as determined from pilot studies.

and no more than 10 standards between each deviant. The inter-trial interval (ITI, onset to onset) was 700 ms. There were 4 regularly placed pauses within a block to give participants brief breaks. There were also short pauses between blocks of trials, which typically lasted about 30 seconds.

2.2.3 Conditions

The participants were exposed to the stimuli under two conditions: **Passive** and **Active**.

During the **Passive** condition, adult participants in Experiments 1 and 3 read text (Readers, $n=10$) or viewed a silent video (Viewers, $n=15$). All child participants in Experiments 2, 3, 4, and 5 viewed a silent video. During the presentation of the tone pairs, participants were asked to ignore the sounds. An experimenter watched the participant on a video monitor throughout the session. During the pauses, the experimenter would speak to the participant (to ask about fatigue, comfort, etc). Children in Experiments 2, 3, 4, and 5 were asked questions about the video to insure they were attending to the movie and were motivated to respond correctly in order to earn “points” (stickers placed on a cut-out shape) needed to “buy” a prize at the end of the session (all children received a prize at the end of each session regardless of the number of “points” they received).

Adults (Experiments 1 and 3) received a minimum of 4 and maximum of 6 different blocks, with Passive blocks always preceding Active blocks. For all children (Experiments 2, 3, 4, 5), a total of 4 blocks were presented in the following order: Passive A, Passive B, Active A, Active B. The stimuli in the first and third blocks (A) were the same, and the stimuli in the second and fourth blocks were the same (B). Due to the

length of the session¹⁷, children received only two of the three ISIs (300, 70, or 10 ms): either 300 and 70 ms (Group I), or 70 and 10 ms (Group II). Presentation order was counterbalanced. In this way, all children received the 70ms ISI stimuli so that the two groups (300/70 vs. 70/10) could be compared¹⁸.

Some children (Experiments 2, 3, 4, 5) were unable to complete all 4 blocks due to the length of the session. If a child appeared fatigued, uncooperative, or complained of being very tired, the experimenter would administer the 70ms ISI Active block to insure that this data was obtained, and the 300 or 10ms ISI Active block was aborted or omitted. The rationale for prioritizing the 70 ms ISI is based on how processing non-verbal tones can inform us about processing language. While some elements of speech are constant and relatively long in duration (i.e. vowels), stop consonants (/b, d, p, g, k, t/) are characterized by rapid changes in frequency over a short period of time in the tens of milliseconds range. Deficits in accurately processing auditory cues in this tens of millisecond range have been found in children with language impairments (LI), (for a review, see Leonard, 1998), in children with a familial risk for specific language impairment (SLI) (Benasich and Tallal 2002), and in adults with a childhood history of reading problems (Ahissar, Protopapas et al. 2000). Deficits in such basic rapid auditory processing skills have been linked to the emergence of disordered language (Leonard, 1998; Benasich & Tallal, 2002; Benasich et al., 2006). In a series of seminal studies,

¹⁷ In pilot testing, it was found that the session was too long if all six blocks of stimuli were presented. Children became fatigued and restless, and this was problematic for the sustained attention task in the Active blocks presented in the second half of the ERP session.

¹⁸ In a previous study in our lab, it was shown that the MMN elicited by the 70ms ISI stimuli in two groups of adults did not differ, so further group comparisons were conducted (Thomas et al., 2001). In the present experiment, the same type of group comparison was conducted to verify homogeneity of the MMN with the 70 ms ISI stimuli, allowing more confidence in across-group comparisons of ERP responses to the 300 and 10 ms ISI stimuli.

Tallal and Piercy (1993a; 1993b; 1994; 1975) found that LI children displayed marked deficits in correctly identifying and discriminating both non-verbal (two-tone sequences) and verbal (computer generated consonant-vowel syllables) stimuli when the stimuli were brief and presented rapidly. Specifically, LI children were able to discriminate the cv-syllables /ba/ and /da/ when the formant transitions were synthetically extended to 80ms, but not at 40ms (near the natural speed of speech). Based on these findings, in the present experiment, tone pairs with a 70 ms ISI were designed to target the tens of milliseconds temporal range which has been found to distinguish typically developing children from those with impaired auditory processing skills. In contrast, a 300ms interval does not require rapid auditory processing, and a 10 ms interval may be too brief a time window for complete and accurate auditory processing in this group of young children, even those with typically developing language. Thus the 300ms and 10ms ISIs may not be as sensitive to impaired RAP in this age group.

For all participants (Experiments 1, 2, 3, 4, 5), a 4 minute resting EEG (REEG; no auditory stimuli presented), was administered between the last Passive block and the first Active block.

In the **Active** condition, all participants (Experiments 1, 2, 3, 4, 5) were instructed to press a button located on a response pad as quickly as possible when they heard the deviant (target) tone pair (100 Hz-300 Hz). There were 33 training trials before the experiment began when feedback was given, but during the experiment no feedback was given to the participants. The Passive condition always preceded the Active condition. Block presentation order was counterbalanced among subjects. The ERP session, including net application, lasted approximately 1 to 1.5 hours.

2.2.4 EEG/ERP recording

In all experiments (1, 2, 3, 4, 5), the EEG/ERP data were recorded with 64 Ag/AgCl electrodes connected within a Geodesic Sensor Net (Electrical Geodesics, Inc.). Incoming EEG was amplified 1000 times, sampled at 250 Hz, and bandpass filtered online at 0.1 to 100 Hz. Impedances were maintained below 50 k Ω during the recording.

Electroculogram (EOG) was recorded with electrodes above, below, and lateral to the eyes. The EEG electrodes were referred to the vertex electrode online, and re-referenced off-line to an average (whole head) reference.

2.2.5 Offline EEG/ERP processing (Experiments 1, 2, 3, 4, 5)

All EEG data was exported from Net Station after being re-formatted for import into BESA (Brain Electrical Source Analysis V 5.1.8.10, MEGIS Software GmbH, 2006).

After each data file was imported into BESA, the data were scanned and corrected for eye-movement related artifacts [electrooculogram (EOG) used to detect eye blinks and horizontal eye movements] using a variation of the Berg and Scherg spatial components method (Berg & Scherg, 1994; Ille, Berg & Scherg, 1997; Ille, Berg & Scherg, 2002) with a high-pass (low cut-off) filter setting of 0.1 Hz and a notch filter of 60 Hz (2 Hz wide). The low-pass (high cut-off) filter was disabled. The thresholds for EOG artifact correction were 150 μ V for horizontal eye movements and 250 μ V for vertical eye movements/eye blinks.

After all the data files were artifact corrected for eye movements, each data file was individually scanned for additional artifacts with a high-pass (low cut-off) filter

of 1.0 Hz, 60 Hz notch filter (2 Hz wide), and the following artifact thresholds: Adults: 120 uV amplitude, 75 uV gradient, 0.1 uV low signal; children: 200 uV amplitude, 150 uV gradient, 0.1 uV low signal¹⁹. Epochs of analysis were: 300ms ISI: -300 – 1140ms; 70ms ISI: -300 – 915ms; 10ms ISI: -300 – 855 ms. Channels with excessive artifacts were marked as “bad”. For any given trial, designating a “bad” channel allows that channel to be ignored and the remaining channels to be scanned to determine if a trial is acceptable based on artifact rejection criteria. In children, EOG and movement artifacts are often a significant problem. The use of two-step artifact correction and rejection process in BESA maximizes the potential of extracting artifact-free trials for averaging. A minimum of 50 artifact-free trials were averaged by stimulus type (deviant or pre-deviant standard), and baseline corrected (baseline = -100 ms). After averaging, channels marked as bad were interpolated using a spherical spline method. Data were then grand averaged within participant group (Adult, TLD, LI).

Off-line filtering parameters for waveform viewing and statistical extraction (peak amplitude and latency values) were low-pass = 1 Hz, high-pass = 15 Hz. The low and high filter settings were chosen in order to best isolate the MMN, eliminating frequencies outside the range of this component of interest (Shafer et al., 2000; Kurtzberg et al., 1995; Martin, Kurtzberg & Stapells, 1999) and to provide a uniform method to analyze the data across the different age (adults, 6 – 9 year old children) and clinical (TLD, LI) groups.

¹⁹ In the three artifact rejection criteria, amplitude refers to the absolute difference between the minimum and maximum amplitudes within a single trial and channel, gradient refers to the amplitude difference between two successive sampling points within a trial for a given channel, and low signal refers to the variance of the gradient within a trial for a given channel (to detect channels that were not recording properly).

2.3 Behavioral Testing

2.3.1 Auditory Repetition Task (Experiments 1, 2, 3, 4, 5)

Following the ERP session, participants were given a behavioral rapid auditory processing (RAP) discrimination task called the Auditory Repetition Task (ART) (Tallal and Piercy 1973a, b). In this task, participants listened to a sequence of tones (doublets or triplets) with varying inter-stimulus intervals (ISIs). The participants were required to repeat the sequence of tones that they heard by pressing buttons mounted on a rectangular box (approximately 8" x 6"). One button corresponded to the high tone (fundamental frequency of 300 Hz) and the second button corresponded to the low tone (fundamental frequency of 100 Hz). Both tones were 70ms in duration, with the first 15 harmonics and amplitude roll-off of 6 dB per octave.

Participants were first familiarized with the tones presented in blocks (Detection phase, 5 trials for each tone) and then required to correctly identify the tones as they were presented in a random order (Association phase, 24 trials). If participants could not reach a criterion during Association (Association criterion = 70% correct identification of single tones), then training was repeated. If a participant did not reach Association criterion during the second administration, the task was discontinued.

If a participant did reach Association criterion, two-tone sequences were presented with a 500 ms ISI in the Sequencing phase (12 trials). Participants had to correctly identify at least 7 of 12 tone pairs (~ 60% correct) to achieve the Sequencing criterion. If Sequencing criterion was not achieved, the Association and Sequencing phases were repeated. If Sequencing criterion was not achieved the second time, then testing was discontinued.

If the Sequencing criterion was achieved, this completed training and participants were then administered the Test phase of the task that consisted of 3 different blocks of trials: 2 tone sequences presented with shorter ISIs (2-Fast); 3 tone sequences with a long ISI (3-Slow); 3 tone sequences with short ISIs (3-Fast). For both adults and children, the ISI in the 3-Slow block was 500 ms. For adult participants (Experiments 1 and 3), the ISIs in the 2-Fast and 3-Fast blocks were 300, 70, 40, or 10 ms in duration (Auditory Repetition Test – Adult Version [ART-A]). For children (Experiments 2, 3, 4, 5), the ISIs in 2-Fast and 3-Fast blocks were 500, 150, 70, or 10 ms in duration (Auditory Repetition Test – Child Version [ART-C]). Table 2.3.1 contains information about the ISIs and number of trials in each testing block for the ART-A and ART-C. These two different versions of the ART (also called the Repetition Test Battery), developed and utilized by the Infancy Studies Laboratory, are modified versions of the original task designed by Tallal and Piercy (1973a, 1973b). The ART-A and ART-C were developed keeping in mind the duration of the testing session (i.e. fatigue of young school-age children), and focusing on the ISIs of greatest interest. Tallal and Piercy (1973b) found that children with LI perform significantly poorer than controls at ISIs of 150 ms or less (150, 60, 30, 15, 8 ms) when tones were 75 ms long. The ART-C includes 150, 70 and 10 ms ISIs. Tallal and Piercy (1973a) also note that normal rates of speech approach 80 ms per phoneme, and so examining a threshold close to this value (70 ms) allows for close inspection of rapid auditory processing at rates close to those of natural speech. In adults, differences between “slow” and “fast” rates of presentation have been examined (see Progress Report of R01 DC01854-01 “Twin and Family Genetic Studies of Language Impairment”, Principal Investigator: P. Tallal, 1993 - 1995). Normative data collected

from nearly 800 adult participants revealed differences in processing 2- and 3 tone sequences with “rapid ISIs” (70 and 10 ms) as compared to “slow ISIs (500 ms)”. In the ART-A, slow (500, 300 ms) and rapid (70, 40, 10 ms) ISIs are included for 2- and 3- tone sequences, and more trials are presented than in the ART-C due to higher expectations for adult compliance and lower anticipated rates of fatigue.

The ART-A or ART-C was administered after the ERP session in a quiet testing room with the participant seated at a table. The examiner sat to the left of the participant and played the tone sequences free field from a tape player that was placed on the table in front of the participant. The examiner manually recorded the participant’s response after each trial, and later the *percentage of correct trials* was calculated for each stimulus sequence at each ISI. The ART administration was video taped, and lasted approximately 15 - 20 minutes.

2.3.2 Standardized Behavioral Testing (Experiments 2, 3, 4, 5)

All child participants were given a behavioral battery of standardized language, reading and cognitive tests. During children’s first visit to the lab, parents provided informed consent and children gave verbal assent to participate after the experiment was explained to them. The session was conducted in a quiet testing room with the child and examiner seated at a table. Parents were able to watch the session from an adjacent room on a video monitor. The behavioral battery consisted of the Clinical Evaluation of Language Fundamentals – 4 (CELF-4), The Wechsler Abbreviated Scale of Intelligence (WASI) performance subtests, and Woodcock Reading Mastery Tests (WRMT): Word Identification, Word Attack and Passage Comprehension subtests.

The Clinical Evaluation of Language Fundamentals – 4 (CELF-4) (Semel, Wiig, & Secord, 2003) is the fourth edition of this standardized test designed to assess receptive and expressive language skills in individuals 5 to 21 years of age. There are eight subtests that generate five composite language scores for 5 – 8 year old children: Concepts and Following Directions, Word Structure, Recalling Sentences, Formulated Sentences, Word Classes – Receptive, Word Classes – Expressive, Sentence Structure, and Expressive Vocabulary. In addition to these, for 9 – 21 year old children and young adults there are four additional subtests: Word Definitions, Understanding Spoken Paragraphs, Sentence Assembly, and Semantic Relationships. All subtest standard scores have a mean of 10 and a standard deviation of 3. For all ages, the test yields five composite scores: Core Language, Receptive Language, Expressive Language, Language Content, and Language Structure (5-8 yrs) or Language Memory (9-21 years). Composite standard scores have a mean of 100 and a standard deviation of 15. A test-retest study (interval of 1-5 weeks) of the CELF-4 revealed that composite scores increased an average of 4 points for the overall sample, and that many, but not all, of the participants' scores were higher on the second administration of the test (Semel, Wiig, & Secord, 2003).

The Wechsler Abbreviated Scale of Intelligence (WASI) (The Psychological Corporation, 1999) assesses general intellectual functioning and reasoning in individuals aged 6 to 89 years. It is composed of two areas: Verbal, which assesses skills such as vocabulary and comprehension, and Performance, which assesses the ability to reconstruct patterns, reproduce shapes, and understand spatial relations. Only the Performance subtests Block Design and Matrices were administered as part of this study.

WASI subtest T-scores from 40 to 60 are within the average range. The composite WASI Performance IQ standard score has a mean of 100 with a standard deviation of 15, and also yields percentile ranks.

The Woodcock Reading Mastery Tests (WRMT) (Woodcock, 1987) is a standardized reading assessment with norms for ages 5 to 75 years. It consists of a battery of tests measuring various aspects of reading ability. In the present experiment, the Word Identification, Word Attack, and Passage Comprehension subtests were administered. The Word Identification subtest requires a participant to identify (i.e. produce a natural reading of) isolated printed words of which they may or may not know the meaning. As the test progresses, the participant is asked to identify words that are encountered less and less frequently in written English. The Word Attack subtest assesses a participant's ability to apply phonic and structural analysis skills to read novel words. Most of the stimuli are nonsense words, though some are words that are rarely encountered in the English language, and thus are most likely unfamiliar to the participant. The Passage Comprehension subtest assesses an individual's ability to study a short passage (usually 2 or 3 sentences) and to identify a key word missing from the passage (position indicated by a blank space). To successfully complete the items, the participant must understand all the sentences in the passage, and not just the one containing the blank space. Thus, a variety of comprehension and vocabulary skills must be employed. For all subtests, the WRMT yields a number of derived scores, including standard scores (mean = 100, standard deviation = 15), grade equivalent scores, age equivalent scores, and percentile ranks.

Children were given colorful stickers to place on a cut-out paper shape when each subtest was completed. The children were told the stickers were “points” needed to “buy” a prize at the end of the session. When testing was complete, the children chose a small toy or game, regardless of the amount of “points” earned. The behavioral testing session usually lasted 1.5 to 2 hours.

2.3.3 Auditory Training Procedure – Fast ForWord-Language® (Experiment 5)

The Fast ForWord-Language® (FFWD) intervention program (Scientific Learning Corporation, 2002) is a computer-based training program designed to improve auditory processing skills underlying language abilities, as well as memory, sequencing and attention abilities (FFWD product information can be found at <http://www.scilearn.com/index.php>). The FFWD program aims to drive neural plasticity through intensive, repetitive training that is adaptive. Early training with FFWD utilizes auditory stimuli in which some aspects of the stimuli are “stretched” and amplified (e.g. rapid transitions in speech that characterize formants of stop consonants are increased in duration and made louder). As a child progresses through the program and performance improves, the stimuli are modified so that they gradually approach and then reach the speed and amplitude levels found in normal speech. The FFWD program requires training 5 days a week for 4 to 8 weeks. Below are descriptions of the exercises in the program:

Block Commander: This exercise targets concepts (e.g. color, size, spatial relations) and following directions as children listen to commands and then identify

appropriate targets contained in an array (e.g. “Touch the big blue circle and the small red square”).

Circus Sequence: Children must repeat a sequence of frequency-modulated tones (upward or downward gliding) with variable inter-stimulus intervals (the time between the two tones) and durations.

Language Comprehension Builder: Four pictures depicting an action are displayed, and the child must match a spoken sentence with the correct picture.

Old MacDonald's Flying Farm: The participant hears a repeated consonant-vowel combination and must detect when the stimulus changes.

Phoneme Identification: In this exercise a child must discriminate consonant-vowel syllables in order to match two that are the same.

Phonic Match: This exercise involves matching consonant-vowel syllables within simple words.

Phonic Words: A participant must distinguish between words that differ only by an initial or final consonant by identifying which of two pictures represents a target word.

Children begin FFWD at a level of modified speech and non-verbal stimuli duration where they can achieve a 90% success rate. After reaching this level of mastery, the program brings them to the next level until a 90% success rate is again achieved. This continues through all levels (5 levels for exercises with speech stimuli, and 6 levels for exercises with non-speech stimuli) until a child reaches 90% success rate at the highest level (normal speech and 25 ms non-verbal stimuli) on all exercises. At this point they are finished with the program. In some cases, children cannot reach 90% on all seven exercises. In such an event, it is left to the discretion of the FFWD provider to determine

if it is in the best interest of the child to discontinue the program due to a plateau in performance that cannot be overcome, coupled with general fatigue and loss of motivation to continue. In general, FFWD training continues until an individual child has completed the entire program rather than for a pre-determined, fixed amount of time.

LI children participating in Experiment 5 completed FFWD under the supervision of licensed speech and language pathologists or special education specialists trained by Scientific Learning Corporation to administer this program. Children completed the program either at the office of a FFWD provider or at home and participation and progress were monitored daily. At either location, administration of the program was the same. Children were seated in front of a computer monitor where the visual stimuli were presented, and accompanying auditory stimuli were delivered via headphones. Responses were delivered by mouse clicks at appropriate locations in the visual array. The presentation of trials was self-paced.

2.4 Post-Fast ForWord-Language Assessments (Experiment 5)

One to four weeks following completion of FFWD for LI children, and after a comparable interval (approximately 12 weeks) for the TLD children, all participants completed another behavioral session and an ERP session that were identical to those described above (Behavioral Testing) except that the Performance subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) were not administered. It has been found that the practice effects on the Performance subtests are greater than on the Verbal subtests and, to date, there is no universal agreement regarding the shortest test – retest interval that will not result in significant practice effects. Research with the full Wechsler

Intelligence scales suggests that practice effects on the Performance subtests decrease significantly after a 1 – 2 year interval (Matarazzo, 1972; Matarazzo, Carmody & Jacobs, 1980). Thus, all children received the CELF-4 and Woodcock Reading Mastery tests at the second behavioral session.

2.5 Analytic Strategy

The data collected in the five experiments described here can be split into three general categories: demographic information, experimental electrophysiological data, and behavioral measures of language, reading, and cognition. The analytic approaches described in the following section were designed to test a number of a priori hypotheses and predictions that are described below. All analytic strategies are described in detail in the following section (3.0 Analytic Strategies, p. 63).

General Hypotheses

1. Rate: The MMN is an electrophysiological index of auditory change detection elicited by a rare, deviant stimulus occurring within a stream of repeated standard stimuli (Näätänen et al., 2007). The MMN has been shown to be larger in amplitude when the difference between the standard and deviant stimuli is large (larger frequency or intensity difference), and diminishes as the difference between the standard and deviant stimuli becomes smaller (Sams et al., 1985). Thus, here it was hypothesized that the MMN elicited by stimuli presented at slower rates will be larger than at faster rates within each sample of participants: adults, children with typical language development (TLD) and children with Language Impairments (LI). It is expected that LI children will have more attenuated or absent MMNs as compared to TLD children in response to stimuli

presented at faster rates. Further, in LI children it was predicted that MMN amplitude would increase following auditory intervention training reflecting improved rapid auditory discrimination.

2. Attention: Previous work has shown that the MMN may be modulated by selective attention when the difference between the standard and deviant stimuli is small, and the discrimination is perceived as difficult by the participant (Alho et al., 1992; Näätänen et al., 1993b; Gomes et al., 2000). Based on these findings, it was predicted that in adults the MMN elicited by rapidly presented stimuli may be enhanced by selective attention, while MMN responses elicited by deviants with longer ISIs may not. It was hypothesized that TLD children would show some attention enhancement of the MMN to stimuli with shorter ISIs, and that LI children would show attention enhancement to stimuli at all ISIs. Following intervention, it was expected that LI children would have a less marked attention enhancement of the MMN at all ISIs due to improvements in automatic auditory processing. These predictions are in line with the idea that the ability to automatically process subtle auditory changes improves over time due to both maturation and experience-related changes in the brain (Gomes et al, 2000). As such changes in processing occur, discrimination becomes automatic, not requiring or aided by focused attention.

3. Relations between ERPs and behavioral measures: The use of converging methodologies (EEG/ERPs and standardized measures of language, cognition and reading) address relations between measures of neural processing and behavior to help identify potential predictive relations between these two domains. MMN measures may correlate with concurrent measures of language, reading and auditory temporal

processing in both TLD and LI children.

These hypotheses and predictions were systematically tested using two levels of statistical analyses conducted using SPSS 13.0. The first level was data reduction, generation of descriptive statistics, and standard exploratory analyses. The second level involved the testing of specific hypotheses using multivariate general linear model techniques (i.e. multivariate analysis of variance).

3.0 Analytic Strategies

3.1. Analytic Strategies for Demographic and Descriptive Data Preliminary Analyses

3.1.1 Participant Information

Demographic and descriptive information will be reported for the adult, TLD and LI samples.

3.1.2 Verification of TLD and LI Participant status

To insure that TLD and LI groups satisfied the inclusion criteria for the present study, independent samples t-tests were conducted to test whether the groups differed significantly on language and reading measures, as well as non-verbal cognitive ability. Language measures were standard scores (mean 100, SD 15) of the Clinical Evaluation of Language Fundamentals, 4th Edition for three composite scores: Core Language, Receptive Language and Expressive Language. Reading measures were standard scores (mean 100, SD 15) of the Woodcock Reading Mastery Tests (WRMT) for three subtests: Word Identification, Word Attack and Passage Comprehension. The measure of non-verbal cognitive ability was the WASI Performance IQ standard score (mean 100, SD 15). It was predicted that the groups would differ significantly on both language and reading measures, as normal or impaired language and reading were components of the inclusion criteria for TLD and LI participants, respectively.

Further, paired samples t-tests were run within each group to ascertain whether there was a significant discrepancy between language (CELF-4 Core, Receptive, and

Expressive Language standard scores) and non-verbal cognitive ability (WASI Performance IQ), a hallmark feature of LI. The clinical diagnostic features for language disorders (Expressive, Receptive or Mixed subtypes) include language ability that is “substantially below” nonverbal cognitive ability (DSM-IV-TR, 2000, pp. 58 - 64), and the research community also generally employs such a criteria of discrepancy between verbal and non-verbal competence when identifying a group of children with Specific Language Impairment or a language based learning disorder (Bishop, 1997). It was predicted that the LI children, but not the TLD children, would show a significant discrepancy between language and non-verbal cognitive ability.

3.1.3 Verification of Demographic Comparability in TLD and LI Participants

To insure that the TLD and LI groups were well matched on demographic measures, demographic variables were subjected to independent samples t-tests to investigate whether or not the TLD and LI groups significantly differed in birthweight (grams), gestational age (weeks), socioeconomic status (Hollingshead Index), maternal age (years), maternal education level (years of school completed beginning with 9th grade/high school), and chronological age (age in years at time of first session for pre- and post-intervention visits). Additionally, the intervals between pre- and post-intervention visits (the number of days between first and second Behavioral sessions, and the number of days between first and second ERP sessions) were examined to insure that there were no significant differences in these intervals across groups. It was predicted that the TLD and LI groups would not significantly differ on any demographic measures as the two groups were matched as closely as possible on all of these measures.

3.2 Analytic Strategies for Preliminary Analyses of EEG/ERP Data

3.2.1 Visual Inspection of Grand Averaged Waveforms and Identification of

Obligatory Auditory ERP Components:

Adults (Experiments 1 and 3): The grand averaged standard and deviant waveforms were examined for the presence of the obligatory auditory component N1, a major long latency auditory peak in the adult ERP waveform. The N1 typically occurs with a latency of 80 to 120 ms and is thought to reflect pre-attentive auditory detection to sounds that exceed a perceptual threshold (Näätänen, 1990). The N1 is mainly generated by bilateral sources in the supratemporal cortex (Schroger, 1997; Hari et al., 1982; Lu et al., 1992; Picton et al., 1999) that produce a negativity that is maximal at fronto-central electrodes (McCallum & Curry, 1980). Many additional brain areas have been implicated in the generation of the N1, including prefrontal cortex (Alcaini et al., 1994), the thalamoreticular formation (Velasco and Velasco, 1986), and the cingulus (Giard et al., 1994). These multiple generators likely underlie several subcomponents that have been observed contributing to the N1. One subcomponent peaks around 75 ms at frontocentral channels and is thought to be generated in the auditory cortex (on the dorsal surface of the temporal lobes); two other subcomponents peak slightly later and with different topography (100 ms at vertex and c.a. 150 ms laterally) (for a review see Näätänen & Picton, 1987). In the present study we will examine the frontocentrally peaking N1 subcomponent, which will be referred to simply as the N1 from this point onward. The N1 peak amplitude and latency in the standard and deviant waves will be obtained.

Children (Experiments 2, 3, 4, 5): The grand averaged standard and deviant waveforms were examined for the presence of the obligatory auditory components P1 and N2, the first major positive and negative peaks that dominate the child ERP waveform at fronto-central sites (Csepe et al., 1992; Gomes et al., 1999). The P1 and N2 (also called the N250 based on the component's latency) are obligatory peaks in the child ERP waveform that occur in response to auditory stimuli presented at fast rates (less than 1 second, Ceponiene et al., 1998; Takeshita et al., 2002; Ponton et al., 2000; Shafer, Morr, Kreuzer, & Kurtzberg, 2000)²⁰. The N2 is the most prominent negative component in the child ERP waveform, increasing in amplitude from ages 4 – 10 years (Ponton et al., 2000), peaking at frontal and fronto-central channels in 7 – 9 year old children (Bruneau and Gomot, 1998). The child P1 occurs at a latency of approximately 50 to 100 ms post-onset of an auditory stimulus, and is maximal at frontocentral sites. The P1 is thought arise from secondary auditory cortex on the lateral part of Heschl's gyrus (Smith & Krauss, 1988; Liegeois-Chauvel, Musolino, Badier, Marquis & Chauvel, 1994). The peak amplitudes and latencies of the P1 and N2 components in the standard and deviant waves will be measured.

3.2.2 Identification of the Mismatch Negativity – (Experiments 1, 2, 3, 4, 5):

In all groups at all conditions, the grand averaged waveforms were visually inspected to look for the presence of an MMN response. Following the onset of the deviant tone, the standard and deviant waves were inspected for differences in amplitude

²⁰ At slower rates of presentation (i.e. longer than 1 second), an adult-like N1 has been observed in children less than 9 years of age (but not younger than 4 years) within a P1-N1-N2 complex (Ceponiene, Rinne, & Näätänen, 2002). In the present studies an inter-trial interval of 700 ms was used, and it was predicted that only the N2 component would be observed in this group of 6 to 9 year old children.

and morphology in frontocentral channels in expected MMN latency ranges (adult MMN: 100 – 150 ms; child early MMN: c.a. 100 – 300 ms; child late MMN/LDN: c.a. 400 – 600 ms). The topographic distribution of maximal amplitudes in the deviant wave were inspected to look for higher amplitudes in frontocentral and central channels, the expected MMN topography. The difference wave was also inspected for a negative peak in the MMN latency ranges. Another hallmark of the MMN was also examined: relative inversion of polarity of the MMN at mastoid channels in both the deviant and difference waves.

3.2.3 Event Related Potentials – Age Subgroups

Maturational changes in auditory evoked ERPs have been the subject of a growing literature within the developmental ERP field (e.g. Sussman, et al., 2008; Ceponiene, Rinne, Näätänen, 2002; Morr, et al., 2002; Shafer et al., 2000). Concern has been noted regarding the use of participant groups that span several years in young children due to significant maturational changes occurring in many brain regions throughout childhood and extending well into adolescence, including myelination of axons, changes in synaptic density, and volumetric changes in auditory cortex (Moore & Guan, 2004; Eggermont, 1985; 1988). Averaging ERPs across a wide age-range may obscure significant maturational differences in components. For these reasons, a constrained age range was used in the current studies (6 to 9 years). However, even more narrowly defined age ranges within the TLD and LI groups were examined to investigate potential differences in morphology in the standard, deviant and difference grand averaged waveforms.

The TLD and LI groups were each split into two age subgroups based on age at Visit 1: “6 – 7 year olds” (6 years, 0 months through 7 years, 11 months) and “8 – 9 year olds” (8 years, 0 months through 9 years, 0 months). Individual participants’ averaged ERP waveforms were grand averaged for the TLD and LI age groups for the Ignore condition 70 ms ISI at Visit 1 only. This one block was chosen because every child completed this block and thus it provided the largest amount of data for these analyses. Only Visit 1 was examined because maturational differences at Visit 2 could be confounded by additional factors of previous exposure to the stimuli and, in the case of LI children, the Fast ForWord-Language intervention program. All subjects at Visit 1 were naïve to the stimuli and the obtained ERPs reflect neural responses to their first experience with the tone pairs with a 70 ms ISI, allowing for the best assessment of potential fine-grained maturational differences. The morphology of the standard, deviant and difference waves will be described and discussed for the TLD and LI age groups. If age related differences are noted (e.g. large differences in amplitude or latency of the P1, N2 or MMN components, or additional peaks are present/absent in the grand averaged waveforms), amplitude and latency values within an appropriate time window(s) will be analyzed using independent samples t-tests to compare 6 – 7 year olds and 8 – 9 year olds within each group. If significant differences are revealed between the age groups, then Age will be used as a factor in relevant subsequent analyses. Overall Group and Visit related differences will be analyzed and discussed elsewhere.

3.3 Analytic Strategies for Event Related Potentials Statistical Analyses

3.3.1 Determination of Time Windows for Peak Amplitude and Latency

Extraction

Time windows around peaks of interest (Adults: N1 and MMN; Children: P1, eMMN, IMMN/LDN) were determined by visually inspecting the averaged waveforms of each individual subject within a subject group for a particular block type (i.e. Adults, Ignore 300 ms ISI). Obligatory auditory components (Adults: N1; Children: P1) were identified in the Standard and Deviant waves, while MMN components were identified in the Difference wave and verified by inspecting the Standard and Deviant waves using the criteria described above for MMN identification (latency, polarity and topography). The peak latency of each component of interest was determined using BESA 5.1.8, and a range was determined for each block type that was just wide enough to capture the peaks of all participants, while sufficiently narrow to exclude other peaks that were not the peak of interest. If a participant did not have a clear component (i.e. missing MMN), this was noted and that data was excluded from all subsequent relevant analyses.

3.3.2 Selection of Electrodes for Peak Amplitude and Latency Extraction

Fourteen channels were selected from the 64-channel EGI sensor net based on topography (see Table 3.3.2 and Figure 3.3.2) for extraction of peak amplitude and latency values (Jurak et al., 2007). The frontal and central channels were of greatest interest for the MMN components (highest amplitudes expected in these areas), and the parietal and occipital channels were chosen to verify that MMN activity was not observed in these regions. Temporal channels were important for detecting inversion of polarity of

the MMN. The N1 (for adults) and P1 (for children) are also typically identified in frontal and central regions.

The frontocentral channel selection was further informed by correlational analyses that were performed for a different study within the laboratory that utilized the same EGI sensor net (Choudhury & Benasich, in preparation). Clusters of highly correlated electrodes were identified in frontal and central regions. The channels selected here reflect single electrodes from distinct clusters, thus significant correlations between channels were not expected to confound statistical analyses in frontocentral regions.

Using the determined time windows described above, peak latency (in milliseconds) and amplitude (in microvolts) values were extracted from individual averages using BESA 5.1.8. The resulting data files were reformatted and imported into SPSS for statistical analyses.

3.4 Within Group Statistical Analyses

3.4.1 Analyses of Rate (comparisons of 300, 70 and 10 ms ISIs)

Paired samples t-tests were planned to compare peak amplitude and latency²¹ measures between the different ISIs within each condition (Ignore or Attend) and within each participant group (Adult, TLD, LI) at all channels of interest described above (in section 3.3.2: Selection of Electrodes for Peak Amplitude and Latency Extraction). T-tests were used because approximately half of the participants in each group received the 70 and 300 ms ISI blocks (Group 1), and the other half received the 70 and 10 ms ISI blocks (Group 2). The experimental protocol was designed this way in order to shorten

²¹ All latencies for statistical analyses are relative to the onset of the second (deviant) tone in the pair, and so latencies can be compared between the different ISIs. These relative latencies were calculated by subtracting the duration of the first tone (70 ms) plus the ISI (300, 70 or 10 ms) from the absolute latency.

the ERP recording session to a tolerable duration for the children. The two groups (Group 1 = 70/300 ms ISIs vs. Group 2 = 70/10 ms ISIs) were then compared with Independent Samples t-tests on the 70 ms ISI blocks. If no significant differences were revealed, then Independent Samples t-tests were run to examine differences between the 300 ms ISI (Group 1) and 10 ms ISI (Group 2).

Given the large number of planned t-tests, a criterion was formulated for interpreting the results. For the MMN components, frontal and central channels will be examined in the deviant and difference waves²². Temporal, parietal and occipital channels will also be investigated to improve confidence in the data and insure that the MMN is observed in the predicted frontocentral regions. T-tests yielding an alpha value of $\leq .05$ in two or more adjacent or complimentary (i.e. same topographic location in the right and left hemispheres) frontal or central channels will be taken as a significant finding and included in the results sections that follow. T-tests with an alpha value of $\leq .05$ occurring in isolation will not be included in the results.

Bonferroni corrections, in which the significance level of a statistical test is adjusted in order to protect against Type I errors when multiple comparisons are being made²³, will not be applied to these analyses, or any of the analyses consisting of multiple t-tests in the series of studies described here for the following reasons. First, each series

²² Standard waves are not examined in these MMN analyses since the standard waves exhibit very different morphologies at different ISIs. For example, in Adults in the 300 and 70 ms ISI, an N1 to the second tone was observed in the standard waves at the MMN latency range, but in the 10 ms ISI there was baseline activity in the MMN time window. Thus, comparisons of the standard waves elicited with different rates of presentation are not informative since they do not represent similar processes underlying the MMN.

²³ A Type 1 error is rejecting the null hypothesis when it is true. A Type II error is an error of failing to reject the null hypothesis when it is false. There are two main types of Bonferroni procedures. The first is the standard procedure, where if 10 t tests are performed on a set of data, the Bonferroni-corrected significance level of $0.05/10 = 0.005$ is used instead of the standard 0.05. The second is the sequential Bonferroni procedure (Holm, 1979).

of planned t-tests are based on a single *a priori* hypothesis rather than a statistical “fishing expedition” where multiple hypotheses are being tested using the same set of data. Secondly, Bonferroni corrections reduce Type I errors, but consequently increase the risk of Type II errors. Given the small sample sizes in the present set of experiments, the statistical power available to detect a medium or even large effect is relatively low. A Bonferroni procedure would further lower statistical power to unacceptable levels (Nakagawa, 2004). Third, in the present experiments, isolated or spurious findings resulting from Type I errors should not impact the interpretation of results given the criterion established to look for patterns of related results rather than isolated findings. It would likely be more detrimental to increase the risk of Type II errors in the present data analyses by employing a Bonferroni correction procedure (Jennions and Moller, 2003). Finally, there are no standard guidelines for when a Bonferroni procedure should be used (Perneger, 1998), and thus it is at the discretion of the researcher whether or not to employ this type of correction. Indeed, the decision to utilize a Bonferroni correction in the case of multiple comparisons remains controversial (e.g. Nakagawa, 2004; Moran, 2003; Perneger, 1998). Here, based on the reasons given, a Bonferroni procedure will not be applied to statistical analyses consisting of multiple t-tests.

Finally, for all Independent samples t-tests (in all comparisons), Levene’s Test for Equality of Variances will be conducted. If the variances are found to be unequal, the t-statistic reflecting that equal variances are not assumed will be reported and noted. Otherwise, unnoted t-statistics reported will reflect that equal variances are assumed (i.e. Levene’s Test for Equality of Variances was not significant).

3.4.2 Analyses of Condition (comparison of Ignore vs. Attend)

Paired samples t-tests were planned to compare peak amplitude and latency measures between the Ignore and Attend conditions within each ISI, participant group (Adult, TLD, LI) and visit (1 or 2) for each channel of interest. T-tests were used to conserve as much data as possible, because more children completed the 70 ms ISI Ignore and Attend blocks as compared to the 300 and 10 ms ISI blocks²⁴. The same criterion for t-test interpretation described above will be observed for these analyses as well.

3.5 Between Group Statistical Analyses

For Experiment 3 (Adults and TLD children), and Experiments 4 and 5 (TLD and LI children), independent samples t-tests were planned to compare peak amplitude and latency measures within each Condition (Ignore, Attend) and within each Rate of presentation (300, 70, 10 ms ISI) for each channel of interest. The same criterion for t-test interpretation described above will also be observed for these analyses.

3.5.1 Hemispheric Comparisons

As part of the between-groups analyses, an additional question that will be addressed within Experiments 3 and 5 is whether the MMN response (peak amplitude and latency) differs between the left and right hemispheres. In Experiment 3, a series of 2 x 2 mixed factors ANOVAs will be conducted to explore this question. Group (Adult, TLD) x Hemisphere (Left, Right) ANOVAs will be conducted for three pairs of channels: Frontocentral (Channels 17 and 54), Frontal (Ch. 13 and 62), and Central (Ch. 21 and

²⁴ The 300 or 10 ms ISI Attend block was the last block type administered in the ERP recording session, and a number of children were too fatigued or restless to complete this final block.

53). In Experiment 5, a series of 2 x 2 x 2 mixed factors ANOVAs will be conducted. Group (TLD, LI) x Hemisphere (Left, Right) x Visit (1, 2) ANOVAs will be conducted for three pairs of channels: Frontocentral (Channels 17 and 54), Frontal (Ch. 13 and 62), and Central (Ch. 21 and 53). Significant findings will be followed up by examination of simple effects: within-group paired-samples t-tests comparing left vs. right hemisphere MMN peak amplitude or latency for the aforementioned pairs of channels.

Given that multiple t-tests are planned for these hemispheric analyses, a criterion for interpreting multiple t-tests similar to that described above will also be applied here. T-tests yielding an alpha value of $\leq .05$ in two or more *pairs* of channels (frontocentral, frontal or central) will be taken as a significant finding and reported in the results sections. A t-test with an alpha value of $\leq .05$ that occurs in a single pair of channels will not be included in the results. For the same reasons discussed above, Bonferroni corrections will not be applied to these t-tests.

3.6 Analytic Strategies for Statistical Analyses of Behavioral Measures

3.6.1 Comparison of TLD and LI groups on Language and Reading Measures at Visit 1 and Visit 2

To examine potential differences in language and reading scores from Visit 1 to Visit 2 in both the TLD and LI children, a series of 2 (Group) x 2 (Visit) ANOVAs were performed with outcome variables CELF-4 Core Language Standard Score (Core), CELF-4 Receptive Language Standard Score (Receptive), CELF-4 Expressive Language Standard Score (Expressive), WRMT Word Identification Standard Score (Word ID), WRMT Word Attack Standard Score (Word Attack), and WRMT Passage

Comprehension Standard Score (Passage Comprehension). If the assumption of sphericity was violated for any variable, Greenhouse-Geisser corrected F values are reported. In the case of a main effect of Group and/or Visit without a significant Group x Visit interaction, paired samples t-tests were planned to further investigate the changes in language and reading abilities from Visit 1 to Visit 2 in the TLD and the LI groups.

3.6.2 Investigating LI subtypes: Receptive, Expressive and Mixed

The homogeneity and varying degrees of symptoms in children diagnosed with a language impairment are often concerns in both the clinical and research communities. Children classified as LI may exhibit different patterns of receptive and/or expressive language difficulties. The DSM-IV-TR (2000) recognizes several subtypes of communication disorders, including Expressive Language Disorder (315.31), Mixed Receptive-Expressive Language Disorder (315.32), and Phonological Disorder (315.39). To date, there are no studies known to us that compare subtypes of LI in an experimental paradigm combining ERP and behavioral measures. However, one group recently investigated hemispheric specialization of language in different subgroups of LI using a dichotic listening paradigm (Pecini et al., 2005). Pecini and colleagues found that children with Expressive and Phonological subtypes of SLI showed reduced left hemispheric specialization for language, this was not the case for children with Mixed Receptive-Expressive SLI. The Mixed Receptive-Expressive group also performed more poorly on a task assessing working memory. Aside from this study, there are very few investigations that specifically address LI subtypes (Crespo-Eguilaz & Narbona, 2006; Craig & Evans, 1989). Therefore, we aimed to classify LI children in the present study by

subtype in order to better understand the different patterns of behavior and neural processing in LI children. Here, we first classify children according to LI subgroup and then compare behavioral performance between subtypes to see if the groups differ on language and reading measures at Visit 1 and Visit 2.

The CELF-4 provides a standardized method for determining significant differences between receptive and expressive language performance (Semel, Wiig & Secord, 2003, pp. 112 - 118). This procedure was carried out for all LI participants to determine if their language impairment was generalized (Mixed; no significant difference between receptive and expressive language performance) or if the deficit was primarily Receptive (Receptive < Expressive) or Expressive (Expressive < Receptive). LI children were classified according to these three subgroups.

Given sufficient statistical power (i.e. adequate number subjects in each subgroup), a series of 3 (LI subtype: Mixed, Receptive, Expressive) x 2 (Visit 1, 2) ANOVAs were planned to examine potential differences in language and reading performance before and after FFWD using CELF-4 (Core, Expressive and Receptive Standard Scores) and WRMT (Word ID, Word Attack and Passage Comprehension Standard Scores) measures. It was predicted that LI children with a Receptive and Mixed subtypes would benefit maximally from FFWD since this intervention is aimed specifically at improving auditory processing skills that underlie oral language processing (e.g. working memory, phonemic decoding, rapid processing) and does not directly target expressive language skills (e.g. vocabulary, word retrieval, grammar, syntax). It was expected that gains would be made in Expressive language given that receptive and expressive language abilities are closely linked, but more substantial improvements were

expected for Receptive language skills. If there are no significant differences in language and reading measures between the three LI subgroups at either Visit 1 or Visit 2, the subgroups will be combined for all further analyses.

3.7 Analytic Strategies for Statistical Analyses of the Auditory Repetition Test

(ART)

3.7.1 Statistical Analyses of the Auditory Repetition Test – Adult Version (ART-A)

In the adult version of the Auditory Repetition Test (ART-A), participants were tested with 2- and 3- tone sequences with 5 different ISIs (500, 300, 70, 40, 10 ms). A block of “slow” trials were presented with a fixed ISI of 500 ms (8 trials), and “fast” blocks were presented with the remaining ISIs (300, 70, 40, 10 ms) in a random order (32 trials). This was done first for 2-tone sequences, followed by 3-tone sequences. There were the same number of “slow” and “fast” trials in both the 2- and 3- tone sequences blocks (8 and 32 trials, respectively). Participants’ responses were manually recorded during testing, and later the Percent of correct trials was calculated **for each ISI** as a measure of performance for statistical analysis ($[\text{number of correct trials at ISI} / \text{number of trials presented at ISI}] * 100$).

Initial descriptive statistics were generated for the Percent of correct trials at each ISI for 2- and 3-tone sequences, and then paired samples t-tests were performed to compare performance (percent of correct trials) between 2- and 3-tone sequences at each ISI (e.g. Percent of correct trials at 500 ms ISI for 2-tone sequences vs. Percent of correct trials at 500 ms ISI for 3-tone sequences). Variables from paired samples t-test with $p \leq$

.05 were entered into a repeated measures ISI x Tone Sequence Length (TSL) (2 or 3-tone sequences) ANOVA to investigate interactions between ISI and length of the tone sequences. For any variables that violate Mauchly's Test of Sphericity, Greenhouse-Geisser corrected F values will be reported.

3.7.2 Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

In the child version of the Auditory Repetition Test (ART-C), participants were tested with 2- and 3- tone sequences with 4 different ISIs (500, 150, 70, 10 ms). For **2-tone sequences**, a block of “slow” trials (12 trials) were presented with a fixed ISI of 500 ms, followed by a “fast” block in which trials with all ISIs (500, 150, 70, 10 ms) were presented in a random order (32 trials). Next, for **3-tone sequences**, a block of “slow” trials (10 trials) were presented with a fixed ISI of 500 ms, followed by a “fast” block in which trials with ISIs of 150, 70, and 10 ms were presented in a random order (10 trials).

For **2-tone sequences**, the Percent of Correct Trials at each ISI was calculated as a measure of performance for statistical analysis ([number of correct trials at ISI / number of trials presented at ISI] * 100). For **3-tone sequences**, the Percent of Correct Trials was calculated for the *entire block* of trials 3-Slow and 3-Fast since there were only 10 trials in each block, and thus there were not enough trials at each “fast” ISI to generate a separate and reliable statistical variable. Within and between group comparisons were then carried out and these are described below.

3.7.3 Between group Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

To compare performance on the ART-C between TLD and LI children, first a Pearson Chi-Square test was conducted to see if children from the two groups were able to learn the ART-C (achieve criterion following one full training phase) at the same rates at Visit 1 and Visit 2. Children who achieved criterion (70 % correct for Association, and 60% correct for Sequencing phases of the ART-C) during a single administration of the training phases (Association and Sequencing) were classified as “1-Training”, and children who required a second training (repetition of Association and/or Sequencing) were classified as “2-Training”. The Number of Training Trials (NTT) (total number of trials administered during Association and Sequencing²⁵) was compared between the TLD and LI groups at Visit 1 and Visit 2 with independent samples t-tests. During the training phase of the ART-C, when a participant makes a mistake, the examiner re-presents the trial (a maximum of 3 times) until the child responds correctly, and if a child does not reach criterion on Association and/or Sequencing, the entire training phase is repeated. Analysis of the NTT required by the TLD and LI participants may provide further information about group differences that may not be captured in the analysis of the ART-C testing phases alone.

For children who passed criterion and completed the testing phases of the ART-C (blocks 2-Fast, 3-Slow, 3-Fast), descriptive statistics were generated by Group (TLD or LI) for the Percent of Correct Trials at each ISI for 2-tone sequences (500, 150, 70, 10

²⁵ Detection was not included in the NTT calculation since this is a familiarization phase (5 presentations of each tone) that was presented only once for all children, except LI participant 09056. The Association phase requires discrimination between the tones, and the Sequencing phase requires memory for the order of the tones. Acquisition of these discrimination and sequencing skills are necessary for successful training and were therefore combined to create the NTT variable.

ms), and for 3-Slow and 3-Fast at Visit 1 and Visit 2. Independent samples t-tests were conducted to compare the Percent of Correct Trials between groups for each 2-tone sequence ISI, and 3-Slow and 3-Fast at Visit 1 and Visit 2. For **2-tone sequences**, variables that significantly differ ($p \leq .05$) in the independent samples t-tests at either Visit will be entered into a Group (TLD, LI) x ISI x Visit (1, 2) Mixed Factors ANOVA to investigate interactions between Group and rate of presentation from Visit 1 to Visit 2. For **3-tone sequences**, variables that significantly differ in the independent samples t-tests at either Visit will be entered into a Group (TLD, LI) x Rate (Slow, Fast) x Visit (1, 2) Mixed Factors ANOVA to investigate interactions between Group and rate of presentation from Visit 1 to Visit 2. For any variables that violate Mauchly's Test of Sphericity, Greenhouse-Geisser corrected F values will be reported.

3.7.4 Within group Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

Within each group, the effect of repeated testing and, in the case of the LI group only, the Fast ForWord-Language intervention, were examined by comparing performance on the ART-C at Visit 1 vs. Visit 2. First, the Number of Training Trials (NTT) (total number of trials administered during Association and Sequencing) was compared between Visit 1 and Visit 2 within each group using paired samples t-tests. Second, paired samples t-tests were conducted to compare the Percent of Correct Trials at each ISI for 2-tone sequences, and 3-Slow and 3-Fast at Visit 1 vs. Visit 2 for the TLD and LI groups. For **2-tone sequences**, variables that significantly differ ($p \leq .05$) in the paired samples t-tests for either or both groups will be entered into a Group (TLD, LI) x

ISI x Visit (1, 2) Mixed Factors ANOVA to investigate ART-C performance between groups and rates of presentation from Visit 1 to Visit 2. For **3-tone sequences**, variables that significantly differ ($p \leq .05$) in the paired samples t-tests for either or both groups will be entered into a Group (TLD, LI) x Rate (Slow, Fast) x Visit (1, 2) Mixed Factors ANOVA.

4.0 Preliminary Analyses

4.1 Participants

4.1.1 Participant Information

Descriptions of the groups of participants included in each experiment are shown in Table 4.1.1.

4.1.2 Adult Participant Information (Experiments 1 and 3)

Twenty-nine healthy adults (13 male) participated in Experiments 1 and 3. Four participants were excluded from analyses due to reported hearing loss ($n = 3$) or use of medication ($n = 1$) that came to light after experimental testing was completed. The final sample included 25 (12 male) adults between ages 18 and 51 years (mean = 27 years, $SD = 9.0$ years). Twenty-three participants were right-handed and two were left-handed (both female). Participants had no reported hearing, language, or neurological problems, and were paid \$15 for participating. Please see Table 4.1.2 for demographic information for individual adult subjects.

4.1.3 Children with Typical Language Development (TLD) (Experiments 2, 3, 4, 5)

In the final Typical Language Development (TLD) sample there were 18 children (9 male, 17 right-handed). Of these 18 children, 12 (6 male, 12 right handed) returned to the lab to participate in Experiment 5 by completing another behavioral and ERP session.

TLD children did not participate in any intervention program during the pre- (Experiment 4) to post- (Experiment 5) testing interval. In a previous study it was found that typically developing children who participated in FFWD did not show any significant improvements in language performance when compared to a group of

typically developing children who did not participate in FFWD (Stevens, Sanders et al. 2006). In this present experiment, control children received standardized “post-testing” so that test-retest and short-term developmental changes (not due to intervention training) could be ascertained. Control participants returned to the lab after a mean of 92 days (SD = 37, range 43 to 163 days) for the behavioral session and 95 days (SD = 53, range 41 to 222) for the ERP session. Please see Table 4.1.3 for individual participants’ pre and post testing intervals.

4.1.4 Children with a Language Impairment (LI) (Experiments 4, 5)

Fifty-one children with language difficulties were referred to the study from speech and language clinicians in New Jersey and New York, and were assessed with the behavioral battery described in General Methods (CELF-4, WRMT Word ID, Word Attack and Passage Comprehension, and WASI Performance subtests), and 30 of these children met the LI criteria for this experiment. One eligible LI child withdrew from the study, and thus there were 29 children in the final sample of Experiment 4, (20 male; 25 right handed, 2 left handed, 2 ambidextrous). The 29 LI children who participated in Experiment 4 were invited to participate in Experiment 5 in which LI children completed the Fast ForWord-Language-Language® (FFWD) intervention program and then return to the lab for post-intervention testing. Eight children withdrew from the study: 3 children were unable to complete FFWD in a timely manner and discontinued the program, 4 decided not to participate due to time or financial constraints, and 1 could not be reached for post-testing. The final sample consisted of 21 children (15 male; 18 right handed, 2 left handed, 1 ambidextrous) ages 6.5 to 10.1 years (mean 8.4 years, SD 0.95). These children completed FFWD under the guidance of a certified provider who was a licensed

speech and language pathologist. The FFWD program was administered at the provider's office or in the child's home. After finishing FFWD, these 21 children returned to the lab for post-intervention behavioral and ERP sessions. The FFWD completion report of each child was requested from the FFWD provider and was received in all cases except one (09040). LI children completed FFWD in an average of 32 days ($SD = 11$, range 13 to 56 days), and returned to the lab for the two post-training assessments after a mean of 116 days ($SD = 45$, range 57 to 202 days) for the behavioral session and 102 days ($SD = 42$, range 46 to 193) for the ERP session. The intervals for individual participants are provided in Table 4.1.3.

Two LI children received a slightly different intervention protocol than the other LI children. While 19 LI children received the FFWD-Language program only, Subject 09052 received FFWD-Language to Reading for 23 days, and Subject 09064 received FFWD-Language for 14 days followed by FFWD-Language to Reading for 42 days. The decision to implement FFWD Language to Reading was made by the children's FFWD provider and their parents, and this decision was made known to the experimenter at the first post-FFWD session. FFWD Language to Reading is the program recommended for older children and children who have completed FFWD- Language. This program focuses on sound-letter comprehension, phonological awareness, beginning word recognition and language conventions (for English) using the same adaptive training principles (modified speech, adaptive progress through multiple levels within each exercise) and intervention schedule described above for FFWD-Language (in Methods: Auditory Training procedure – Fast ForWord-Language®). Given that FFWD-Language and FFWD-Language to Reading both target auditory, visual and linguistic processing

and aim to improve sequencing skills using the same training methods, subjects 09052 and 09064 were retained in Experiment 5. Their data, however, was first examined separately to insure that their data consistent with the rest of the sample. Both ERP morphology and behavioral data patterns were inspected.

One LI subject (09012) completed FFWD and the post-FFWD sessions but was excluded from all Visit 2 analyses due to extremely poor state (uncooperative, unresponsive, restless, and seeking to end the sessions) during both the post-FFWD behavioral and ERP sessions.

4.2 Verification of TLD and LI Participant status

Independent samples t-tests were conducted to test whether the groups differed significantly on language and reading measures. As expected, there were significant group differences in all language (CELF-4) and reading (Woodcock Reading Mastery Tests) variables, with LI children having lower scores. Further, there was a significant group difference in non-verbal cognitive ability (WASI Performance IQ) with the TLD group having higher WASI PIQ scores as compared to the LI group [$t(45) = 2.46, p < .05$] though both were within the normal range. These findings are summarized in Table 4.2a.

Paired samples t-tests were run within each group to identify potential discrepancies between language (CELF-4 Core, Receptive, and Expressive Language standard scores) and non-verbal cognitive ability (WASI PIQ), a diagnostic feature of LI (DSM-IV-TR, 2000; Bishop, 1997). Both the CELF and WASI yield standard scores on the same scale (mean of 100, SD 15) and so standard scores could be directly compared. As expected, for the TLD children, there were no significant differences between WASI

PIQ and CELF-4 Core Language [$t(17) = 0.29$, ns], CELF-4 Receptive Language [$t(17) = 0.46$, ns], or CELF-4 Expressive Language [$t(17) = 0.31$, ns]. However, as expected there were significant differences in the LI group between WASI PIQ and all CELF-4 measures: CELF-4 Core [$t(28) = -6.34$, $p < .001$], CELF-4 Receptive [$t(28) = -4.91$, $p < .001$], and CELF-4 Expressive [$t(28) = -5.70$, $p < .001$]. Thus, LI children had lower language scores than would be expected given their non-verbal cognitive ability (all within the normal range), and satisfied the clinical diagnostic criteria of language and non-verbal incongruity described in the DSM-IV (2000). These results are summarized in Table 4.2b.

4.3 Verification of Demographic Comparability in TLD and LI Participants

Demographic variables were subjected to independent samples t-tests to investigate whether or not the TLD and LI groups significantly differed on any demographic measures. As controls were selected to match the demographic parameters of the LI experimental group, there were no significant group differences in Birthweight, Gestational Age, SES (Hollingshead Index), years of Maternal Education, or Maternal Age. These findings are summarized in Table 4.3a. Also, as expected, there were no significant group differences in Age at Test (Visit 1 and Visit 2), and number of days between visits (for both Behavioral and ERP sessions). These findings are summarized in Table 4.3b.

4.4 Event Related Potentials Preliminary Analyses

4.4.1 Visual Inspection of Grand Averaged Waveforms and Identification of Obligatory Auditory ERP Components

The grand averaged waveforms for each group at each condition at each visit were visually inspected to verify the presence of the expected obligatory auditory components: the N1 in adults only, and the P1 and N2 in children only. Table 4.4.1 shows the number of participants in each grand average after all off-line ERP processing (i.e. artifact rejection, etc). Individuals with less than 50 artifact-free trials in a block type were not averaged. The obligatory components of interest were identified in all grand averaged waveforms, verifying that the data were following a predictable pattern.

4.4.2 Identification of the Mismatch Negativity – (Experiments 1, 2, 3, 4, 5):

In all groups at all conditions, the grand averaged waveforms were visually inspected to look for the presence of an MMN response(s). Following the onset of the deviant tone, the standard and deviant waves were inspected for differences in amplitude and morphology in frontocentral channels in expected MMN latency ranges (adult MMN: 100 – 200 ms; child early MMN: c.a. 100 – 300 ms; child late MMN/LDN: c.a. 400 – 600 ms). The topographic distribution of maximal amplitudes in the deviant waves were inspected to look for higher amplitudes in frontocentral and central channels, the expected MMN topography. The difference wave was also inspected for a negative peak(s) in the MMN latency ranges. Another hallmark of the MMN was also examined: relative inversion of polarity of the MMN at mastoid channels in both the deviant and difference waves. MMN components were identified in the grand averaged waveforms of Adults for all conditions (described in detail in Results of Experiment 1). In the grand averaged waveforms of the children (TLD and LI), an emerging adult-like MMN

component was identified in the difference waves, and early and late MMN components were also identified at later latencies. These are described in detail in the following sections (4.4.3 Event Related Potentials - Age Subgroups).

4.4.3 Event Related Potentials – Age Subgroups

Maturational changes in auditory evoked ERPs have been the subject of a growing literature within the developmental ERP field (e.g. Sussman, et al., 2008; Ceponiene, Rinne, Näätänen, 2002; Morr, et al., 2002; Shafer et al., 2000). Concern has been noted regarding the use of participant groups that span several years in young children due to significant maturational changes occurring in many brain regions throughout childhood and extending well into adolescence, including myelination of axons, changes in synaptic density, and volumetric changes in auditory cortex (Moore & Guan, 2004; Eggermont, 1985; 1988). Averaging ERPs across a wide age-range may obscure significant maturational differences in components. For these reasons, a constrained age range was used in the current studies (6 to 9 years). However, here we examine even more narrowly defined age ranges within the TLD and LI groups to investigate potential differences in morphology in the standard, deviant and difference grand averaged waveforms.

The TLD and LI groups were each split into two age subgroups based on age at Visit 1: “6 – 7 year olds” and “8 – 9 year olds”. Detailed information about participants ages are shown below in Tables 4.4.3a and b. In the **TLD 6 – 7 year old** group ($n = 7$) the age range was 6.38 years to 7.44 years, with a mean of 6.94 years (standard deviation 0.36 yrs), and in the **TLD 8 – 9 year old** group ($n = 10$) the age range was 7.97 to 9.47 years with a mean of 8.71 years (standard deviation 0.5 yrs). In the **LI 6 – 7 year old**

group (n = 11) the age range was 6.23 years to 7.45 years, with a mean of 7.00 years (standard deviation 0.37 yrs), and in the **LI 8 – 9 year old** group (n = 17) the age range was 7.96 to 9.91 years with a mean of 8.74 years (standard deviation 0.69 yrs).

Individual participants' averaged ERP waveforms were grand averaged for the TLD and LI age groups for the Ignore condition 70 ms ISI at Visit 1 only. This one block was chosen because every child completed this block and thus it provided the largest amount of data for these analyses. Only Visit 1 was examined because maturational differences at Visit 2 could be confounded by additional factors of previous exposure to the stimuli and, in the case of LI children, the Fast ForWord-Language intervention program. All subjects at Visit 1 were naïve and the obtained ERPs reflect neural responses to their first experience with the stimuli, allowing for the best assessment of potential fine-grained maturational differences. Below the morphology of the standard, deviant and difference waves are described for the TLD and LI age groups. Following these descriptions, differences between age groups within each group are discussed. Group and visit related differences will be analyzed and discussed elsewhere.

4.4.3.1 Ignore 70 ms ISI: TLD children ERP waveform morphology:

As in all preceding waveform descriptions, here the descriptions of the major components are based on electrode Fcz (Channel 4) after verifying that activity at Fcz was similar to surrounding channels. Figure 4.4.3.1 shows the grand averaged standard, deviant and difference waves for the two TLD age groups.

TLD 6 – 7 year olds: The first peak in the standard wave is a positivity (2.06 uV) at 100 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-2.4 uV) at 260 ms. This is the child N2. The next identifiable peak in the standard waveform is a negativity at 432 ms (-0.9 uV), followed by a positivity at 580 ms (1.0 uV). There are no additional identifiable peaks in the standard wave.

In the deviant wave, there is a robust P1 (1.4 uV) at 108 ms followed by the N2 that peaks 260 ms (-1.4 uV). After the N2 there is another negative peak of almost equal amplitude at 364 ms (-1.3 uV), and the last identifiable peak in the wave is a broader negativity at 564 ms (-0.4 uV).

In the difference wave, there is a negative peak (-1.0 uV) at 368 ms that corresponds to the previously described early MMN (eMMN) in children. After the eMMN there was another negative peak (-1.4 uV) at 576 ms corresponding to the late MMN described in children. These early and late MMN components invert at the mastoids and are maximal at frontocentral channels.

TLD 8 – 9 year olds: The first peak in the standard wave is a large positivity (2.1 uV) at 92 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-2.8 uV) at 252 ms. This is the child N2. There is a negative-going “notch” in the standard wave at 410 ms, followed by a broad positivity before returning to baseline. There are no additional identifiable peaks in the standard wave.

In the deviant wave, there is a robust P1 (2.0 uV) at 96 ms followed by the N2 that peaks 264 ms (-2.6 uV). After the N2 there is another negative peak that is smaller in amplitude at 404 ms (-1.3 uV). The last identifiable peak in the wave is a negativity at 616 ms (-0.4 uV).

In the difference wave, the first identifiable peak is a negative-going peak that barely crosses the baseline at the latency of the N2 (268 ms, 0.1 uV). This is identified as the emerging adult-like MMN since it occurs close to the adult MMN latency. Next there is a negative peak (-1.0 uV) at 416 ms that corresponds to the previously described early MMN (eMMN) in children. After the eMMN, there was another negative peak (-1.0 uV) at 624 ms corresponding to the late MMN (lMMN, or LDN) described in children. These early and late MMN components invert at the mastoids and are maximal at frontocentral channels.

Comparison between TLD 6 – 7 year olds and 8 – 9 year olds: Overall, the two TLD age groups have waveforms with similar morphology, namely the same number of peaks appearing at similar latency ranges in the standard and deviant waves. There are some small differences in latency and amplitude. In the 6 – 7 year olds, the P1 has slightly longer latency in both the standard and deviant waves, and the N2 has slightly longer latency in standard wave, and smaller amplitude in deviant wave. Due to the larger amplitude of the N2 in the deviant wave of 8 – 9 year old children, the emerging adult-like MMN is more robust for this group.

In sum, the overall morphologies of the grand averaged waveforms are similar for the 6 – 7 year old and 8 – 9 year old TLD children. Latencies of the major peaks (P1 and N2) are generally shorter in the 8 – 9 year olds as compared to the 6 – 7 year olds by up to 8 to 12 ms (although the N2 latency in the deviant wave is longer for 8 – 9 year olds as compared to 6 – 7 year olds). Reduced latencies are a feature of maturational changes in ERPs (Sussman et al., 2008), however here the latency differences were not systematic (from child to child) nor that robust. Thus, given the similarity of the waveform

morphologies and the small differences in P1 and N2 latencies across age groups, it was concluded that Age would not be a factor in subsequent analyses. All TLD children were analyzed as a single group.

4.4.3.2 Ignore 70 ms ISI: LI children ERP waveform morphology:

As in all preceding waveform descriptions, here the descriptions of the major components are based on electrode Fcz (Channel 4) after verifying that activity at Fcz was relatively similar to surrounding channels. Figure 4.4.3.2 shows the grand averaged standard, deviant and difference waves for the two LI age groups.

LI 6 – 7 year olds: The first peak in the standard wave is a positivity (2.5 uV) at 100 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-2.4 uV) at 244 ms. This is the child N2. The next identifiable peak in the standard waveform is a positivity at 588 ms (-1.0 uV), followed by two smaller negative-going peaks at 680 and 820 ms (-0.1 uV and -.01 uV, respectively).

In the deviant wave, there is a robust P1 (2.5 uV) at 100 ms followed by the N2. In frontocentral channels the N2 appears to consist of three peaks. At Fcz, the first peak is a negative going “notch” at 208 ms, and this first “peak” of the N2 is larger in right as compared to left frontocentral channels. The “notch” is followed by a large negative peak at 276 ms (-1.8 uV), that is then followed by a smaller third peak at 380 ms (-0.9 uV). The final identifiable peak in the deviant wave was a negativity at 604 ms (-0.4 uV).

In the difference wave, the first component of interest is a negative-going peak that corresponds in latency to the emerging adult-like MMN (288 ms), though this peak does not cross the baseline and is therefore not in the negative range (0.2 uV). The next

component is a negative peak (-0.6 uV) at 384 ms that corresponds to the previously described early MMN (eMMN) in children. After the eMMN there is a larger negative peak (-1.3 uV) at 592 ms corresponding to the late MMN (IMMN/LDN) described in children. These early and late MMN components invert at the mastoids and are maximal at frontocentral channels.

LI 8 – 9 year olds: The first peak in the standard wave is a large positivity (2.1 uV) at 92 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-3.2 uV) at 252 ms. This is the child N2. There are no additional identifiable peaks in the standard wave.

In the deviant wave, there is a robust P1 (2.2 uV) at 100 ms followed by the N2 that peaks 264 ms (-2.7 uV). After the N2 there is another negative peak that is smaller in amplitude at 404 ms (-1.0 uV). The last identifiable peak in the wave is a negativity at 552 ms (-0.4 uV).

In the difference wave, the first identifiable peak is a negative-going peak that is in the positive domain (below the baseline) close to the latency of the N2 (272 ms, 0.4 uV). This is identified as the emerging adult-like MMN since it occurs close to the adult MMN latency. Next there is a negative peak (-1.2 uV) at 404 ms that corresponds to the previously described early MMN (eMMN) in children. After the eMMN, there was another negativity corresponding to the late MMN (IMMN, or LDN) described in children. The IMMN at Fcz had two distinct peaks. The first was the larger peak at 544 ms (-1.1 uV), and the second smaller peak occurred at 612 ms (-0.9 uV). Examination of the difference waves at all channels in their topographic arrangement revealed that at *right* frontal and frontocentral channels, there are two peaks identified within the

IMMN/LDN, and at *left* frontal and frontocentral channels there is only one broader peak. These early and late MMN components invert at the mastoids and are maximal at frontocentral channels.

Comparison between LI 6 – 7 year olds and 8 – 9 year olds: Overall, the two LI Visit 1 age subgroups have waveforms with similar morphologies, namely the same number of peaks appearing at similar latency ranges in the standard and deviant waves. There are some small differences in latency and amplitude, and minor differences in the morphology in the deviant waves (peak shape, presence or absence of a “notch” or multiple peaks). In the 6 – 7 year olds, the P1 has a slightly longer latency in the standard wave, and the amplitude of the N2 is smaller in the deviant wave. The latency of the N2 in the deviant wave is shorter in the 8 – 9 year old children as compared to the 6 – 7 year olds. Additionally, the 6 – 7 year old grand averaged deviant wave has a “notch” as it rises to the N2 peak. Individual averaged waveforms were inspected and it was found that in the 6 – 7 year old group, 6 out of 11 children (55%) had a “notch” on the negative going part of the N2 component or multiple peaks within the N2. In the 8 – 9 year old children it was found that 10 out of 17 children (59%) also had this pattern. Additionally, in the 6 – 7 year olds the IMMN (in the difference wave) appears as a single peak, while in the 8 – 9 year olds the IMMN consists of two peaks. Again, individual averages were examined and it was found that 6 of 11 children in the 6 – 7 year old group had multiple IMMN peaks, so although the grand average appeared as a single peak, the pattern of multiple peaks was well distributed across younger children. Thus, it was concluded that although the grand averaged waveforms appear different for the two age groups, the patterns of multiple peaks in the N2 (or presence of an N2 “notch”) and IMMN are

distributed nearly equally across the 6 – 7 and 8 – 9 year olds. There appeared to be no significant, systematic maturational differences between the 6 – 7 year old and 8 – 9 year old LI groups, so it was determined that Age would not be a factor in subsequent analyses. All LI children were analyzed within a single group.

4.4.3.4 Summary of Age Subgroups Comparisons

In both the TLD and LI age groups, some indication of normal maturational changes were found after examination of the grand averaged waveforms. These were mainly reflected in shorter latencies in the older children as compared to the younger children (maximum of 8 – 12 ms differences), but these differences were not universal (applying to both the P1 and N2) nor that robust. Overall, the similarities between the age groups were greater than any detected differences, and so it was decided that Age would not be a factor in subsequent statistical or descriptive analyses. Thus the TLD and LI children were analyzed as single groups.

4.4 Determination of Time Windows for Peak Amplitude and Latency Extraction

Time windows were determined by visually inspecting the averaged waveforms of each participant within each group (adult, TLD, LI) to determine a range that would be wide enough to capture the component of interest for all participants, but sufficiently narrow to exclude other components (See Table 4.4a and b – Time Windows). This was done for each block type (Condition + ISI). If a subject did not have a clearly identifiable component, this was noted and that data was excluded from the relevant analyses.

The time window for the adult N1 for all block types was 75 to 150 ms, and the time window for the child P1 for all block types was also 75 – 150 ms. The latencies of these obligatory components were very consistent, and thus the 75 – 150 ms time window was used for all ISIs in both the Ignore and Attend conditions. The MMN components were more variable, and so time windows differed between groups, ISIs, conditions, and visits.

5.0 Results of Experiment 1: Modulation of Mismatch Negativity Elicited by Tone Doublets with Variable Interstimulus Intervals in Normal Adults

The main research question addressed in this experiment is: Is the MMN modulated by (1) rate of presentation of paired complex tones and (2) attention to the auditory stimuli in a group of normal adults?

5.1 Event Related Potentials – Waveform Morphology

5.1.1 Ignore Condition: Adult ERP waveform morphology

Visually inspecting the standard and deviant grand averaged waveforms in all channels, the greatest activity (higher amplitudes) is observed in fronto-central channels. There are much lower amplitude fluctuations in parietal and occipital channels. Figures 5.1.1.1a – 5.1.1.3a show the grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior). All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) (Figures 5.1.1.1b – 5.1.1.3b) where the MMN is large and easily identified, after verifying that activity at Fcz was similar to that of surrounding channels. In all figures, the standard wave is shown in blue, the deviant wave in red, and the difference wave (Deviant – Standard) in green.

5.1.1.1 Ignore 300 ms ISI- Adult ERP waveform morphology

The first peak in the standard and deviant waves is a small positivity (0.5 uV) at 68 ms, corresponding to the P50 component. This is followed by a negative peak (-0.2 uV) at 108 ms that is the adult N1. The N1 is followed by a small positive peak (0.5 uV)

at 160 ms and a broader negative peak (-0.6 uV) at 336 ms. After this, the standard and deviant waveforms have different morphologies due to the presentation of the second tone at 370 ms (standard = 100Hz, deviant = 300 Hz).

In the standard wave, there is a small negative peak (-0.2 uV) at 480 ms followed by a small positive peak (0.6 uV) at 540 ms, and this is followed by a small broad negativity (-0.4 uV) peaking at 664 ms.

In the deviant wave, there is a large negative peak (-1.6 uV) at 480 ms followed by a large positive peak (2.5 uV) at 580 ms. These are the adult N1/MMN and P3a components, respectively. After the P3a, there is a large broad negativity (-1.0 uV) peaking at 780 ms.

In the difference wave, the MMN is identified as a large negative peak (-1.4 uV) at 484 ms. The MMN is largest in frontocentral channels and inverts at the mastoids. The MMN is followed by a large positive peak (2.4 uV) at 580 ms. All electrodes in topographic arrangement are shown in Figure 5.1.1.1a, and channel Fcz is shown in Figure 5.1.1.1b.

5.1.1.2 Ignore 70 ms ISI: Adult ERP waveform morphology:

The first peak in the standard and deviant waves is a small positivity (0.4 uV) at 64 ms, corresponding to the P50 component. This is followed by a negative peak (-0.4 uV) at 112 ms that is the adult N1. The N1 is followed by a small positive peak (0.7 uV) at 172 ms. After this, the standard and deviant waveforms have different morphologies due to the presentation of the second tone at 140 ms (standard = 100Hz, deviant = 300 Hz).

In the standard wave, there is a broad negative peak (-1.1 uV) at 292 ms followed by a return to baseline activity.

In the deviant wave, there is a large, sharp negative peak (-2.7 uV) at 268 ms followed by a large positive peak (2.8 uV) at 360 ms. These are the adult N1/MMN and P3 components, respectively. After the P3, activity returns to baseline levels.

In the difference wave, the MMN is identified as a large negative peak (-1.7 uV) at 268 ms. The MMN has the highest amplitude at frontocentral channels and inverts at the mastoids. The MMN is followed by a large positive peak (2.9 uV) at 360 ms. All electrodes in topographic arrangement are shown in Figure 5.1.1.2a, and channel Fcz is shown in Figure 5.1.1.2b.

5.1.1.3 Ignore 10 ms ISI: Adult ERP waveform morphology:

The first peak in the standard and deviant waves is a small positivity (0.3 uV) at 60 ms, corresponding to the P50 component. This is followed by a negative peak (-0.7 uV) at 108 ms that is the adult N1. After this, the standard and deviant waveforms have different morphologies due to the presentation of the second tone at 80 ms (standard = 100Hz, deviant = 300 Hz).

In the standard wave, there are no other identifiable peaks after the N1.

In the deviant wave, there is a large, sharp negative peak (-1.4 uV) at 200 ms followed by a large positive peak (2.6 uV) at 288 ms. These are the adult MMN and P3 components, respectively. After the P3, there are two more small, broad negative peaks: -1.2 uV at 388 ms and -0.8 uV at 512 ms.

In the difference wave, the MMN is identified as a large negative peak (-1.5 uV) at 200 ms. The MMN has the highest amplitude at frontocentral channels and inverts at

the mastoids. The MMN is followed by a large positive peak (2.8 uV) at 284 ms. There are two more small, broad negativities after the P3: the first (-0.7 uV) at 384 ms, and the second (-1.0 uV) at 520 ms. All electrodes in topographic arrangement are shown in Figure 5.1.1.3a, and channel Fcz is shown in Figure 5.1.1.3b.

5.1.2 Attend Condition - Adult ERP Waveform Morphology

Upon visual inspection of the grand averaged adult ERP waveforms, the highest amplitudes are observed in frontocentral and central channels and appear to be equal bilaterally. Smaller amplitudes are observed in parietal and occipital channels (see Figures 5.1.2.1a – 5.1.2.3a). In both the standard and difference waves, the peaks in the Attend condition are sharper and higher in amplitude as compared to the Ignore condition. In the following sections, all waveform descriptions are based on ERPs recorded at electrode Fcz (Channel 4) (Figures 5.1.2.1b – 5.1.2.3b) after verifying that activity at Fcz was similar to that of surrounding channels. Figures 5.1.2.1a – 5.1.2.3a show the grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior).

5.1.2.1 Attend 300 ms ISI – Adult ERP Waveform Morphology

In the standard wave, the first peak is a small positivity (P50; 0.6 uV) at 64 ms which is followed by a negative peak (-0.7 uV) at 112 ms that is the adult N1. The N1 is followed by a positive peak (0.6 uV) at 260 ms, and then a large negative peak (-1.2 uV) at 292 ms. All these peaks invert at the mastoids and are largest at central channels.

The morphology of the deviant wave is similar to that of the standard wave until the onset of the deviant tone at 370 ms. There is a P50 (0.3 uV) at 64 ms followed by an N1 (-0.8 uV) at 112 ms. Then there is a broader positive peak (0.6 uV) at 184 ms followed by a negative peak (-0.8 uV) at 288 ms. The next peak is identified as the MMN/N1 to the second (deviant) tone (-1.6 uV) at 516 ms, and was followed by a large positive peak (2.3 uV) at 636 ms. All peaks invert at the mastoid channels.

In the difference wave, the first prominent peak is a large negativity (-1.5 uV) at 520 ms that is largest in frontocentral and central channels and inverts at the mastoids. This is the MMN. The MMN is followed by a large positive peak (2.4 uV) at 644 ms. The last identifiable peak in the difference wave is a large negative peak (-1.7) at 816 ms. All electrodes in topographic arrangement are shown in Figure 5.1.2.1a, and channel Fcz is shown in Figure 5.1.2.1b.

5.1.2.2 Attend 70 ms ISI: Adult ERP Waveform Morphology

The Attend 70 ms ISI standard wave overlaps almost completely with the Ignore 70 ms ISI standard wave. The P50 (0.5 uV) at 64 ms is followed by the N1 (-0.5 uV) at 112 ms. The next peak is positive (0.8 uV) at 188 ms, and is followed by a larger negative peak (-1.1 uV) at 296 ms. All of these peaks invert at the mastoid channels.

The Attend 70 ms ISI deviant wave has a P50 (0.3 uV at 60 ms) and N1 (-0.8 uV at 112 ms) similar to those in the Ignore 70 ISI deviant wave. The MMN (-3.6 at 296 ms), however, is higher in amplitude and has a longer latency than the Ignore 70 ms ISI MMN. In the Attend 70 ms ISI deviant wave, the MMN is followed by a large positive peak (2.7 uV) at 396 ms.

In the difference wave, the first identifiable peak is a large negativity (-2.6 uV) at 296 ms that inverts at the mastoids and is largest over frontocentral and central channels. This is the MMN. The MMN is followed by a large positive peak (2.7 uV) at 396 ms. This peak also inverts at the mastoids. All electrodes in topographic arrangement are shown in Figure 5.1.2.2a, and channel Fcz is shown in Figure 5.1.2.2b.

5.1.2.3 Attend 10 ms ISI: Adult ERP Waveform Morphology

In the standard wave, the first peak is the P50 (0.2 uV) at 56 ms. The P50 is followed by the N1 (-0.8 uV) at 112 ms. The next peak is positive (0.4 uV) at 220 ms, and is followed by a larger negative peak (-0.6 uV) at 292 ms. There is a final positive peak (0.3 uV) at 352 ms followed by a final negative peak (-0.4 uV) at 404 ms. All of these peaks invert at the mastoid channels.

The deviant P50 (0.1 uV at 52 ms) and N1 (-0.8 uV at 108 ms) are similar to those in the standard wave. After the N1 there is a positive peak (0.4 uV) at 168 ms followed by a negative peak (-1.6 uV) at 240 ms. Next there is a bifurcated broad positivity that peaks at 356 ms (1.1 uV). The last prominent peak is negative (-1.5 uV) at 516 ms. The MMN (-3.6 at 296 ms), however, is higher in amplitude and has a longer latency than the Ignore 70 ms ISI MMN. In the Attend 70 ms ISI deviant wave, the MMN is followed by a large positive peak (2.7 uV) at 396 ms.

In the difference wave, the first identifiable peak is a large negativity (-1.8 uV) at 236 ms that inverts at the mastoids and is largest over frontocentral and central channels. This is the MMN. The MMN is followed by a large positive peak (1.7 uV) at 300 ms, and the final peak in the wave is negative (-1.7) at 520 ms. All electrodes in topographic arrangement are shown in Figure 5.1.2.3a, and channel Fcz is shown in Figure 5.1.2.3b.

5.2 Event Related Potentials – Statistical Analyses

5.2.1 Within Group Analyses of Rate

Paired samples t-tests were performed to compare peak amplitude and latency measures between the different ISIs (300 vs. 70 ms ISIs; 70 vs. 10 ms ISIs) within each condition (Ignore or Attend). A t-test was run for each channel of interest in the deviant and difference waves. The 300 and 10 ms ISIs were compared in the same way with Independent Samples t-tests after verifying that Group 1 (300/70 ms ISIs) and Group 2 (70/10 ms ISIs) did not differ in amplitude or latency in the 70 ms ISI.

Given the large number of planned t-tests, a criterion was formulated for interpreting the results. For the MMN components, frontal and central channels were examined in the deviant and difference waves²⁶. Temporal, parietal and occipital channels were also investigated to improve confidence in the data and insure that the MMN was observed in the predicted frontocentral regions. T-tests yielding an alpha value of $\leq .05$ in two or more adjacent or complimentary (i.e. same topographic location in the right and left hemispheres) frontal or central channels was taken as a significant finding and included in the results sections below. T-tests with an alpha value of $\leq .05$ occurring in isolation were not included in the results. The ranges of t statistic and p values are reported.

Ignore Condition – MMN: For Adults, the greatest MMN amplitudes are observed for the 70 ms ISI (Amplitude: $70 > 300$, and $70 > 10$ ms ISI) in the deviant waves only.

²⁶ Standard waves were not examined in these MMN analyses since the standard waves exhibited very different morphologies at different ISIs. For example, in Adults in the 300 and 70 ms ISI, an N1 to the second tone was observed in the standard waves at the MMN latency range, but in the 10 ms ISI there was baseline activity in the MMN time window. Thus, comparisons of the standard waves elicited with different rates of presentation are not informative since they do not represent similar processes underlying the MMN.

The only significant effect of MMN latency is observed for the 70 vs. 300 ms ISI comparison; MMN latency is longer for the 70 ms ISI as compared to the 300 ms ISI in the deviant wave only. There are no other significant differences in latency. All significant amplitude ($t = -3.25 - 4.11$, $p = .012 - .001$) and latency ($t = -4.94 - 3.02$, $p = .000 - .006$) effects are seen in the deviant waves, but not the difference waves at frontocentral channels. These findings are illustrated in Figure 5.2.1a.

Attend condition – MMN: The same pattern of results is observed in the Attend condition that was reported for the Ignore condition. In the Attend condition, the greatest MMN amplitudes are observed for the 70 ms ISI ($70 > 300$, and $70 > 10$ ms ISI) in the deviant waves only. MMN latency is longer for the 70 ms ISI as compared to the 300 ms ISI in the deviant waves only. There are no other significant differences in latency between ISIs. All significant amplitude ($t = -4.48 - 6.05$, $p = .003 - .000$) and latency ($t = -4.05 - 2.00$, $p = .002 - .062$) effects are seen in the deviant waves, but not the difference waves at frontocentral channels. These findings are illustrated in Figure 5.2.1b.

Summary of Within Group Analyses of Rate: In both the Ignore and Attend conditions, the 70 ms ISI elicits greater MMN amplitudes and longer latencies as compared to the 300 or 10 ms ISIs in the deviant waves only. These effects are not observed in the difference waves, suggesting that the amplitudes and latencies of the MMN (traditionally identified and measured in the difference wave) elicited using tone pairs with different ISIs (300, 70 and 10 ms) do not significantly differ in this sample of normal adults.

5.2.2 Within Group Analyses of Condition (Ignore vs. Attend)

Paired samples t-tests were performed to compare peak amplitude and latency measures between the Ignore and Attend conditions within each ISI in deviant, standard and difference waves. The criterion for significant results described above for the Within Group Analyses of Rate was employed for these analyses as well. The ranges of t statistic and p values are reported.

300 ms ISI: In the difference wave only, MMN amplitude in the Attend condition is greater than that in the Ignore condition ($t = -0.56 - 2.60$, $p = .586 - .000$). The latency of the MMN is greater in the Attend condition as compared to the Ignore condition in the standard wave only ($t = -2.37 - 1.10$, $p = .037 - .297$) (in the MMN time window, the N1 to the second tone in the pair is captured in the standard wave).

70 ms ISI: Overall, MMN amplitude and latency are greater in the Attend condition as compared to the Ignore condition. Amplitudes in the standard, deviant and difference waves are greater in the Attend condition as compared to the Ignore condition in channels of all regions examined (frontal, central, temporal, parietal and occipital) ($t = -0.38 - 3.69$, $p = .970 - .002$). Latencies in the deviant and difference waves are greater in the Attend condition as compared to the Ignore condition in frontal and central channels ($t = -4.67 - 0.50$, $p = .000 - .623$).

10 ms ISI: MMN amplitude does not significantly differ between the Attend and Ignore conditions in the deviant, standard or difference waves ($t = -2.29 - 2.12$, $p = .052 - .067$). MMN latency is longer in the Attend condition as compared to the Ignore condition in all three waves and in all regions ($t = -5.46 - -0.38$, $p = .001 - .713$).

Summary of Within Group Analyses of Condition: In general, over all three ISIs, active listening (Attend condition) is associated with greater MMN amplitudes and longer

MMN latencies measured in the deviant, standard and difference waveforms (see Figures 5.2.2a and b). These findings are most robust for the 70 ms ISI. In the 10 ms ISI, MMN amplitude in the Attend and Ignore conditions do not significantly differ. In all t-tests yielding significant results, MMN amplitude and latency in the Attend condition is greater than that in the Ignore condition (Attend > Ignore). There are no instances in which the reverse (Attend < Ignore) is true. These findings show that at the 300 and 70 ms ISIs, active listening increases MMN amplitude, but at the fastest rate of presentation (10 ms ISI), active listening has no effect on MMN amplitude (Figure 5.2.2a). For all three rates of presentation, MMN latency increases when adult participants are engaged in active as compared to passive listening (Figure 5.2.2b).

5.3 Summary of Experiment 1 Results

The research question addressed in this experiment was: Is the MMN modulated by (1) rate of presentation of paired complex tones and (2) attention to the auditory stimuli in a group of normal adults. Overall it was found that the amplitudes and latencies of the MMN were similar for the three rates of presentation investigated (300, 70, and 10 ms ISI) during passive listening (Ignore condition). Attending to the stimuli resulted in generally larger amplitudes and longer latencies (Attend condition). Attention-related increases in *amplitude* were observed for the 300 and 70 ms ISI, but not for the 10 ms ISI. Attention-related increases in *latency* were observed for 300, 70 and 10 ms ISIs.

These results suggests that in normal adults, attention to paired tones separated by 300 and 70 ms may result in the recruitment of additional neural resources, and/or induce greater neural synchrony, reflected in MMN responses with higher amplitudes, as

compared to those elicited during passive listening (Gomes et al., 2000). However, for tones separated by 10 ms, the MMN does not appear to be modulated by attention, suggesting that the auditory system may be functioning at maximum efficiency to process such rapidly presented stimuli and attention does not confer an advantage for discrimination indexed by the MMN. Longer MMN latencies in the Attend condition also suggest that attention may enhance processing by extending processing time, even when no differences in amplitude are apparent.

6.0 Results of Experiment 2: Modulation of Mismatch Negativity Elicited by Tone Doublets with Variable Interstimulus Intervals in 6 – 9 year old Children with Typical Language Development

The main research question addressed in this experiment is: Is the MMN response in 6 – 9 year old children with typical language development (TLD) modulated by (1) rate of presentation of paired complex tones and (2) attention to the auditory stimuli? Here, the morphology of grand averaged waveforms for each rate of presentation (300, 70 and 10 ms ISI) within each condition (Ignore, Attend) are described, followed by results of the statistical analyses examining differences in amplitudes and latencies the mismatch components across rates of presentation and conditions.

6.1 Event Related Potentials – Waveform Morphology

6.1.1 Ignore Condition: ERP waveform morphology in Children with Typical Language Development

Visually inspecting the standard and deviant grand averaged waveforms in all channels, overall there is more widely distributed activity for TLD children as compared to adults. However, like adults, the highest amplitudes are observed in fronto-central channels. Figures 6.1.1.1a – 6.1.1.3a show the grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior). All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) (Figures 6.1.1.1b – 6.1.1.3b) after verifying that activity at Fcz was similar to that of surrounding channels.

6.1.1.1 Ignore 300 ms ISI: TLD children ERP waveform morphology – Visit 1

The first peak in the standard and deviant waves is a positivity (2.0 uV) at 92 ms, corresponding to the P1 component. This peak is then followed by a large negative peak (-3.2 uV) at 236 ms that is the child N2. The N2 is followed by a large positive peak (2.5 uV) at 456 ms. After this, the standard and deviant waveforms have different morphologies due to the presentation of the second tone at 370 ms (standard = 100Hz, deviant = 300 Hz).

In the standard wave, there is a large negative peak (-1.9 uV) at 596 ms. This is the last identifiable peak in the standard wave.

In the deviant wave, there is a small negative-going peak (0.5 uV) at 504 ms followed by a small positive-going peak (1.0 uV) at 540 ms. The next peak is a large negativity (-2.0 uV) at 616 ms followed by a small positive peak (1.0 uV) at 720 ms.

In the difference wave, the first prominent peak is negative (-0.5 uV) at 496 ms, is maximal at frontocentral channels and inverts at the mastoids. This appears to be the child early MMN (eMMN). The eMMN appears larger and has a shorter latency in the left hemisphere as compared to the right hemisphere (Ch. 13: -0.6 uV at 512 ms; Ch. 62: -1.1 uV at 492 ms). The eMMN is followed by a positive peak (1.6 uV) at 556 ms, which is followed by another negative peak (-0.3 uV) at 624 ms. This negative peak only inverts at the left mastoid (Ch. 24). The last peak in the difference wave is a large negativity (-1.3 uV) at 808 ms. This peak inverts at both mastoids and is identified as the late MMN/LDN. All electrodes in topographic arrangement are shown in Figure 6.1.1.1a, and channel Fcz is shown in Figure 6.1.1.1b.

6.1.1.2 Ignore 70 ms ISI: TLD children ERP waveform morphology – Visit 1

The first peak in the standard and deviant waves is a positivity (1.8 uV) at 100 ms, corresponding to the P1 component. After the P1, the standard and deviant waves have different morphologies.

In the standard wave, following the P1 there is a large negative peak (-2.8 uV) at 256 ms. This is the child N2, and is the last identifiable peak in the standard wave.

In the deviant wave, following the P1 there is a negative peak (-2.4 uV) at 264 ms that has a small “notch” in the rising (negative-going) part of the component. In the right and left frontal channels (channels 13 and 62) there is a more noticeable “notch” making the peak appear bimodal. This “notch” may be the emerging N1 overlapping with the more dominant N2. Following the N2 there is a small positive peak (0.04) at 336 ms and then a negative peak (-1.0 uV) at 392 ms. After this there is a positive peak (0.7 uV) at 496 ms followed by a final broader negative peak (-0.3 uV) at 604 ms.

In the difference wave, there is a small negative-going peak at the expected N2 latency (0.4 uV at 268 ms). This is visible at frontocentral channels and inverts at the mastoids, and appears to be the emerging adult-like MMN. There is a second negative peak (-0.6 uV) at 388 ms that corresponds to the previously described early MMN in children. Finally, there is a negative peak (-1.1) at 576 ms corresponding to the late MMN described in children. These early and late MMN components invert at the mastoids and are maximal at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 6.1.1.2a, and channel Fcz is shown in Figure 6.1.1.2b.

6.1.1.3 Ignore 10 ms ISI: TLD children ERP waveform morphology – Visit 1

The first peak in the standard and deviant waves is a positivity (1.7 uV) at 88 ms, corresponding to the P1 component. After the P1, the standard and deviant waves have different morphologies.

In the standard wave following the P1, there is a large negative peak (-3.1 uV) at 228 ms. This is the child N2, and is the last identifiable peak in the standard wave.

In the deviant wave, following the P1 there is a small negative-going peak (0.5 uV) at 132 ms followed by a small positive peak (1.2 uV) at 164 ms. Then there is a large negative peak (-2.3 uV) at 244 ms that is the child N2.

In the difference wave, there is a small negative peak (-0.6 uV) at 124 ms followed by a broad positive peak (1.5 uV) at 184 ms. The next peak is a broad negativity (-0.3 uV) at 308 ms that is identified as the early MMN (eMMN). The eMMN is followed by a broad positive-going peak (0.6 uV) at 376 ms. This is followed by a large negative peak (-1.5 uV) at 496 ms that is the late MMN (lMMN). These early and late MMN components invert at the mastoids and are maximal at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 6.1.1.3a, and channel Fcz is shown in Figure 6.1.1.3b.

6.1.2 Attend Condition: ERP waveform morphology in Children with Typical Language Development

Visually inspecting the standard and deviant grand averaged waveforms in all channels, overall there was more widely distributed and higher amplitude activity for TLD children as compared to adults. Also, like adults, the highest amplitudes were observed in fronto-central and occipital channels. Figures 6.1.2.1a – 6.1.2.3a show the

grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior). All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) (Figures 6.1.2.1b – 6.1.2.3b) after verifying that activity at Fcz was similar to that of surrounding channels.

6.1.2.1 Attend 300 ms ISI: TLD Children ERP Waveform Morphology – Visit 1

The first peak in the standard wave is a large positivity (1.6 uV) at 88 ms, corresponding to the P1 component. This is followed by a large negative peak (-3.0 uV) at 228 ms that is the child N2. The N2 is followed by a large positive peak (2.4 uV) at 456 ms. The last identifiable peak in the standard wave is a large negativity (-2.9 uV) at 596 ms.

In the deviant wave, the first peak is a large positivity (1.6 uV) at 88 ms that is the child P1 component. The P1 is followed by a large negativity (-3.0 uV) at 236 ms that is the child N2. After the N2, there is a large positivity that has two distinct peaks: the first (1.7 uV) at 380 ms, and the second (1.9 uV) at 448 ms. The next series of similar-sized peaks follows a negative-positive-negative pattern: a negativity (-1.6 uV) at 500 ms, is followed by a positive peak (1.3 uV) at 564 ms, and finally a negative peak (-1.6 uV) at 580 ms. After this, there is a large positive peak (2.7 uV) at 744 ms, and the final peak in the deviant wave is a broad negativity (-1.6 uV) at 948 ms.

In the difference wave, the first identifiable peak is a negativity (-2.1 uV) at 488 ms that corresponds to the child early MMN (eMMN). This is followed by a large positive peak (3.4 uV) at 576 ms, and then a smaller negative peak (-0.6 uV) at 664 ms. The last peak of interest in the difference wave is a negativity that has two peaks: the first

is a smaller “notch” (-1.3 uV) at 864, followed by a larger peak (-2.0 uV) at 948 ms. This second and larger negative peak is the child late MMN/LDN. The child MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 6.1.2.1a, and channel Fcz is shown in Figure 6.1.2.1b.

6.1.2.2 Attend 70 ms ISI: TLD Children ERP Waveform Morphology – Visit 1

The first peak in the standard wave is a positivity (2.1 uV) at 88 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.9 uV) at 252 ms. This is the N2. After the N2, the last peak in the standard is a small negative peak (-0.2 uV) at 448 ms.

In the deviant wave, the first peak is a positivity (2.4 uV) at 88 ms, corresponding to the P1. The P1 is followed by a large N2 (peak: -2.9 uV at 264 ms) that had a “notch” on the rising (negative-going) portion of the component (-1.8 uV at 232 ms). This notch is more apparent at frontal channels, and is not present at central channels. The N2 is followed by a smaller negative peak (-1.4 uV) at 436 ms, and then a positive peak (1.7 uV) at 564 ms. Finally, there is a very small negative deflection (-0.5 uV) at 688 ms.

In the difference wave, the posited emerging adult-like MMN is observed as a negative-going peak (-0.2 uV) that barely crosses the baseline at 272 ms. The next peak is the early MMN (-1.6 uV) at 412 ms, and the last peak in the difference wave is a broad negativity that is the late MMN/LDN (-0.5 uV) at 784 ms. The MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 6.1.2.2a, and channel Fcz is shown in Figure 6.1.2.2b.

6.1.2.3 Attend 10 ms ISI: TLD Children ERP Waveform Morphology – Visit 1

The first peak in the standard wave is a positivity (1.6 uV) at 84 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-2.9 uV) at 224 ms. This is the child N2 of the standard wave and is the last identifiable peak in the standard wave.

In the deviant wave, the first peak is the P1 (1.4 uV) at 88 ms, followed by a small negative peak (-0.4 uV) at 132 ms, before rising to a large negative peak (-3.0 uV) at 236 ms that is the child N2 of the deviant wave. The N2 is followed by a very small negative deflection (-0.1 uV) at 436 ms, then the last peak in the deviant wave is a positivity (1.8 uV) at 528 ms.

In the difference wave, the first peak of interest is a negative peak (-1.0 uV) at 444 ms identified as the child eMMN. Following the eMMN, there is another negative peak of similar size (-1.0 uV) at 644 ms that is the late MMN (lMMN). These early and late MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 6.1.2.3a, and channel Fcz is shown in Figure 6.1.2.3b.

6.2 Event Related Potentials – Statistical Analyses

6.2.1 Within Group Analyses of Rate

Paired samples t-tests were performed to compare peak amplitude and latency measures between the different ISIs (300 vs. 70 ms ISIs; 70 vs. 10 ms ISIs) within each condition (Ignore or Attend). A t-test was run for each channel of interest in the deviant and difference waves. The 300 and 10 ms ISIs were compared in the same way with

Independent Samples t-tests after verifying that Group 1 (300/70 ms ISIs) and Group 2 (70/10 ms ISIs) did not differ in amplitude or latency in the 70 ms ISI.

As in Experiment 1, given the large number of planned t-tests, a criterion was used for interpreting the results. For both early and late MMN components (eMMN, IMMN/LDN), frontal and central channels were examined in the deviant and difference waves²⁷. Temporal, parietal and occipital channels were also investigated to improve confidence in the data and insure that the eMMN and IMMN/LDN was observed in the predicted frontocentral regions. T-tests yielding an alpha value of $\leq .05$ in two or more adjacent or complimentary (i.e. same topographic location in the right and left hemispheres) frontal or central channels was taken as a significant finding and included in the results sections below. T-tests with an alpha value of $\leq .05$ occurring in isolation were not included in the results. The ranges of t statistic and p values are reported.

Ignore Condition – eMMN: For TLD children, the eMMN amplitude in the 70 ms ISI is greater than that of the 300 ms ISI in the deviant waves only, like adults ($t = 0.54 - 3.65$, $p = .604 - .008$). There are no other significant rate-related differences in amplitude (see Figure 6.2.1a). *Longer eMMN latencies* are observed with *shorter ISIs* (70 and 10 > 300 ms ISI) in both the deviant and differences waves ($t = -10.20 - 0.34$, $p = .000 - .742$) (see Figure 6.2.1b).

Ignore Condition – IMMN/LDN: There are no significant differences in IMMN amplitudes among the different ISIs, but significantly *longer IMMN/LDN latencies* are

²⁷ Standard waves were not examined in these MMN analyses since the standard waves exhibited very different morphologies at different ISIs. For example, in Adults in the 300 and 70 ms ISI, an N1 to the second tone was observed in the standard waves at the MMN latency range, but in the 10 ms ISI there was baseline activity in the MMN time window. Thus, comparisons of the standard waves elicited with different rates of presentation are not informative since they do not represent similar processes underlying the MMN.

found at *longer ISIs* (see Figure 6.2.1c). LMMN/LDN latency in the 300 ms ISI is longer than in the 70 ms ISI ($300 > 70$) in the difference wave only ($t = 0.23 - 3.09$, $p = .831 - .036$), $70 > 10$ ms ISI in the deviant wave only ($t = -0.48 - 3.14$, $p = .963 - .016$), $300 > 10$ ms ISI in both the deviant and difference waves ($t = 0.56 - 3.30$, $p = .583 - .006$). In sum, there are no differences in IMMN/LDN amplitudes, but significant results in the difference wave show that IMMN/LDN latencies at 300 ms ISI are longer than those in the 70 and 10 ms ISIs ($300 > 70/10$).

Attend Condition – eMMN: For the TLD children, the same patterns of results are found for the Attend and Ignore conditions for the eMMN. In the Attend condition, the eMMN amplitude in the 70 ms ISI is greater than that of the 300 ms ISI in the deviant wave only ($t = -0.10 - 4.30$, $p = .923 - .013$). There are no other significant rate-related differences in amplitude. *Longer eMMN latencies* are observed with *shorter ISIs* (70 and $10 > 300$ ms ISI) in the differences waves ($t = -9.68 - -0.61$, $p = .001 - .574$) (see Figure 6.2.1d).

Attend Condition – IMMN/LDN: For the TLD children in the Attend condition, the IMMN amplitude in the 300 ms ISI is greater than that of the 10 ms ISI in the deviant wave only ($t = -4.78 - 0.22$, $p = .002 - .830$). There are no other significant amplitude differences. In the latency analyses, IMMN latency is shorter for the 300 ms ISI as compared to the 10 ms ISI in the deviant wave only ($t = -2.89 - 0.94$, $p = .023 - .380$). Thus, in the difference waves, where MMN components are generally indexed, there are no rate-related differences in IMMN/LDN amplitude or latency.

Summary of Within Group Analyses of Rate: For the eMMN, the same pattern of results are found in the Ignore and Attend conditions with higher eMMN amplitude in the 70 ms ISI as compared to the 300 ms ISI in the deviant waves only, and *longer eMMN latencies* are observed with *shorter ISIs* (70 and 10 > 300 ms ISI) in the differences waves.

For the IMMN/LDN, no rate-related differences are found in IMMN/LDN amplitude in the difference wave in both the Ignore and Attend conditions. In the latency analyses, IMMN/LDN display *longer latencies* at the *longest ISI* (300 > 70/10 ms ISI) in the Ignore condition, but in the Attend condition there are no significant rate-related differences in IMMN/LDN latency. Thus, there are different patterns of results for the eMMN and IMMN/LDN during passive and active listening.

It should be noted that in the Attend condition, the number of subjects is very small in most of the analyses ($n = 3, 4$, or 5). Thus, the small number of significant findings should not be interpreted as evidence that eMMN and IMMN/LDN amplitudes and latencies are not influenced by rate of presentation during active listening. Future studies with greater numbers of participants will be needed to substantiate such conclusions. At present, the significant results that were found are taken to represent real and robust differences in the amplitude and latency of children's MMN components.

6.2.2 Within Group Analyses of Condition (Ignore vs. Attend)

Paired samples t-tests were performed to compare peak amplitude and latency measures between the Ignore and Attend conditions within each ISI in deviant, standard and differences waves at frontal and central electrodes for the eMMN and IMMN/LDN.

The criterion for significant results described above for the Within Group Analyses of Rate was employed for these analyses as well. The ranges of t statistic and p values are reported.

6.2.2.1 Within Group Analyses of Condition for Early MMN

300 ms ISI – eMMN: In the deviant and difference waves, eMMN amplitude is greater in the Attend condition as compared to the Ignore condition ($t = -2.61 - 7.99$, $p = .059 - .001$). In the standard wave only, eMMN latency is shorter in the Attend condition as compared to the Ignore condition ($t = 0.50 - 3.97$, $p = .643 - .017$). In sum, eMMN amplitude is greater in the Attend condition as compared to the Ignore condition, but there are no latency differences between the two conditions.

70 ms ISI – eMMN: In the deviant and difference waves, eMMN amplitude is greater in the Attend condition as compared to the Ignore condition ($t = 0.30 - 5.21$, $p = .773 - .001$). There are no significant differences between conditions for eMMN latency.

10 ms ISI – eMMN: There are no significant differences between conditions in amplitude or latency.

Summary of Within Group Analyses of Condition for Early MMN: For TLD children, in the 300 and 70 ms ISIs, attending to the auditory stimuli results in eMMNs with larger amplitudes. This attention enhancement is not seen for the 10 ms ISI (see Figure 6.2.2.1). There are no attention-related effects on eMMN latency at any rate of presentation.

6.2.2.2 Within Group Analyses of Condition for Late MMN/LDN

300 ms ISI – IMMN/LDN: In the standard wave only, IMMN/LDN amplitude is greater and latency is shorter for the Attend condition as compared to the Ignore condition (Amplitude: Attend > Ignore, $t = 1.69 - 7.05$, $p = .233 - .020$; Latency: Attend < Ignore, $t = 0.58 - 24.61$, $p = .618 - .002$). There are no significant findings in the deviant or difference waves for either amplitude or latency.

70 ms ISI – IMMN/LDN: In the standard wave only, IMMN/LDN amplitude is greater in the Attend condition as compared to the Ignore condition (Amplitude: Attend > Ignore, $t = -0.26 - 4.58$, $p = .802 - .002$). In the deviant, standard and difference waves, IMMN/LDN latency is longer for the Attend condition as compared to the Ignore condition (Latency: Attend > Ignore, $t = -4.03 - -0.08$, $p = .004 - .937$). In sum, in the difference waves there are no attention-related effects for amplitude, but IMMN/LDN latencies are longer in the Attend as compared to the Ignore condition.

10 ms ISI – IMMN/LDN: There are no significant differences between conditions in IMMN/LDN amplitude. In the standard and deviant waves, IMMN/LDN latency is longer for the Attend condition as compared to the Ignore condition (Latency: Attend > Ignore, $t = -4.03 - -0.33$, $p = .016 - .762$). Overall, no attention-related effects are seen in the difference waves for amplitude or latency.

Summary of Within Group Analyses of Condition for Late MMN/LDN: For the 300 and 70 ms ISIs, active listening only appears to significantly impact the way the standard stimulus is processed (Attend: greater amplitude, shorter latency), but no effects are seen in the deviant or difference waveforms. Overall, no attention-related effects are seen in the difference waves for IMMN/LDN amplitude. Analyses of IMMN/LDN latencies revealed an effect of attention for the 70 ms ISI only, where latencies were

longer in the Attend condition as compared to the Ignore condition. There were no attention-related affects on IMMN/LDN latencies in the 300 or 10 ms ISIs.

6.3 Summary of Experiment 2 Results

The research question addressed in this experiment was: Is the MMN modulated by (1) rate of presentation of paired complex tones and (2) attention to the auditory stimuli in a group of 6 – 9 year old children with typical language development? Overall, TLD children exhibit the expected waveform morphology, with prominent P1 and N2 components in both the standard and deviant waves. Two MMN components were identified in the difference waveforms, the eMMN and IMMN/LDN. These two mismatch components have been previously described in the literature in children (for a review, see Cheour et al., 2001).

Statistical analyses of **rate** revealed that for both the eMMN and IMMN/LDN there are no rate-related effects on *amplitude* observed in the differences waves. In the analyses of *latency*, however, the eMMN component exhibits longer latencies at the shorter ISIs in the difference waves (70 and 10 ms ISI > 300 ms ISI). The opposite pattern is observed for the IMMN/LDN where longer latencies are seen at the longest ISI (300 > 70 and 10). The latency findings may suggest that for the eMMN, for two stimuli within the temporal window of integration (c.a. in 5 – 11 year old children, less than 300 – 350 ms, Wang et al., 2005) peak latency may be somewhat delayed due to the processing of these stimuli as a unitary event. The IMMN/LDN on the other hand, may exhibit shorter latencies for stimuli that tap in to rapid auditory processing and are therefore, arguably, more complex, due to its proposed involvement in further inspection of complex stimuli.

Statistical analyses of **condition** for the eMMN showed that attending to the auditory modality results in larger eMMN amplitudes for the 300 and 70 ms, but not the 10 ms ISI. This suggests that for the slower rates of presentation, attending to the stimuli may confer a benefit in automatic discrimination indexed by a larger mismatch response. The lack of an effect in the 10 ms ISI may indicate that even in the passive condition, the automatic discrimination processes are functioning at maximum efficiency in response to a compound stimulus, and so attending to the tone pairs does not result in a measurable increase in eMMN amplitude. There are no attention-related effects observed for eMMN latency.

Statistical analyses of **condition** for the IMMN/LDN revealed no significant attention related effects on IMMN/LDN *amplitude*. However, analyses of *latency* showed that for the 70 ms ISI only, attending to the stimuli resulted in longer IMMN/LDN latencies. Since the IMMN/LDN is thought to be involved in further processing of complex (often linguistic stimuli) (Cheour et al., 2001; Hämäläinen et al., 2008), it is interesting to note that an attention effect is observed only for the ISI that falls in the time range (tens of milliseconds) that is important for speech processing (Tallal & Gaab, 2006).

7.0 Results of Experiment 3: Developmental Changes in Mismatch

Negativity Elicited by Tone Doublets with Variable Interstimulus

Intervals: Adults and 6 – 9 year old Children

This experiment comprises a series of analyses examining maturational differences in the mismatch negativity (MMN) response in adults who participated in Experiment 1 as compared to 6 to 9 year old children with typical language development (TLD) who participated in Experiment 2. The EEG/ERP stimuli and recording protocols in Experiments 1 and 2 were identical. Specifically, the comparisons in the present study were designed to examine how attention may modulate the MMN differently in the mature and developing brain as a function of the rate of presentation of the auditory stimuli. Potential hemispheric differences in the MMN of adults and TLD children are also explored. The main research question addressed here is: **How does auditory processing, reflected in the MMN, differ between Adults and TLD children when stimuli are presented at different rates depending on whether the participants are attending to the stimuli or passively listening?**

7.1 ERP Waveform Morphology

Detailed descriptions of the grand averaged ERP waveforms, specifically the identification of the MMN responses, are reported in “Results – Experiment 1” for Adults, and “Results – Experiment 2” for TLD children. Briefly, visually inspecting the standard, deviant and difference grand averaged waveforms in all channels, adults display typical MMN morphology and topography (Näätänen, 1992, 1995). A distinct adult-like

MMN response with a latency of 110 – 160 ms is observed in the difference wave in frontocentral channels and inverts behind the mastoids. The MMN occurs at all rates of presentation (300, 70 and 10 ms ISI) in both the Ignore and Attend conditions. The highest amplitudes are observed in frontocentral channels, and much lower activity is seen in frontal, parietal and occipital areas. At channels located along the periphery of the Geodesic sensor net, amplitudes are lower than those seen in the frontocentral region, but higher than those in frontal, parietal and occipital areas.

For TLD children, visual inspection of the standard, deviant and difference grand averaged waveforms shows that overall there is more widely distributed and higher amplitude fluctuations for TLD children as compared to adults. However, like adults, the highest amplitudes are observed in frontocentral channels, with lower activity in frontal and posterior parietal areas. Two mismatch negativity components were identified in TLD children's ERP waveforms that have been previously described in the literature (for a review, see Cheour et al., 2001; Shafer et al., 2000; Korpilahti et al., 1995, 2001; Hämäläinen et al., 2008). The first is the early MMN (eMMN) that occurs at all rates of presentation (300, 70 and 10 ms ISI) in both the Ignore and Attend conditions. The eMMN is maximal at frontocentral channels and inverts behind the mastoids. The eMMN latency varies depending on the rate of presentation: 300 ms ISI, 118 – 126 ms; 70 ms ISI, 248 – 272; 10 ms ISI, 228 – 360 ms.

The second mismatch negativity component identified is the late MMN, or Late Discriminative Negativity (IMMN/LDN). This later occurring component also has a frontocentral topography and inverts behind the mastoids. The IMMN/LDN latency

varies most with Condition. In the Ignore condition the IMMN/LDN latency range is 416 – 438 ms, and in the Attend condition the latency range is 564 – 578 ms.

Here, the adult MMN and the child eMMN are compared since these components more likely reflect the same underlying automatic auditory change detection process (Cheour et al., 2001). It is less plausible that the adult MMN and child IMMN/LDN share similar neural mechanisms. The IMMN/LDN is thought to reflect further discriminative processing of a deviant stimulus in addition to that reflected in the eMMN, and may also be associated with overall brain maturation as it is related to the development of attention, though its function is still not fully understood (Hämäläinen et al., 2008; Ceponiene et al., 2002, 2004). The IMMN/LDN has been reported more often in children and has not been well characterized in adults as IMMN/LDN amplitude tends to decrease rapidly with age (Cheour et al., 2001).

7.2 Event Related Potentials – Statistical Analyses

A series of ANOVAs were planned to examine how attention may affect MMN²⁸ peak amplitude and latency in Adults and TLD children. The planned analyses were 2 x 2 mixed factors ANOVAs: Group (Adult, TLD) x Condition (Ignore, Attend). However, there were very few TLD participants who completed both the Ignore and Attend conditions for the 300 and 10 ms ISIs (n = 5 in both cases), so the planned 2 x 2 ANOVAs could not be carried out given the lack of sufficient statistical power due to small sample sizes. Instead, Independent Samples t-tests were conducted comparing MMN peak amplitude and latency in the difference waves in Adults and TLD children

²⁸ MMN refers to the adult MMN and the eMMN in TLD children. The label “MMN” will be used to refer to these components from this point on for this section.

within each ISI (300, 70 and 10 ms) and within each condition (Ignore, Attend). The explanation and justification of the criteria for interpreting multiple t-tests is detailed in Analytic Strategies (pp. 71 – 72). Descriptive statistics are shown in Tables 7.2a – f, and the ranges of significant t statistic and p values are reported.

7.2.1 Between Groups Analyses of Amplitude: Adults and TLD Children

Ignore Condition – MMN Amplitude: For the 300 and 70 ms ISI, there are no differences in MMN peak amplitude between Adults and TLD children. In the 70 ms ISI there are some significant t-tests in both the deviant ($t_{33} = -3.23 - 3.84$, $p = .003 - .001$) and difference waves ($t_{33} = -3.05 - 3.03$, $p = .004 - .005$), but examination of the means reveals no consistent pattern: in some cases Adults have larger amplitudes than TLD children (Ch. 17 and Cz), and in some cases the reverse is true (Adults < TLD children, Ch. 13 and 53). These results are inconsistent and inconclusive. Finally, in the 10 ms ISI, there is clear pattern of results in the difference wave indicating that Adults have larger MMN amplitudes than TLD children ($t_{18} = -2.65 - 1.44$, $p = .015 - .168$). These results are shown in Figure 7.2.1a.

Attend Condition – MMN Amplitude: For all three ISIs, there are no significant differences in MMN amplitude between Adults and TLD children. These results are shown in Figure 7.2.1b.

7.2.2 Between Groups Analyses of Latency: Adults and TLD Children

Ignore Condition – MMN Latency: For all three ISIs, Adults have shorter MMN latencies as compared to TLD children (Difference wave: 300 ms ISI, $t_{22} = -4.86 - -0.72$,

$p = .000 - .482$; 70 ms ISI, $t_{33} = -9.39 - -4.37$, $p = .000 - .001$; 10 ms ISI, $t_{18} = -9.08 - -5.99$, $p = .000 - .000$).

Attend Condition – MMN Latency: For the 300 ms ISI, there are no significant differences in MMN latencies between Adults and TLD children. For the 70 and 10 ms ISIs, however, Adults have significantly shorter MMN latencies as compared to TLD children (Difference wave: 70 ms ISI, $t_{33} = -6.02 - -3.22$, $p = .000 - .006$; 10 ms ISI, $t_{14} = -6.79 - -0.15$, $p = .000 - .881$).

7.2.3 Summary of Between Groups Analyses: Adults and TLD Children

In the Ignore condition, Adults display significantly larger MMN amplitudes *only* at the fastest rate of presentation (10 ms ISI). In this case, even though TLD children exhibit larger amplitude fluctuations (evident in the deviant wave), Adults have a more robust MMN response (evident in the difference wave). However, when participants are actively attending to the auditory stimuli, there are no significant differences in MMN amplitude between Adults and TLD children at any ISI. This suggests that during active listening, Adults and TLD children discriminate the paired tone stimuli in a similar manner, even for the fastest rate of presentation.

For the analyses of MMN latency, in the Ignore condition Adults have shorter latencies than TLD children at all rates of presentation. This finding was predicted based on the literature (Jing & Benasich, 2006; Wang et al., 2005; Shafer et al., 2000). During the Attend condition, however, at the 300 ms ISI Adults and TLD children have similar latencies. For the 70 and 10 ms ISIs in the Attend condition, adults have shorter MMN latencies than TLD children. This suggests that at the slowest rate of presentation, when

TLD children attend to the auditory stimuli, they process the tone pairs in a manner similar to that of adults.

7.3 Event Related Potentials – Statistical Analyses of Hemispheric Differences

A series of 2 x 2 mixed factors ANOVAs were planned to examine potential differences in MMN amplitude and latency between hemispheres in Adults and TLD children. For each rate of presentation (300, 70, 10 ms ISI) within each condition (Ignore, Attend), Group (Adult, TLD) x Hemisphere (Left, Right) ANOVAs were conducted to investigate changes in MMN peak amplitude and latency at three pairs of channels: frontocentral (Ch. 17 and 54), frontal (Ch. 13 and 62), and central (Ch. 21 and 53). Significant main effects or interactions were further investigated by examining simple effects via repeated measures t-tests within each group of participants comparing MMN amplitudes or latencies in the Left and Right hemispheres for the three pairs of channels described above. The explanation and justification of the criteria for interpreting multiple t-tests is detailed in Analytic Strategies (pp. 71 – 72).

As these analyses were being set up, it was apparent that in some of the planned ANOVAs the sample sizes were disparate (e.g. Ignore 300 ms ISI, Adult n = 15, TLD n = 9). These are noted in the descriptions of results that follow. In such cases, the ANOVAs were conducted, but the results are interpreted with caution. Also, simple effects were examined to look for patterns of results that informed the research question, regardless of the results of the mixed factors ANOVAs. The ranges of t statistic and p values are reported for significant simple effects comparisons.

7.3.1 Ignore Condition – MMN Amplitude Statistical Analyses of Hemispheric Differences

For the 300 ms ISI, the mixed factors ANOVAs revealed a main effect of Group at central channels only ($F=4.98$, $p<.05$), reflecting larger MMN amplitudes in the TLD children's waveforms as compared to Adults. Because of disparate sample sizes (Adult $n=15$, TLD $n=7$) the simple effects were examined. There are no hemispheric differences in MMN amplitude in Adults or TLD children.

For the 70 ms ISI, there is a main effect of Group at frontal ($F=5.24$, $p<.05$) and central ($F=4.24$, $p<.05$) channels, and a Hemisphere x Group interaction at frontal channels ($F=4.10$, $p\leq.05$). Examination of the simple effects did not reveal any hemisphere-related MMN amplitude differences in either group.

For the 10 ms ISI, there is a main effect of Group at frontocentral channels ($F=6.95$, $p<.05$), with Adults displaying larger MMN amplitudes as compared to TLD children. There is also a Hemisphere x Group interaction in frontal channels ($F=8.38$, $p\leq.01$). Examination of the simple effects did not reveal any hemisphere-related MMN amplitude differences in either group.

7.3.2 Ignore Condition – MMN Latency Statistical Analyses of Hemispheric Differences

For the 300 ms ISI, the mixed factors ANOVAs revealed a main effect of Group for frontal ($F=11.19$, $p<.01$) and central ($F=21.65$, $p<.01$) channels, with Adults displaying shorter MMN latencies as compared to TLD children. Because of disparate

sample sizes (Adult $n=15$, TLD $n=7$) the simple effects were examined. There are no hemispheric differences in MMN latency in Adults or TLD children.

For the 70 ms ISI, the mixed factors ANOVAs revealed a main effect of Group for frontocentral ($F=82.09$, $p<.001$), frontal ($F=89.56$, $p<.001$), and central ($F=68.42$, $p<.001$) channels, with Adults displaying shorter MMN latencies as compared to TLD children. Because of disparate sample sizes (Adult $n=22$, TLD $n=13$) the simple effects were examined. There are no hemispheric differences in MMN latency in Adults or TLD children.

For the 10 ms ISI, the mixed factors ANOVAs revealed a main effect of Group for frontocentral ($F=56.66$, $p<.001$), frontal ($F=41.15$, $p<.001$), and central ($F=69.02$, $p<.001$) channels, with Adults displaying shorter MMN latencies as compared to TLD children. The sample sizes were relatively equal (Adult $n=10$, TLD $n=9$), and so the simple effects were not examined because there are no significant effects of Hemisphere in the ANOVAs.

7.3.3 Summary of Statistical Analyses of Hemispheric Differences: Ignore Condition

Overall, there are very few results suggesting hemispheric differences in the MMN in both adults and TLD children in the Ignore condition. Significant Hemisphere x Group interactions revealed in the ANOVAs are not supported by the simple effects analyses, thus no consistent patterns of hemispheric asymmetry in the MMN can be reported here.

7.3.4 Attend Condition –MMN Amplitude Statistical Analyses of Hemispheric Differences

For the 300 ms ISI, the mixed factors ANOVAs (with disparate samples sizes noted: Adult $n=12$, TLD $n=5$) revealed a main effect of Group at frontal ($F=5.81$, $p<.05$) and central ($F=10.76$, $p<.01$) channels, reflecting larger MMN amplitudes in the TLD children's waveforms as compared to Adults. There is also a significant main effect of Hemisphere in frontal channels only ($F=42.648$, $p<.001$) with smaller amplitudes on the Left as compared to the Right side across both groups of participants. Finally, there is a significant Hemisphere x Group interaction at frontal channels ($F=16.70$, $p<.01$). Examination of the simple effects did not reveal any hemisphere-related MMN amplitude differences in either group.

For the 70 ms ISI, there is a main effect of Group at frontal ($F=7.23$, $p<.05$) and central ($F=10.61$, $p<.01$) channels, reflecting larger MMN amplitudes in the TLD children's waveforms as compared to Adults. There is also a significant Hemisphere x Group interaction at central channels only ($F=4.58$, $p<.05$). Examination of the simple effects did not reveal any hemisphere-related MMN amplitude differences in either group.

For the 10 ms ISI, there is a main effect of Group at central channels only ($F=4.53$, $p\leq.05$), reflecting larger MMN amplitudes in the TLD children's waveforms as compared to Adults. Examination of the simple effects did not reveal any hemisphere-related MMN amplitude differences in either group.

7.3.5 Attend Condition – MMN Latency Statistical Analyses of Hemispheric Differences

For the 300 ms ISI, the mixed factors ANOVAs did not reveal any significant main effects or interactions. Because of disparate sample sizes (Adult $n=12$, TLD $n=5$) the simple effects were examined. There are no hemispheric differences in MMN latency in Adults or TLD children.

For the 70 ms ISI, the mixed factors ANOVAs revealed a main effect of Group at frontocentral ($F=29.51$, $p<.001$), frontal ($F=51.83$, $p<.001$), and central ($F=93.16$, $p<.001$) channels, with Adults displaying shorter MMN latencies as compared to TLD children. Since there are no significant hemispheric-related differences revealed in the ANOVAs, the simple effects were not examined.

For the 10 ms ISI, the mixed factors ANOVAs revealed a main effect of Group at frontal channels only ($F=24.13$, $p<.001$), with Adults displaying shorter MMN latencies as compared to TLD children. There is also a significant Hemisphere x Group interaction at frontocentral ($F=5.49$, $p<.05$) and central ($F=5.97$, $p<.05$) channels. Examination of the simple effects revealed that only Adults exhibit significantly shorter MMN latencies in the Left as compared to the Right hemisphere at frontocentral and central channels (see Table 7.3.5). There are no hemispheric differences in MMN latency for TLD children in the Attend 10 ms ISI condition.

7.3.6 Summary of Statistical Analyses of Hemispheric Differences: Attend Condition

Overall, very few results suggest hemispheric differences in the MMN in either adults or TLD children in the Attend condition. There are no significant hemispheric differences in MMN amplitude for adults or TLD children. In the analyses of MMN latency, in the 10 ms ISI condition only, Adults display shorter latencies on the Left as compared to the Right hemisphere (Left < Right), but no hemispheric differences emerged in the small sample of TLD children (n=5).

7.4 Summary of Experiment 3 Results

The main research questions addressed in this experiment was: How does auditory processing, reflected in the MMN, differ between Adults and TLD children when stimuli are presented at different rates depending on whether the participants are attending to the stimuli or passively listening?

Statistical analyses of **rate** show that during passive listening, adults and TLD children have comparable MMN *amplitudes* when tone pairs are presented with ISIs of 300 and 70 ms. For the 10 ms ISI rate of presentation, however, Adults have significantly larger MMNs as compared to TLD children. This suggests that in TLD children between the ages of 6 and 9 years, rapid auditory processing abilities (for the fastest rate of presentation investigated here) have not yet reached adult levels. However, when effects of **condition** were examined, analyses show that during active listening (Attend condition) MMN amplitudes of adults and TLD children are not significantly different at any of the rates of presentation tested. These results support the idea that in TLD children where RAP abilities for stimuli presented at very fast rates are still developing and thus

are not under automatic control, attention enhances the discrimination and here “boosts” the MMN to adult levels (Gomes et al., 2000).

Turning to the analyses of MMN *latency*, in the Ignore condition, as expected, Adults have shorter latencies than TLD children at all rates of presentation (Thomas and Crow, 1994; Shafer et al., 2000). However, in the Attend condition, for the 300 ms ISI only, Adults and TLD children have similar latencies. This suggests when TLD children attend to auditory stimuli, processing may occur in a manner similar to adults, but only for the slowest rate of presentation investigated (300 ms ISI). More rapid maturational changes in amplitude and more gradual changes in latency have been reported (Ponton et al., 2000), and the present results are consistent with such findings. In contrast to MMN amplitudes which appear to be at adult levels even in passive listening for the tone pairs with longer ISIs, this slower development of mature MMN latencies may be attributed to neurobiological changes in the auditory cortex, especially myelination, that extend throughout childhood and well into adolescence (Eggermont, 1988). So, although the neuronal populations that are responsible for adult-like auditory discrimination processes are functioning (due to increases in synaptic density), the speed of transmission (reliant upon myelination and synaptic changes) may follow a more lengthy maturational time course (Huttenlocher & Dabholkar, 1997).

Hemispheric differences in adults and TLD children were also investigated in the present experiment, but no consistent pattern of hemispheric asymmetry emerged for either group. The only significant finding occurred in the Attend 10 ms ISI condition where adults display shorter MMN latencies in the Left as compared to the Right hemisphere. There are no hemispheric differences displayed by TLD

children in this condition. These results suggest that for Adults, active listening enhances processing of very rapidly presented stimuli (10 ms ISI), reflected in shorter latencies to MMN peak on the Left side as compared to the Right side. In passive listening, all results indicate relatively equal processing bilaterally as indexed by MMN amplitudes and latencies.

These findings are consistent with recent EEG/ERP investigations of the left hemisphere advantage for processing linguistic and/or rapidly presented, brief stimuli in both adults and normally developing children. In these studies *no hemispheric asymmetry* was found in the MMN elicited by complex non-verbal stimuli, except when it was presented within a linguistic context (Uther et al., 2003; Shytrov et al., 2005, Ceponiene et al., 2002; but see Alho et al., 1998). The present results are consistent with that literature.

8.0 Results of Experiment 4: Modulation of Mismatch Negativity Components Elicited by Tone Doublets with Variable Interstimulus Intervals in Children with a Language Impairment and Controls

This experiment compares the MMN components (eMMN and IMMN/LDN) elicited by two complex tones separated by a short gap (300, 70 or 10 ms) in 6 – 9 year old children with a Language Impairment (LI) and children with typical language development (TLD) during both passive and active listening. The control participants in this experiment are the children with Typical Language Development (TLD) who participated in Experiment 2. The EEG/ERP stimuli and recording protocols in Experiment 2 and the current experiment are identical. Please see the Results section of Experiment 2 for all TLD grand averaged waveform morphological descriptions and within group statistical analyses of Rate (comparisons between ISIs) and Condition (Ignore vs. Attend).

Specifically, the comparisons in the present study were designed to examine how attention may modulate the MMN differently in the LI and TLD children as a function of the rate of presentation of two complex tones. Potential hemispheric differences in these two groups of children are also explored. The main research question addressed here is:

How does auditory processing, reflected in the MMN, differ between LI and TLD children when stimuli are presented at different rates depending on whether the participants are attending to the stimuli or passively listening?

8.1 Event Related Potentials – Waveform Morphology

8.1.1 Ignore Condition: ERP Waveform Morphology in Children with a Language Impairment

Visually inspecting the standard and deviant grand averaged waveforms in all channels, overall there is more widely distributed and higher amplitude activity for children with a Language Impairment (LI) as compared to adults, but similar to TLD children. Also, like adults and TLD children, the highest amplitudes are observed in fronto-central channels. Figures 8.1.1.1a – 8.1.1.3a show the grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior). All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) (Figures 8.1.1.1b – 8.1.1.3b) after verifying that activity at Fcz was similar to that of surrounding channels.

8.1.1.1 Ignore 300 ms ISI: LI children ERP waveform morphology – Visit 1

The first peak in the standard wave is a positivity (2.1 uV) at 100 ms, corresponding to the P1 component. This is followed by a large negative peak (-2.9 uV) at 240 ms that is the child N2. The N2 is followed by a large positive peak (2.2 uV) at 468 ms. The last identifiable peak in the standard wave is a large negative peak (-2.3 uV) at 604 ms.

The first peak in the deviant wave is a positivity (2.5 uV) at 96 ms, corresponding to the P1 component. This is followed by a large negative peak (-2.7 uV) at 244 ms that is the child N2. The N2 is followed by a large positive peak (2.2 uV) at 460 ms. This is

followed by a small negative-going peak (-0.6 uV) at 520 ms. The last peak in the deviant wave is a large negativity (-1.7 uV) at 628 ms.

In the difference wave, the first identifiable peak is negative (-1.3 uV) at 508 ms, is most prominent at frontocentral channels, and inverts at the mastoids. This appears to be the eMMN. The eMMN is followed by a positive peak (2.1 uV) at 580 ms. The IMMN/LDN is a negativity (-1.5 uV) at 844 ms. The early and late MMN components invert at the mastoids and are largest at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 8.1.1.1a, and channel Fcz is shown in Figure 8.1.1.1b.

8.1.1.2 Ignore 70 ISI - LI children ERP waveform morphology – Visit 1

The first peak in the standard and deviant waves is a positivity (2.3 uV) at 100 ms (the standard and deviant waves completely overlap), corresponding to the P1 component. After the P1 the standard and deviant waves have different morphologies.

In the standard wave, the P1 is followed by a large negative peak (-2.8 uV) at 252 ms. This is the N2. After the N2, the standard wave returns to baseline level activity.

In the deviant wave, the P1 is followed by a large N2 (-2.2 uV at 268 ms) that has a small “notch” on the rising (negative-going) portion of the component. This notch is barely apparent at Fcz, but is more noticeable at right frontal channels (e.g. channel 62). The N2 is followed by a small negative peak (-0.9 uV) at 396 ms that is the last identifiable peak in the deviant wave.

In the difference wave, the posited emerging adult-like MMN is observed as a negative-going notch (0.4 uV) at 276 ms. The early MMN is identified as a negative peak

(-0.8 uV) at 396 ms, and the late MMN/LDN is identified as a broader negative peak (-0.9 uV) at 560 ms. All MMN components are largest at frontocentral channels and invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 8.1.1.2a, and channel Fcz is shown in Figure 8.1.1.2b.

8.1.1.3 Ignore 10 ISI - LI children ERP waveform morphology – Visit 1

The first peak in the standard wave is a positivity (1.8 uV) at 96 ms, corresponding to the P1 component. After the P1, there is a large negative peak (-2.9 uV) at 224ms. This is the child N2 of the standard wave and is the last identifiable peak in the standard wave.

The first peak in the deviant wave is the P1 (1.6 uV at 96 ms). After the P1, there is a small negative-going “notch” (0.9 uV) at 132 ms followed by a large negative peak (-2.2 uV) at 240 ms identified as the child N2 of the deviant wave. The last peak in the deviant wave is a smaller negativity (-0.8 uV) at 436 ms.

In the difference wave, the first peak of interest is a negative-going “notch” that is the emerging adult-like MMN (0.4 uV) at 276 m. The next peak is the child eMMN (-0.8 uV) at 369 ms. Then the lMMN/LDN (-0.9 uV) occurs at 560 ms and is a broader negativity. All MMN components invert at the mastoids and are maximal at frontocentral channels with the eMMN distributed more frontocentrally and the lMMN distributed more centrally. All electrodes in topographic arrangement are shown in Figure 8.1.1.3a, and channel Fcz is shown in Figure 8.1.1.3b.

8.1.2 Attend Condition – LI Children ERP Waveform Morphology – Visit 1

On visual inspection, the standard and deviant grand averaged waveforms in all channels, are more widely distributed and show higher amplitude activity for LI children as compared to adults, but are similar to those seen in TLD children. Also, like adults and TLD children, the highest amplitudes are observed in fronto-central and occipital channels (see Figures 8.1.2.1a – 8.1.2.3a). All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) (Figures 8.1.2.1b – 8.1.2.3b) after verifying that activity at Fcz was similar to that of surrounding channels.

8.1.2.1 Attend 300 ms ISI: LI Children ERP Waveform Morphology – Visit 1

The first peak in the standard wave is a large positivity (2.0 uV) at 112 ms, corresponding to the P1 component. This is followed by a large negative peak (-2.2 uV) at 232 ms that is the child N2. The N2 is followed by a large positive peak (1.9 uV) at 456 ms. The last identifiable peak in the standard wave is a large negativity at 636 ms (-1.6 uV).

In the deviant wave, the first peak is a large positivity (1.6 uV) at 112 ms that is the child P1 component. The P1 is followed by a large negativity (-2.0 uV) at 256 ms that is the child N2. After the N2, there is a large positivity (2.3 uV) at 448 ms, followed by a large negative peak (-3.4 uV) at 516 ms. The next identifiable peak is a smaller, broader negativity (-1.5 uV) at 648 ms, followed by a positive peak (2.2 uV) at 808 ms. The final peak in the deviant wave is a negative peak (-1.8 uV) at 972 ms.

In the difference wave, the first prominent identifiable peak is a robust negative peak (-3.0 uV) at 512 ms that corresponds to the child early MMN (eMMN). This is followed by a large positive peak (3.0 uV) at 580 ms, and then a smaller negative peak (-

1.1 uV) at 692 ms. The last peak of interest in the difference wave is a negative peak (-1.8 uV) at 960 ms that is the child late MMN/LDN. The MMN components invert at the mastoids and are maximal at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 8.1.2.1a, and channel Fcz is shown in Figure 8.1.2.1b.

8.1.2.2 Attend 70 ISI - LI children ERP waveform morphology – Visit 1

The first peak in the standard wave is a positivity (1.8 uV) at 92 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.7 uV) at 252 ms. This is the N2. After the N2, the standard wave returned to baseline level activity.

In the deviant wave, the first peak is a positivity (2.1 uV) at 92 ms, corresponding to the P1. The P1 is followed by a large N2 (-2.6 uV at 268 ms) that has a “notch” on the rising (negative-going) portion of the component (-1.9 uV at 188 ms). This notch is more apparent at central channels, but at more frontal electrodes the notch appears as a distinct peak. The N2 is followed by a small positive peak (0.8 uV) at 356 ms, and then a negative peak (-0.7 uV) at 468 ms. Finally there is a positive deflection (1.3 uV) at 572 ms followed by a final negative peak (-0.6 uV) at 660 ms.

In the difference wave, the posited emerging adult-like MMN is observed as a negative-going peak (-0.1 uV) at 272 ms. The early MMN is a negative peak (-0.9 uV) at 464 ms, and the late MMN/LDN is a negative peak (-1.1 uV) at 656 ms. The MMN components invert at the mastoids and are maximal at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 8.1.2.2a, and channel Fcz is shown in Figure 8.1.2.2b.

8.1.2.3 Attend 10 ISI - LI children ERP waveform morphology – Visit 1

The first peak in the standard wave is a positivity (2.0 uV) at 72 ms, corresponding to the P1 component. Following the P1, there is a large negative peak (-3.4 uV) at 228 ms. This is the child N2 of the standard wave. The N2 has a “notch” on the rising (negative-going) portion of the component (-1.4 uV at 188 ms) visible at frontocentral channels. The N2 is the last identifiable peak in the standard wave.

In the deviant wave, the first peak is the P1 (1.7 uV) at 92 ms, followed by a large negative peak (-1.9 uV) at 276 ms that is the child N2 of the deviant wave. The N2 has a slightly smaller second peak (-1.8 uV) at 276 ms. The first, main peak is maximal at frontocentral channels and inverts at the mastoids, while the second peak is maximal at frontal channels and does not invert at the mastoids. The N2 is followed by a positive deflection (1.1 uV) at 348 ms, then the last peak is the deviant wave is a smaller negative peak (-1.2 uV) at 448 ms.

In the difference wave, the first peak of interest is a small negative-going peak that barely crosses the baseline (-0.4 uV) at 284 ms. The next peak of interest is a negativity (-1.5 uV) at 456 ms that is the eMMN. Following the eMMN, there is another negative peak (-0.7 uV) at 568 ms that is the late MMN (IMMN). These early and late MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 8.1.2.3a, and channel Fcz is shown in Figure 8.1.2.3b.

8.2 Event Related Potentials – Statistical Analyses

8.2.1 Within Group Analyses of Rate

Paired samples t-tests were performed to compare peak amplitude and latency measures between the different ISIs (300 vs. 70 ms ISIs; 70 vs. 10 ms ISIs) within each condition (Ignore or Attend). A t-test was run for each channel of interest in the deviant and difference waves. The 300 and 10 ms ISIs were compared in the same way with Independent Samples t-tests after verifying that Group 1 (300/70 ms ISIs) and Group 2 (70/10 ms ISIs) did not differ in amplitude or latency in the 70 ms ISI.

As in Experiments 1 and 2, given the large number of planned t-tests, a criterion was used for interpreting the results. Briefly, for both early and late MMN components (eMMN, IMMN/LDN), frontal and central channels were examined in the deviant and difference waves²⁹. Temporal, parietal and occipital channels were also investigated to improve confidence in the data and insure that the eMMN and IMMN/LDN was observed in the predicted frontocentral regions. T-tests yielding an alpha value of $\leq .05$ in two or more adjacent or complimentary (i.e. same topographic location in the right and left hemispheres) frontal and/or central channels was taken as a significant finding and included in the results sections below. T-tests with an alpha value of $\leq .05$ occurring in isolation were not included in the results. The range of t statistic and p values are reported for significant findings.

Ignore Condition – eMMN: For LI children, the eMMN amplitude in the 70 ms ISI is significantly smaller than that of the 10 ms ISI in the deviant wave only ($t_6 = 0.43 - 5.05$, $p = .681 - .002$). There are no other significant rate-related differences in amplitude. In the deviant wave only, eMMN latencies are shorter for the 70 ms ISI condition as

²⁹ Standard waves were not examined in these MMN analyses since the standard waves exhibited very different morphologies at different ISIs. For example, in Adults in the 300 and 70 ms ISI, an N1 to the second tone was observed in the standard waves at the MMN latency range, but in the 10 ms ISI there was baseline activity in the MMN time window. Thus, comparisons of the standard waves elicited with different rates of presentation are not informative since they do not represent similar processes underlying the MMN.

compared to the 10 ms ISI condition ($t_6 = 0.74 - 4.44$, $p = .487 - .004$), and shorter for the 10 ms ISI as compared to the 300 ms ISI ($t_{21} = 0.99 - 5.65$, $p = .335 - .000$). There are no rate-related amplitude or latency differences in the difference waves.

Ignore Condition – IMMN/LDN: There are no rate-related differences in IMMN/LDN amplitudes in the deviant or difference waves. However, the latencies of the IMMN/LDN are longer at the slowest (300 ms ISI) as compared to the faster (70, 10 ms ISI) rates of presentation in the deviant and difference waves (300 > 70 ms ISI: $t_9 = 0.54 - 3.41$, $p = .602 - .008$; 300 > 10 ms ISI: $t_{21} = 1.59 - 4.56$, $p = .132 - .000$).

Attend Condition – eMMN: For the LI children, in the Attend condition, only the 300 and 10 ms ISI rates of presentation were compared with paired samples t-tests because there was not enough data to complete the other analyses (only 2 participants were available for the 300 vs. 70 ms ISI comparison, and only 1 participant was available for the 70 vs. 10 ms ISI comparison). There are no significant differences in eMMN amplitude or latency between the 300 and 10 ms ISIs in the deviant or difference waves.

Attend Condition – IMMN/LDN: As mentioned above, only the 300 and 10 ms ISIs were subject to paired samples t-tests because there was not enough data to perform the other rate comparisons. No significant differences are found in IMMN amplitude, but IMMN latency is longer for the 300 ms ISI as compared to the 10 ms ISI in both the deviant and difference waves (300 > 10 ms ISI: $t_8 = -0.08 - 3.58$, $p = .942 - .024$).

Summary of Within Group Analyses of Rate: For both the eMMN and IMMN/LDN there are no differences in *amplitude* observed in the differences waves in both the Ignore and Attend conditions. There are also no rate-related *latency* differences

in the eMMN in either the Ignore or Attend condition. However, in the IMMN/LDN, slower rates of presentation resulted in longer latencies in both the Ignore (300 > 70 and 10 ms ISI) and Attend (300 > 10 ms ISI) conditions. In the Attend condition only one pair of ISIs could be compared (300 vs. 10 ms ISI) because there was not enough data available to conduct the other repeated measures analyses. Therefore, it is difficult to make any summary statements about how rate might influence the amplitude and latency of mismatch components during active listening in this group of LI children. In the Ignore condition, though, the results demonstrate that there is no modulation of the eMMN or IMMN/LDN amplitude as a function of rate of presentation. Similarly, eMMN latency does not vary with rate of presentation. Only IMMN/LDN latency varies by rate, with longer latencies occurring with slower rates of presentation.

8.2.2 Within Group Analyses of Condition (Ignore vs. Attend)

Paired samples t-tests were performed to compare peak amplitude and latency measures between the Ignore and Attend conditions within each ISI in deviant, standard and differences waves at frontal and central electrodes for the eMMN and IMMN/LDN. The criterion for significant results described above for the Within Group Analyses of Rate was employed for these analyses as well.

8.2.2.1 Within Group Analyses of Condition for Early MMN

300 ms ISI – eMMN: These analyses could not be performed because there was not sufficient data available (only 2 participants).

70 ms ISI – eMMN: For the 70 ms ISI, there are larger eMMN amplitudes in the Attend condition as compared to the Ignore condition in the deviant, standard and

differences waves (Amplitude: Attend > Ignore, $t_7 = 0.78 - 6.39$, $p = .459 - .000$). In the deviant and standard waves, there are shorter eMMN latencies in the Attend condition as compared to the Ignore condition (Latency: Attend < Ignore, $t_7 = 0.47 - 5.78$, $p = .656 - .001$).

10 ms ISI – eMMN: For the 10 ms ISI, there are larger eMMN amplitudes in the Attend condition as compared to the Ignore condition in the difference wave only (Amplitude: Attend > Ignore, $t_2 = 1.10 - 5.84$, $p = .388 - .028$). There are no significant condition-related differences in latency. In these analyses, data from only three participants was available. The small amount of data may account, in part, for the lack of significant findings.

Summary of Within Group Analyses of Condition for Early MMN: At relatively fast rates of presentation (70 and 10 ms ISIs), actively attending to the auditory modality results in greater eMMN amplitudes in LI children. There are no significant effects of attention on eMMN latencies in the difference waves. Unfortunately, planned analyses could not be carried out for the slowest rate of presentation, the 300 ms ISI.

8.2.2.2 Within Group Analyses of Condition for Late MMN/LDN

300 ms ISI – IMM/LDN: The present analyses were carried out with data from three participants. There are no significant differences in IMM/LDN amplitude or latency between the Attend and Ignore conditions in frontal or central channels.

70 ms ISI – IMM/LDN: For the 70 ms ISI, IMM/LDN amplitude was greater in the Attend condition as compared to the Ignore condition in the standard wave only (Amplitude: Attend > Ignore, $t_{12} = 1.37 - 5.70$, $p = .196 - .000$). In the deviant, standard

and difference waves, IMMN/LDN latencies are longer in the Attend as compared to the Ignore condition (Latency: Attend > Ignore, $t_{12} = -6.48 - -2.72$, $p = .000 - .019$).

10 ms ISI – IMMN/LDN: There are no significant condition-related differences in IMMN/LDN amplitudes or latencies for the 10 ms ISI at frontal or central channels.

Summary of Within Group Analyses of Condition for Late MMN/LDN:

Significant differences between active and passive listening were revealed for IMMN/LDN *latency* in the 70 ms ISI only, with longer latencies in the Attend condition. There are no attention related effects on IMMN/LDN *amplitude*. There are no significant attention-related differences in the 300 or 10 ms ISIs for amplitude or latency.

8.2.3 Between Groups Analyses: TLD vs. LI children

A series of ANOVAs were planned to examine how attention may affect eMMN and IMMN/LDN peak amplitudes and latencies differently in TLD and LI children. The planned analyses were 2 x 2 mixed factors ANOVAs: Group (TLD, LI) x Condition (Ignore, Attend) within each Rate at channel Fcz. However, there were very few participants who had sufficient data in both the Ignore and Attend conditions for the 300 and 10 ms ISIs (e.g. 300 ms ISI: TLD n=5, LI n = 2; 10 ms ISI: TLD n=5, LI n=3), so the planned 2 x 2 ANOVAs could not be carried out since they lacked sufficient statistical power. Additionally, for the 70 ms ISI 2 x 2 ANOVA, the sample sizes were disparate (TLD n=18, LI n=8) due to several variables: completion of the experimental blocks, loss of data due to artifact rejection criteria and loss of data due to the absence of a clear MMN response (see Analytic Strategies). The decision was made not to conduct the planned 2 x 2 ANOVAs for any ISI.

Given these circumstances, instead of mixed factors ANOVAs, Independent Samples t-tests were conducted comparing peak amplitude and latency of the eMMN or IMMN/LDN in the difference wave between TLD and LI children within each ISI (300, 70 and 10 ms) and within each condition (Ignore, Attend). The explanation and justification of the criteria for interpreting multiple t-tests is detailed in Analytic Strategies (pp. 71 – 72). Descriptive statistics are shown in Tables 8.2.3.1a – f for the eMMN, and Tables 8.2.3.2a – f for the IMMN/LDN. The ranges of t statistic and p values are reported for all significant comparisons.

8.2.3.1 Between Groups Analyses of eMMN: TLD vs. LI Children

Ignore Condition – eMMN: The independent samples t-tests did not reveal any significant differences in eMMN amplitude between TLD and LI children at the 300, 70 and 10 ms ISI in the Ignore condition. However, at the 300 and 70 ms ISIs, TLD children had significantly shorter eMMN latencies than the LI children in the deviant and difference waves (300 ms ISI: $t_{18} = -4.66$ - -0.83 , $p = .000$ - $.416$; 70 ms ISI: $t_{32} = -7.75$ - -1.23 , $p = .000$ - $.227$). There were no group differences in eMMN latency for the Ignore 10 ms ISI condition in the deviant or difference waves. These results are shown in Figure 8.2.3.1.

Attend Condition – eMMN: The independent samples t-tests did not reveal any significant differences in eMMN amplitude or latency between TLD and LI children at the 300, 70 and 10 ms ISIs in the Attend condition in the deviant or difference waves.

8.2.3.2 Between Groups Analyses of IMMN/LDN: TLD vs. LI Children

Ignore Condition – IMMN/LDN: The independent samples t-tests did not reveal any significant differences in IMMN/LDN amplitude or latency between TLD and LI children at the 300, 70 and 10 ms ISIs in the Ignore conditions.

Attend Condition – IMMN/LDN: The independent samples t-tests did not reveal any significant differences in IMMN/LDN amplitude or latency between TLD and LI children at the 300, 70 and 10 ms ISIs in the Attend conditions.

8.2.3.3 Summary of Between Groups Analyses

Independent samples t-tests were conducted to investigate potential differences in the amplitudes and latencies of children's MMN components at each rate of presentation (300, 70 and 10 ms ISIs) during passive (Ignore condition) and active (Attend condition) listening. There were limited significant findings indicative of systematic group differences in eMMN and IMMN/LDN amplitudes and latencies between TLD and LI children. In the Ignore 300 and 70 ms ISI conditions, TLD eMMN latencies were shorter than those of LI children. This might suggest slower or less efficient automatic auditory processing in the LI group as compared to TLD children at these two rates of presentation.

8.2.4 Event Related Potentials – Statistical Analyses of Hemispheric Differences

A series of 2 x 2 mixed factors ANOVAs were planned to examine potential differences in eMMN and IMMN/LDN amplitudes and latencies between hemispheres in TLD and LI children. For each rate of presentation (300, 70, 10 ms ISI) within each condition (Ignore, Attend), Group (TLD, LI) x Hemisphere (Left, Right) ANOVAs were

conducted to investigate changes in MMN peak amplitude and latency at three pairs of channels: frontocentral (Ch. 17/Left and 54/Right), frontal (Ch. 13 and 62), and central (Ch. 21 and 53). Significant main effects or interactions were further investigated by examining simple effects via repeated measures t-tests within each group of participants comparing eMMN or IMMN/LDN amplitudes or latencies in the Left and Right hemispheres for the three pairs of channels described above. The explanation and justification of the criteria for interpreting multiple t-tests is detailed in Analytic Strategies (pp. 71 – 72).

As these analyses were being set up, it was noted that in some of the planned ANOVAs the sample sizes in the Attend condition were very small (Attend 300 ms ISI, TLD n = 5, LI n= 4; Attend 10 ms ISI, TLD n=5, LI n=3). These are noted in the descriptions of results that follow. In such cases, the ANOVAs were conducted, but the results were interpreted with caution. Also, simple effects were examined to look for patterns of results that informed the research question, regardless of the results of the mixed factors ANOVAs.

8.2.4.1 Statistical Analyses of Hemispheric Differences in the eMMN

Ignore Condition – eMMN Amplitude: The mixed factors ANOVAs did not reveal any significant effects or interaction in the 300, 70 and 10 ms ISIs. Due to the lack of significant findings and sufficient sample sizes (Ignore 300 ms ISI, TLD n=9, LI n=11; Ignore 70 ms ISI, TLD n=13, LI n=16; Ignore 10 ms ISI, TLD n=9, LI n=13), the simple effects were not investigated.

Ignore Condition – eMMN Latency: For the 300 ms ISI, the mixed factors ANOVAs revealed a main effect of Group for frontocentral ($F=4.60$, $p<.05$) and frontal

($F=4.35$, $p \leq .05$) channels, with TLD children displaying shorter eMMN latencies as compared to LI children. However, no hemispheric effects in eMMN latency are seen.

Similarly, for the 70 ms ISI, the mixed factors ANOVAs revealed a main effect of Group for frontocentral ($F=20.31$, $p < .001$), and central ($F=4.23$, $p \leq .05$) channels, with TLD children displaying shorter eMMN latencies as compared to LI children. However, no hemispheric effects in eMMN latency are seen.

For the 10 ms ISI, the mixed factors ANOVAs did not reveal any significant effects or interactions.

Again, due to the lack of significant findings indicating differences in eMMN latencies between the Left and Right hemispheres, and sufficient sample sizes in all ANOVAs (Ignore 300 ms ISI, TLD $n=9$, LI $n=11$; Ignore 70 ms ISI, TLD $n=13$, LI $n=16$; Ignore 10 ms ISI, TLD $n=9$, LI $n=13$), the simple effects were not investigated.

Attend Condition – eMMN Amplitude: For the 300 ms ISI, the mixed factors ANOVAs (with small samples sizes noted: TLD $n=5$, LI $n=4$) revealed a significant Hemisphere x Group interaction at frontal channels ($F=5.82$, $p < .05$). Examination of the simple effects did not reveal any significant hemisphere-related eMMN amplitude differences in either group.

For the 70 ms ISI, the mixed factors ANOVAs did not reveal any significant effects or interactions. Because there were sufficient sample sizes (TLD $n=14$, LI $n=20$), the simple effects were not investigated.

Also, for the 10 ms ISI, the mixed factors ANOVAs did not reveal any significant effects or interactions. Due to small sample sizes (TLD $n=5$, LI $n=3$), the simple effects were investigated but did not reveal any significant hemisphere-related effects.

Attend Condition – eMMN Latency: For the 300 and 70 ms ISIs, the mixed factors ANOVAs did not reveal any significant main effects or interactions. Because of small sample sizes in the Attend 300 ms ISI only (TLD $n=5$; LI $n=4$) the simple effects were examined. No hemispheric differences in MMN latency were revealed for TLD or LI children.

For the 10 ms ISI, the mixed factors ANOVAs revealed a main effect of Group at frontocentral channels only ($F=5.96$, $p \leq .05$), with TLD children displaying shorter eMMN latencies as compared to LI children. Because of small sample sizes in the Attend 10 ms ISI (TLD $n=5$; LI $n=3$) the simple effects were examined. No hemispheric differences in eMMN latency were revealed for TLD or LI children.

Summary of Statistical Analyses of Hemispheric Differences in the eMMN:

Overall, there is no clear evidence suggesting hemispheric differences in the eMMN in TLD and LI children in both the Ignore and Attend conditions. The only hemisphere-related significant finding is a Hemisphere x Group interaction examining eMMN amplitude the Attend 300 ms ISI condition. The simple effects did not reveal any differences in eMMN amplitude between the Left and Right hemispheres in TLD or LI children. In sum, the analyses here suggests that the eMMN elicited by paired complex tones with ISIs of 300, 70 and 10 ms are similar in amplitude and latency bilaterally at

frontocentral, frontal and central sites in both TLD and LI children during passive and active listening.

8.2.4.2 Statistical Analyses of Hemispheric Differences in the IMMN/LDN

Ignore Condition – IMMN/LDN Amplitude: For the 300 and 10 ms ISIs, the mixed factors ANOVAs did not reveal any significant effects or interactions. Due to disparate sample sizes in the Ignore 300 ms ISI condition only (TLD $n=7$ LI $n=12$), the simple effects were investigated, but did not reveal any significant hemisphere-related effects for either TLD or LI children.

For the 70 ms ISI, the mixed factors ANOVAs revealed a main effect of Hemisphere in central channels ($F=4.00$, $p \leq .05$), with IMMN/LDN amplitudes greater on the Left as compared to the Right side across both subject groups. However, the simple effects analyses did not reveal any significant hemispheric differences in either the TLD or LI groups.

Ignore Condition – IMMN/LDN Latency: For the 300 ms ISI, the mixed factors ANOVAs revealed a significant Hemisphere x Group interaction in frontocentral channels ($F=6.07$, $p < .05$). Examination of the simple effects, however, did not reveal any significant effects of hemisphere for either TLD or LI children.

No other significant main effects or interactions were found in the ANOVAs for the 300, 70 and the 10 ms ISIs. The simple effects were not investigated because sample sizes were relatively equal and sufficient in the Ignore 70 ms ISI (TLD $n=15$. LI $n=22$) and Ignore 10 ms ISI (TLD $n=9$, LI $n=13$) conditions.

Attend Condition – IMMN/LDN Amplitude: Across all three ISIs, the only significant effect revealed by the mixed factors ANOVAs was a main effect of Hemisphere in central channels ($F=5.15$, $p<.05$) for the 70 ms ISI, with IMMN/LDN amplitude greater on the Left as compared to the Right. Examination of the simple effects, however, did not reveal any hemispheric differences for either the TLD or LI groups. Thus, the main effect of Hemisphere resulted from the pooling of all participants, lending more power to the analysis, but did not reflect significant hemispheric asymmetry in IMMN/LDN amplitude in either or both groups of children.

The simple effects analyses for the Attend 300 ms ISI (TLD $n=4$, LI $n=4$) and Attend 10 ms ISI (TLD $n=5$, LI $n=6$) conditions were inspected due to small sample sizes, but failed to reveal any hemispheric effects for either TLD or LI children.

Attend Condition – IMMN/LDN Latency: For the 300 ms ISI condition, mixed factors ANOVAs revealed a main effect of Group at frontocentral channels ($F=47.48$, $p<.001$) with TLD children exhibiting shorter latencies than LI children. The simple effects were investigated due to the small sample sizes (TLD $n=4$, LI $n=4$), but failed to reveal any hemispheric effects for either TLD or LI groups.

For the 70 ms ISI condition, there was a main effect of Hemisphere at central channels ($F=6.14$, $p<.05$), with shorter latencies on the Left as compared to the Right side. Examination of the simple effects, however, did not reveal any hemispheric differences for either the TLD or LI groups in IMMN/LDN latency elicited during active listening.

For the 10 ms ISI condition, there was a significant Hemisphere x Group interaction in frontocentral channels ($F=6.73$, $p<.05$). Examination of the simple effects, once again, did not reveal any hemispheric differences for either the TLD or LI groups.

Summary of Statistical Analyses of Hemispheric Differences in the IMM/LDN:

Overall, there is no clear evidence suggesting hemispheric differences in the IMM/LDN in TLD and LI children in both the Ignore and Attend conditions. These findings are similar to those in the eMMN hemispheric analyses.

There were a few instances in which significant main effects of Hemisphere or Hemisphere x Group interactions were found in the mixed factors ANOVAs, but the simple effects did not reveal any hemispheric differences in either the TLD or LI group. In sum, the analyses here suggests that the IMM/LDN elicited by paired complex tones with ISIs of 300, 70 and 10 ms are similar in amplitude and latency bilaterally at frontocentral, frontal and central sites in both TLD and LI children during passive and active listening.

8.3 Summary of Experiment 4 Results

The main research question addressed in this experiment was: How does auditory processing, reflected in the eMMN and IMM/LDN, differ between LI and TLD children when stimuli are presented at different **rates** depending on whether the participants are attending to the stimuli or passively listening (**condition**)?

Initial visual inspection of the grand averaged waveforms for the LI children revealed the expected waveform morphology, with prominent P1 and N2 components in both the standard and deviant waves. Two MMN components were identified in the

difference waveforms, the eMMN and IMMN/LDN. These two mismatch components have been previously described in the literature in children (for a review, see Cheour et al., 2001). As expected, the waveforms of the LI children had the same morphology as those of the TLD children (pp. 137 – 154).

Statistical analyses of **rate** for the **eMMN** of LI children reveal that for the eMMN and IMMN/LDN there are no rate-related effects on *amplitude* in both the Ignore and Attend conditions. The same pattern of results is reported for TLD children (pp. 158 – 161). There are also no rate-related *latency* differences in the eMMN for LI children, but TLD children exhibit longer eMMN latencies at shorter ISIs (70 and 10 ms ISI > 300 ms ISI) in both the Ignore and Attend conditions (see Figures 8.3a and b). These data may be taken to suggest that for 6 – 9 year old TLD children, when two complex tones are presented within the temporal window of integration (c.a. < 300 – 350 ms, Wang et al., 2005) peak latency might be prolonged due to the processing of two stimuli as a single auditory event. In LI children, difficulty processing two or more brief auditory stimuli presented in rapid succession is a well-documented deficit (for a review, see Tallal, 2004). The present ERP results show that LI children do not exhibit rate modulation of eMMN latency, perhaps because all rates are sufficiently challenging, even the slowest rate of presentation (300 ms), because all are outside the TWI for LI children who may have impaired rapid auditory processing abilities and thus higher TWI thresholds. Further, the finding that TLD children have shorter eMMN latencies as compared to LI children (300 and 70 ms ISIs) again supports the idea of generally slowed or inefficient auditory processing in children with an LI.

Statistical analyses of **rate** for the **IMMN/LDN** of LI children show that slower rates of presentation result in longer latencies in both the Ignore ($300 > 70$ and 10 ms ISI) and Attend ($300 > 10$ ms ISI³⁰) conditions. In TLD children, the same pattern is observed in the Ignore condition only ($300 > 70$ and 10), while no rate-related differences are seen in the TLD group in the Attend condition. These findings suggest that the IMM/LDN is modulated by rate similarly in TLD and LI children during passive listening, but during active listening only LI children exhibit rate-modulation³¹. So, although no group differences are observed in IMM/LDN amplitude or latency in either the Ignore or Attend condition, taken together these findings suggest that during active listening, IMM/LDN latency in LI children only is influenced by rate of presentation. These findings are summarized in Figures 8.3 c and d.

Analyses of the effects of **condition** (Ignore vs. Attend) on the **eMMN** show that in both the LI and TLD children there is an attention-related enhancement of eMMN amplitude, but no effects on eMMN latency³². In general, attention leads to larger eMMN amplitudes, reflecting possible increases in neural synchrony and/or neural recruitment, in both LI and TLD children.

In contrast, analyses of **condition** on the **IMMN/LDN** show that in both the LI and TLD groups there are no effects of attention on IMM/LDN amplitude, but attention increases IMM/LDN latency in the 70 ms ISI only. The IMM/LDN is thought to be involved in further processing of complex (often linguistic) stimuli (Cheour et al., 2001), so it is interesting to note that an attention effect observed in both LI and TLD children

³⁰ Recall that this was the only rate comparison that could be conducted in the Attend condition due to lack of sufficient data.

³¹ Due to lack of sufficient data, more specific rate observations could not be made.

³² Effects of attention specific to the different rates of presentation cannot be discussed since there was not sufficient data to conduct all comparisons.

occurs only for the ISI that is in the time range (tens of milliseconds) that is important for speech processing (Tallal & Gaab, 2006).

Finally, the analyses of **hemispheric differences** found no clear evidence suggesting hemispheric asymmetry in the eMMN or the IMMN/LDN elicited by paired complex tones with ISIs of 300, 70 and 10 ms in TLD and LI children in both the Ignore and Attend conditions. All MMN responses were found to be equal bilaterally at frontocentral, frontal and central sites. Indeed, in normally developing children, laterality has not been observed in MMN elicited by non-linguistic stimuli (Ceponiene et al., 2002), and studies describing IMMN/LDN distribution typically show symmetric responses with no left hemispheric bias (Ceponiene et al., 2002; Escera et al., 1998, 2001; Gumenyuk et al., 2001, 2004). The present results are consistent with that literature. Overall, the hemispheric analyses conducted in the present study are limited by the small numbers of channels examined and small sample sizes in some conditions. Also, a stringent self-imposed t-test interpretation criteria (alpha level of .05 in more than one pair of channels) may have contributed to null results. Future studies would do well to examine potential hemispheric differences more closely by investigating power spectra in the EEG, and conducting additional ERP analyses that include greater statistical power (more subjects).

9.0 Results of Experiment 5: Changes in Rapid Auditory Processing and Language Skills Following a Computerized Auditory Training

Program: An ERP Study

In this experiment, a subgroup of the LI children who participated in Experiment 4 completed the intervention protocol Fast ForWord-Language® (FFWD) aimed at improving RAP via adaptive sound discrimination training. The electrophysiological and behavioral procedures common to Experiments 2 and 4 were administered to assess changes in the mismatch negativity response (MMN) and language abilities in (i) LI children following the intervention, and (ii) a subgroup of children with typical language development (TLD) who participated in Experiment 2 after a time interval equivalent to the FFWD intervention (but no intervention was received). In this way intervention effects and short-term developmental changes were assessed. The results address the questions of **What types of changes occur following an intensive auditory intervention program aimed at improving RAP abilities in LI children in (i) behavioral measures of language, reading and auditory temporal processing, (ii) in MMN components, and (iii) how might such changes in behavioral and electrophysiological measures be related?**

The ERP data reported in Experiments 2 (for TLD children) and 4 (for LI children) served as Visit 1 data for the present study. Visit 1 was the first (naïve) visit for all TLD and LI participants. The ERP data described here are from Visit 2 after a subset of LI participants from Experiment 4 completed the FFWD intervention, and a subset of TLD children from Experiment 2 returned after a similar period of time. Please see

Preliminary Analyses (pp. 82 – 85) for a detailed description of the Visit 1 to Visit 2 intervals for TLD and LI participants in Experiment 5.

9.1 Event Related Potentials – Waveform Morphology - Visit 2

Visually inspecting the standard and deviant grand averaged waveforms in all channels, overall the waveforms of TLD and LI children at Visit 2 are similar to those observed at Visit 1 (Experiment 2 for TLD children, and Experiment 4 for LI children). Figures 9.1.1.1a – 9.1.1.3a (Ignore condition) and 9.1.3.2a – 9.1.3.3a (Attend condition) show the grand averaged waveforms at each electrode in topographic arrangement (top to bottom represents anterior to posterior) for TLD children, and Figures 9.1.2.1a – 9.1.2.3a (Ignore condition) and 9.1.4.2a – 9.1.4.3a (Attend condition) show the grand averaged waveforms of LI children. All subsequent descriptions of the waveforms are based on electrode Fcz (Channel 4) after verifying that activity at Fcz was similar to that of surrounding channels.

9.1.1 Ignore Condition - TLD children ERP waveform morphology – Visit 2

9.1.1.1 Ignore 300 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (2.4 uV) at 92 ms, corresponding to the P1 component. This is followed by a large negative peak (-3.2 uV) at 232 ms that is the child N2. The N2 is followed by a large positive peak (2.6 uV) at 460 ms. The last identifiable peak in the standard wave is a large negative peak (-2.8 uV) at 600 ms.

In the deviant wave, the P1 (1.7 uV) at 92 is followed by a robust N2 (-2.9 uV) at 260 ms. The next series of peaks follows a positive-negative-positive pattern and are of

similar amplitudes. First, there is a positive peak (2.3 uV) at 452 ms that has a “notch” on the positive-going part of the component at 408 ms. This “notch” is visible at frontocentral channels. The second peak is negative (-0.7 uV) at 504 ms. The third peak is positive (1.9 uV) at 568 ms. The last two identifiable peaks in the deviant wave are negative: the first (-0.8 uV) peaks at 664 ms and the second (-1.2 uV) at 800 ms.

In the difference wave, the first peak of interest is a negativity (-1.7 uV) at 488ms. This is the child eMMN. The eMMN is followed by a large positive peak (3.9 uV) at 584 ms. The final peak in the difference wave is a large negativity (-2.2 uV) at 788 ms that is the child IMMN/LDN. The early and late MMN components invert at the mastoids and are largest at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 9.1.1.1a, and channel Fcz is shown in Figure 9.1.1.1b.

9.1.1.2 Ignore 70 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (2.0 uV) at 96 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.5 uV) at 268 ms. This is the N2. There are no other identifiable peaks in the standard wave.

In the deviant wave, the first peak is the P1 (1.8 uV) at 92 ms, followed by the N2 (-2.7 uV at 264 ms) that has a “notch” on the rising (negative-going) portion of the component (-1.0 uV at 208 ms). The next peak is a smaller negativity (-0.5 uV) at 400 ms, and the last peak in the deviant wave is a negativity (-0.8 uV) at 536 ms.

In the difference wave, the posited “emerging” adult-like MMN is observed as a negative-going peak that barely crosses the baseline (-0.2 uV) at 264 ms. The next peak of interest is a small “notch” in the negative range (-0.3 uV) at 400 ms that is the child eMMN. The eMMN is maximal at central channels and inverts at the mastoids. The last

peak in the difference wave is a larger negativity (-1.5 uV) at 532 ms that is the child IMMN/LDN. The IMMN/LDN is largest at frontocentral channels. All MMN components (“emerging”, eMMN, and IMMN/LDN) invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 9.1.1.2a, and channel Fcz is shown in Figure 9.1.1.2b.

9.1.1.3 Ignore 10 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (1.3 uV) at 88 ms, corresponding to the P1 component. The P1 is followed by a large N2 (-2.5 uV) at 216 ms. After the N2, there is a small “notch” (-1.0 uV at 328 ms) on the latter positive-going portion of the component that is visible at frontocentral channels. There are no additional peaks in the standard wave.

In the deviant wave, the first peak is the P1 (1.6 uV) at 88 ms, followed by a small negative-going peak (0.3 uV) that does not cross the baseline at 128 ms. After this, the deviant wave dips in the positive direction (0.9 uV, 156 ms) and then rises to a robust N2 (-2.0 uV) at 216 ms. After the N2, the last peak in the deviant wave is a smaller, broad negativity (-0.7 uV) at 440 ms.

In the difference wave, the only peak of interest is a large, broad negativity (-1.1 uV) at 448 ms that is the child IMMN/LDN. The IMMN/LDN inverts at the mastoids and is maximal at frontocentral channels. There is no eMMN identified in the difference wave. All electrodes in topographic arrangement are shown in Figure 9.1.1.3a, and channel Fcz is shown in Figure 9.1.1.3b.

9.1.2 Ignore Condition - LI children ERP waveform morphology – Visit 2

9.1.2.1 Ignore 300 ms ISI: LI Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (2.1 uV) at 92 ms, corresponding to the P1 component. This is followed by a large negative peak (-2.5 uV) at 232 ms that is the child N2. The N2 is followed by a large positive peak (2.4 uV) at 464 ms that has a “notch” on the positive-going part of the component (0.4 uV) at 400 ms. The last identifiable peak in the standard wave is a large negative peak (-1.9 uV) at 600 ms.

In the deviant wave, the first peak is the P1 (2.2 uV) at 96 is followed by a robust N2 (-2.7 uV) at 232 ms. The next series of peaks follows a positive-negative-positive pattern. The first peak is a positivity (2.1 uV) at 456 ms that has a “notch” on the positive-going portion of the component (0.2 uV) at 400 ms. The second peak is negative (-0.6 uV) at 512 ms. The third peak is positive (2.2 uV) at 572 ms. The last identifiable peak in the deviant wave is a negativity (-1.2 uV) at 804 ms.

In the difference wave, the first peak of interest is negative (-1.5 uV) at 500 ms, is most prominent at frontocentral channels and inverts at the mastoids. This is the child eMMN. The eMMN is followed by a large positive peak (3.7 uV) at 580 ms, and the final peak in the difference wave is a negativity (-1.6 uV) at 796 ms that is the child IMMN/LDN. The early and late MMN components invert at the mastoids and are largest at frontocentral channels. All electrodes in topographic arrangement are shown in Figure 9.1.2.1a, and channel Fcz is shown in Figure 9.1.2.1b.

9.1.2.2 Ignore 70 ms ISI: LI Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (1.9 uV) at 96 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.7 uV) at 260 ms. This is the N2. After the N2, the standard wave returns to baseline level activity.

In the deviant wave, the first peak is the P1 (1.8 uV) at 96 ms, followed by the N2 (-2.7 uV at 268 ms) that has a “notch” on the rising (negative-going) portion of the component (-1.2 uV at 204 ms). The N2 is followed by a large positive peak (1.7 uV) at 356 ms, and the last peak in the deviant wave is a negativity (-1.5 uV) at 552 ms.

In the difference wave, the posited “emerging” adult-like MMN is observed as a negative-going peak that barely crosses the baseline (-0.01 uV) at 272 ms. The second and last peak in the difference wave is a large negativity (-2.1 uV) at 564 ms that is the child IMMN/LDN. The early MMN is not present in the difference wave. This is likely due to the large positive component (P3) following the N2 in the deviant wave. This P3 component is not present in the standard and deviant waveforms at Visit 1, but is quite robust at Visit 2. The “emerging” MMN and IMMN/LDN components are largest at frontocentral channels and invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 9.1.2.2a, and channel Fcz is shown in Figure 9.1.2.2b.

9.1.2.3 Ignore 10 ms ISI: LI Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (2.0 uV) at 92 ms, corresponding to the P1 component. The P1 is followed by a large N2 (-3.0 uV) at 224ms. The N2 is the last identifiable peak in the standard wave.

In the deviant wave, the first peak is the P1 (1.9 uV) at 88 ms, followed by a robust N2 (-1.9 uV) at 236 ms. There is a small “notch” (-0.3 uV at 140 ms) on the rising

portion of the component that is visible at frontocentral channels. After the N2, the last peak in the deviant wave is a negativity (-1.4 uV) at 452 ms.

In the difference wave, the first peak of interest is the posited emerging adult-like MMN that appears as a negative-going peak in the positive range (0.6 uV) at 276 ms. The second and last peak of interest is a large, broad negativity (-1.3 uV) at 456 ms that is the child IMMN/LDN. The emerging MMN and the IMMN/LDN invert at the mastoids and are maximal at frontocentral channels. There is no eMMN identified, likely due to the robust positivity (P3) that follows the N2 in the deviant wave. This positive (P3) component is not present at Visit 1 in the standard and deviant waves. All electrodes in topographic arrangement are shown in Figure 9.1.2.3a, and channel Fcz is shown in Figure 9.1.2.3b.

9.1.3 Attend Condition – TLD Children ERP Waveform Morphology – Visit 2

9.1.3.1 Attend 300 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

Data from only three TLD participants was available for the grand average of the Attend 300 ms ISI condition at Visit 2, and so this data will not be reported. Three individual averages are not sufficient to create a representative grand average due to considerable variability in individual averaged waveforms, especially in this young age group.

9.1.3.2 Attend 70 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (1.9 uV) at 88 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.9

uV) at 248 ms. This is the N2. After the N2, there are no other identifiable peaks in the standard wave.

In the deviant wave, the first peak is a positivity (1.5 uV) at 92 ms, corresponding to the P1. The P1 is followed by a large N2 (-3.3 uV at 264 ms) that has a “notch” on the rising (negative-going) portion of the component (-1.5 uV at 176 ms). This notch is more apparent at central channels, and appears as a peak (resulting in a N2 with multiple peaks) at frontal channels. The N2 is followed by a positivity (1.8 uV) at 348 ms, and then a smaller negative peak (-0.6 uV) at 420 ms. The next peak is a positivity (1.4 uV) at 532 ms, and the last peak in the deviant wave is a negativity (-1.2 uV) at 704 ms.

In the difference wave, the posited “emerging” adult-like MMN is observed as a negative-going peak (-0.4 uV) that barely crosses the baseline at 268 ms. The next peak is the eMMN (-0.7 uV) at 408 ms, and the last peak in the difference wave is the IMM/LDN (-1.2 uV) at 696 ms. All MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 9.1.3.2a, and channel Fcz is shown in Figure 9.1.3.2b.

9.1.3.3 Attend 10 ms ISI: TLD Children ERP Waveform Morphology – Visit 2

It should be noted that there are only four individual averages in the TLD children’s Attend 10 ms ISI grand average at Visit 2, and thus the waveforms described below may contain a bit more noise than the grand averages that consist of a greater number of individual averages (e.g. Attend 70 ms ISI, TLD children at Visit 2 has 12 individual averages in the grand average waveform).

The first peak in the standard wave is a positivity (2.2 uV) at 76 ms, corresponding to the P1 component. The P1 is followed by a large N2 (-2.9 uV) at 212 ms. On the latter positive-going portion of the N2 there is small negative “bump” (-1.5 uV, 308 ms) that appears as a distinct peak at all frontocentral channels. After this, there is a positive peak (1.5 uV) at 472 ms followed by a small negativity (-0.4 uV) at 576 ms. This is the last identifiable peak in the standard wave.

In the deviant wave, the first peak is the P1 (1.8 uV) at 88 ms, followed by a small “notch” (0.2 uV, 140 ms), before rising to a large negative peak (-2.1 uV) at 220 ms that is the child N2 of the deviant wave. The N2 is followed by a small positive deflection (0.8 uV) at 296 ms, then a small negative peak (-0.8 uV) at 360 ms. The last peak in the deviant wave is a negativity (-1.1 uV) at 568 ms.

In the difference wave, the first peak of interest is a small negative-going peak that does not cross the baseline (0.7 uV) at 224 ms that is the potential “emerging” adult-like MMN. The next peak of interest is a negativity (-0.7 uV) at 472 ms that has maximal amplitudes at central and parietal channels. Next, there is another negative peak of similar size (-0.8 uV) at 616 ms that is the late MMN (IMMN). The IMMN is distributed in more frontal channels and is larger at right and midline channels. The IMMN is not really visible in left frontocentral channels. The “emerging” and late MMN components invert at the mastoids. All electrodes in topographic arrangement are shown in Figure 9.1.3.3a, and channel Fcz is shown in Figure 9.1.3.3b.

9.1.4 Attend Condition - LI children ERP waveform morphology – Visit 2

9.1.4.1 Attend 300 ms ISI: LI Children ERP Waveform Morphology

Data from only one LI participant was available for the Attend 300 ms ISI condition, and so no grand average could be computed. No morphological descriptions are reported.

9.1.4.2 Attend 70 ms ISI: LI Children ERP Waveform Morphology – Visit 2

The first peak in the standard wave is a positivity (1.9uV) at 88 ms, corresponding to the P1 component. The P1 is followed by a large negative peak (-2.6 uV) at 248 ms. This is the N2. After the N2, the last identifiable peak is a small negative-going “bump” that just reaches the baseline (0.0 uV) at 460 ms.

In the deviant wave, the first peak is a positivity (1.5 uV) at 88 ms, corresponding to the P1. The P1 is followed by a large N2 (-3.2 uV at 272 ms) that has a smaller peak on the rising (negative-going) portion of the component (-2.1 uV at 184 ms). This “notch” is more apparent at central channels, and appears as a distinct peak (resulting in a N2 with two distinct peaks) at more frontal channels. The N2 is followed by a large positivity (2.1 uV) at 372 ms, and then a small negative peak (-0.2 uV) at 456 ms. The next peak is a positivity (1.5 uV) at 536 ms, and the last peak in the deviant wave is a broad negativity (-0.8 uV) peaking at 712 ms.

In the difference wave, the “emerging” adult-like MMN is observed as a negative peak (-0.9 uV) at 276 ms. The next peak is a small eMMN (-0.2 uV) at 448 ms that barely crosses the baseline, and the last peak in the difference wave is a broad negativity (-1.0 uV) peaking at 748 ms. The emerging adult-like MMN inverts at both the left and right mastoids, and the eMMN inversion is more apparent on the right side. Both the emerging and eMMN have frontocentral distributions. The last negativity in the difference wave is

not identified as the IMMN/LDN because there is no inversion of polarity at the mastoids. All electrodes in topographic arrangement are shown in Figure 9.1.4.2a, and channel Fcz is shown in Figure 9.1.4.2b.

9.1.4.3 Attend 10 ms ISI: LI Children ERP Waveform Morphology – Visit 2

It should be noted that there are five individual averages in the LI children's Attend 10 ms ISI grand average at Visit 2, and thus the waveforms described below may contain more noise than the grand averages that consist of a greater number of individual averages (e.g. Attend 70 ms ISI, LI children at Visit 2 has 17 individual averages in the grand average waveform).

The first peak in the standard wave is a positivity (1.7 uV) at 84 ms, corresponding to the P1 component. The P1 is followed by a large N2 (-2.6 uV) at 216 ms. There are no other identifiable peaks in the standard wave.

In the deviant wave, the first peak is the P1 (1.4 uV) at 84 ms, followed by a small “notch” (-0.8 uV, 140 ms), before rising to a large negative peak (-2.1 uV) at 220 ms that is the child N2 of the deviant wave. The N2 is followed by a smaller negative peak (-1.4 uV) at 396 ms, and then a large positivity (1.9 uV) at 480 ms. The last peak in the deviant wave is a negativity (-1.4 uV) at 576 ms.

In the difference wave, the first peak of interest is a small negative-going peak that barely crosses the baseline (-0.02 uV) at 268 ms that is the emerging adult-like MMN. The next peak of interest is a negativity (-1.8 uV) at 408 ms that is the child eMMN, followed by a large positivity (1.6 uV) at 484 ms. The last peak in the difference wave is a negativity (-1.8 uV) at 576 ms that is the child IMMN/LDN. This IMMN/LDN

is broad and appears to have multiple peaks. The emerging adult-like MMN has the largest inversion at mastoid channels due to the large N2, and the eMMN and the IMM/LDN have smaller inversions. All posited MMN components have a frontocentral distribution. All electrodes in topographic arrangement are shown in Figure 9.1.4.3a, and channel Fcz is shown in Figure 9.1.4.3b.

9.2 Event Related Potentials – Statistical Analyses

Series of mixed factors ANOVAs were planned to investigate changes in eMMN and IMM/LDN peak amplitude and latency from Visit 1 to Visit 2 in TLD and LI children. The main research question is: **Does eMMN/IMMN amplitude/latency change from Visit 1 to Visit 2 differently in TLD (no intervention) as compared to LI children (FFWD intervention)?**

For each rate of presentation (300, 70, 10 ms ISI) within each condition (Ignore, Attend), mixed factors ANOVAs were conducted to investigate changes in eMMN and IMM/LDN peak amplitude and latency. For midline channels Fcz (Ch. 4) and Cz (Vertex), Visit (Visit 1, Visit 2) x Group (TLD, LI) ANOVAs were conducted. Additionally, for pairs of frontocentral (Ch. 17 and 54), frontal (Ch. 13 and 62) and central (Ch. 21 and 53) channels, Visit (Visit 1, Visit 2) x Hemisphere (Right, Left) x Group (TLD, LI) ANOVAs were conducted. Significant main effects or interactions were further investigated by examining simple effects via repeated measures t-tests within each group of children comparing MMN amplitudes or latencies at Visit 1 and Visit 2 (for a full description of repeated measures t-tests and guidelines for interpretation, please see Analytic Strategies (pp. 71 - 72)).

As these analyses were being set up, it was noted that in many of the planned ANOVAs the repeated measures sample sizes were either extremely small and/or disparate (e.g. Ignore 10 ms ISI, eMMN: TLD $n = 5$, LI $n=10$). This was due to the exclusion of individual participants who had insufficient data for analyses (i.e. large numbers of artifacts and thus < 50 acceptable trials for averaging in either the standard or deviant wave, or both) (see p. 96 for number of participants with sufficient data for averaging) or exhibited an abnormal or absent MMN component(s) in the time windows of interest (determined from visual inspection, see pp. 95 – 96) at Visit 1 and/or Visit 2. So, although these experiments were designed and carried out with acceptable numbers of participants in each block type, the data sometimes contained a large number of artifacts, especially in the block types that were administered toward the end of the session when children were becoming fatigued and restless. Unfortunately, difficulties with artifacts are not uncommon in ERP studies with young children.

The planned analyses that included very small and/or disparate sample sizes lacked sufficient power to detect significant effects, and thus the ANOVAs were not carried out. These are noted in the descriptions of results that follow. In these cases, where possible, the simple effects were examined to look for patterns of results that informed the research question. Descriptive statistics for Visit 2 are reported (see 8.0 Results of Experiment 4 for Visit 1 results). Ranges of t statistic and p values are reported for significant simple effects comparisons.

9.2.1 eMMN analyses for the Ignore Condition, Visit 1 to Visit 2

Descriptive statistics are shown in Tables 9.2.1a – c for the eMMN in the Ignore condition.

9.2.1.1 Ignore 300 ms ISIs - eMMN, Visit 1 to Visit 2

Ignore 300 ms ISI – eMMN Amplitude, Visit 1 to Visit 2: Mixed factors

ANOVAs revealed a main effect of Visit at Cz ($F=5.80$, $p<.05$) and bilateral frontocentral channels ($F=21.46$, $p<.05$), with eMMN amplitude at Visit 1 smaller than at Visit 2.

There is also a main effect of Hemisphere at frontocentral channels ($F=5.99$, $p<.05$), with eMMN amplitude smaller on the left than on the right. Significant Visit x Group interactions at Fcz ($F=6.28$, $p<.05$) and bilateral frontocentral channels ($F=6.38$, $p<.05$) were revealed.

Examination of the simple effects for the main effect of Hemisphere revealed that there are no differences in eMMN amplitude between the left and right hemispheres in the TLD and LI groups for both Visit 1 and Visit 2. Thus, the significant main effect resulted only from the pooling of the two groups, and does not inform the research question about how the TLD and LI groups may differ between Visit 1 and Visit 2.

Examination of the simple effects for the Visit x Group interaction show that eMMN amplitude significantly increases from Visit 1 to Visit 2 for the TLD children ($t_6 = 0.15 - 5.11$, $p = .887 - .002$), but does not significantly change for LI children.

Overall, in frontocentral regions, in TLD children eMMN amplitude significantly increases from Visit 1 to Visit 2, while LI children do not show any evidence of eMMN amplitude change in the Ignore 300 ms ISI condition.

Ignore 300 ms ISIs – eMMN Latency, Visit 1 to Visit 2: At bilateral frontocentral ($F=8.57$, $p<.05$), frontal ($F=4.29$, $p<.05$) and central ($F=9.33$, $p<.05$) channels there is a main effect of Visit, such that eMMN latencies are longer at Visit 1 as compared to Visit 2 ($\text{Visit 1} > \text{Visit 2}$). At bilateral central channels only, there is a main effect of Hemisphere ($F=7.89$, $p<.05$), with eMMN latencies on the Left greater than that on the Right.

These main effects were followed up with examination of simple effects within each group. For the main effect of Visit, it was found that eMMN latency do not significantly change from Visit 1 to Visit 2 in either the TLD or LI group. For the main effect of Hemisphere, it was found that there are no significant hemispheric differences at Visit 1 or Visit 2 for either the TLD or LI group. Thus, the main effects of Visit and Hemisphere results only from the pooling of the two groups, due to a larger sample size and therefore more power in the ANOVAs, and does not inform the research question of how eMMN latencies may change differently in the TLD and LI groups from Visit 1 to Visit 2.

Summary – Ignore 300 ms ISI, eMMN, Visit 1 to Visit 2: At Fcz and bilateral frontocentral channels, eMMN amplitude increases from Visit 1 to Visit 2 in TLD children ($\text{Visit 1} < \text{Visit 2}$) only. There are no significant changes in eMMN amplitude for LI children. There are no Visit related changes in eMMN latency in either group.

9.2.1.2 Ignore 70 ms ISIs - eMMN, Visit 1 to Visit 2

Ignore 70 ms ISIs – eMMN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Group at bilateral frontal channels ($F=4.29$, $p<.05$)

and midline channel Fcz ($F=5.00$, $p<.05$), with TLD children having smaller eMMN amplitudes as compared to LI children. Also, at bilateral frontal channels, there is a significant Hemisphere x Group interaction ($F=4.52$, $p<.05$).

Examination of the simple effects revealed that for the main effect of Group, the TLD and LI groups do not significantly differ in eMMN amplitude at Visit 1, but at Visit 2 the LI children have significantly greater eMMN amplitudes than TLD children ($t_{32} = -0.05 - 2.13$, $p = .959 - .041$). To follow up on the Hemisphere x Group interaction, the simple effects revealed that at both Visit 1 and Visit 2 there are no significant differences between eMMN amplitude in the left and right hemispheres for both TLD and LI children. Thus, the interaction resulted from the analyses of data across both Visits, but did not reveal any hemispheric differences within or between the two groups of children at individual visits.

In sum, these analyses show that during passive listening (Ignore condition), tones presented in pairs with a 70 ms ISI elicit larger eMMNs in LI children as compared to TLD children *only* at Visit 2, after the LI children completed the FFWD intervention. The eMMN amplitudes do not significantly differ between the two groups at Visit 1.

Ignore 70 ms ISIs – eMMN Latency, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Visit at midline channels Fcz ($F=7.82$, $p<.05$) and Cz, ($F=5.46$, $p<.05$), and bilateral frontocentral ($F=8.48$, $p<.01$) channels, with eMMN latencies shorter at Visit 1 as compared to Visit 2 ($\text{Visit 1} < \text{Visit 2}$). There is also a main effect of Group at all channels examined: midline channels Fcz ($F=7.77$, $p<.05$) and Cz, ($F=26.40$, $p<.001$), and bilateral frontocentral ($F=30.88$, $p<.001$), frontal ($F=8.47$, $p<.01$) and central ($F=8.28$, $p\leq.01$) channels, with TLD children exhibiting shorter eMMN latencies

than LI children (TLD < LI). There is also a significant Visit x Group interaction ($F=7.06$, $p<.05$) at bilateral frontal channels.

Examination of the simple effects revealed that for the main effect of Visit, there are no significant differences between eMMN latencies at Visit 1 and Visit 2 for the TLD children, but in the LI group eMMN latencies are significantly smaller at Visit 1 as compared to Visit 2 (Visit 1 < Visit 2; $t_{11} = -2.94 - -1.20$, $p = .014 - .254$). This is the expected result, as longer latencies often accompany components with larger amplitudes, and LI children exhibited eMMNs with larger amplitudes and longer latencies at Visit 2, after FFWD intervention. Examination of the simple effects revealed that for the main effect of Group, at both Visit 1 and Visit 2, TLD children have significantly shorter latencies than LI children (TLD < LI; Visit 1: $t_{32} = -4.34 - -1.76$, $p = .000 - .089$; Visit 2: $t_{32} = -5.61 - -1.79$, $p = .000 - .083$). Examining simple effects for the Visit x Group interaction addresses the question of whether eMMN latencies change from Visit 1 to Visit 2 differently in TLD as compared to LI children. Paired samples t-tests showed that eMMN latencies do not significantly change for TLD children, but for the LI children, eMMN latencies increase from Visit 1 to Visit 2 (LI: $t_{11} = -2.94 - -1.20$, $p = .014 - .254$).

Summary – Ignore 70 ms ISI, eMMN, Visit 1 to Visit 2: Statistical analyses of eMMN amplitude revealed that TLD and LI groups do not significantly differ in eMMN amplitude at Visit 1, but at Visit 2 the LI children have significantly larger eMMN amplitudes than TLD children. Additionally, analyses of eMMN latencies showed that there are no significant differences in eMMN latencies between Visit 1 and Visit 2 for the TLD children, but in the LI group eMMN latencies are significantly shorter at Visit 1 as compared to Visit 2 (Visit 1 < Visit 2). The longer latencies at Visit 2 in the LI group

accompany larger eMMN amplitudes. There are no such changes exhibited by the TLD group. The changes exhibited by the LI children reflect alterations in the automatic auditory discrimination of tone pairs with a 70 ms ISI after intervention.

9.2.1.3 Ignore 10 ms ISIs - eMMN, Visit 1 to Visit 2

The mixed factors ANOVAs planned for the Ignore 10 ms ISI condition were found to have small and disparate sample sizes (TLD $n=5$, LI $n=10$) and so the results are interpreted with caution. Simple effects were examined in all cases since there was not sufficient confidence in the results of the ANOVAs.

Ignore 10 ms ISIs – eMMN Amplitude, Visit 1 to Visit 2: The series of mixed factors ANOVAs revealed no significant effects for eMMN amplitude in the Ignore 10 ms ISI condition. Simple effects comparisons examining eMMN amplitude changes from Visit 1 to Visit 2 within each group showed that in both the TLD and LI groups there are no significant Visit related changes. Simple effects were also examined to look at effects of Group, and there are no significant differences at either Visit 1 or Visit 2.

Ignore 10 ms ISIs – eMMN Latency, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Visit at midline channels Fcz ($F=5.06$, $p<.05$) and Cz, ($F=6.02$, $p<.05$), and bilateral frontocentral ($F=15.08$, $p<.01$) and central ($F=8.34$, $p<.05$) channels, with eMMN latencies longer at Visit 1 as compared to Visit 2 (Visit 1 > Visit 2). There is also a main effect of Group at Fcz ($F=5.68$, $p<.05$) and Cz, ($F=7.58$, $p<.05$), and bilateral frontocentral ($F=8.51$, $p<.01$) and frontal ($F=8.39$, $p<.05$) channels, with TLD children having shorter eMMN latencies than LI children. A significant Visit x Group interaction

is observed in Fcz ($F=5.39$, $p<.05$) and Cz, ($F=6.02$, $p<.05$), and bilateral frontocentral ($F=10.09$, $p<.01$) and frontal ($F=5.31$, $p<.05$) channels.

Examination of the simple effects for the main effect of Visit and the Visit x Group interaction revealed that in the TLD group eMMN latency is larger at Visit 1 as compared to Visit 2 (Visit 1 > Visit 2; $t_4 = 1.47 - 3.64$, $p = .217 - .022$). However, in the LI group, there is no significant change in eMMN latency across visits. Additionally, simple effects comparisons investigating Group revealed that at Visit 1, TLD and LI children have comparable eMMN latencies, but at Visit 2 the TLD children have significantly shorter latencies than LI children (TLD < LI; $t_{14} = -3.81 - -1.87$, $p = .002 - .083$). The interaction shows that only TLD children exhibit a decrease in eMMN latency from Visit 1 to Visit 2. There is no change in the LI group. The findings suggest that changes in auditory processing due to FFWD intervention may not be apparent for passive processing of tone pairs separated by a 10 ms ISI. The decrease in eMMN latency seen in the TLD group may be due to effects of previous exposure or experience with the stimuli. Short-term maturational effects are not suspected, as these would likely be observed in both groups.

In sum, in the Ignore 10 ms ISI condition eMMN latency in the TLD group decreases from Visit 1 to Visit 2, while there is no significant change in the LI group.

9.2.2 eMMN Analyses for the Attend Condition, Visit 1 to Visit 2

Descriptive statistics are shown in Tables 9.2.2a – b for the eMMN in the Attend condition.

9.2.2.1 Attend 300 ms ISI - eMMN, Visit 1 to Visit 2

The mixed factors ANOVAs planned for the Attend 300 ms ISI condition were not able to be run because there were only 3 participants in the TLD group, and zero participants in the LI group with sufficient data for analyses. So, simple effects comparisons were conducted only for the TLD group.

Attend 300 ms ISI – eMMN Amplitude, Visit 1 to Visit 2: The paired samples t-tests conducted for the TLD children only, comparing eMMN amplitude at Visit 1 and Visit 2 did not reveal any significant effects.

Attend 300 ms ISI – eMMN Latency, Visit 1 to Visit 2: The paired samples t-tests conducted for the TLD children only, comparing eMMN latency at Visit 1 and Visit 2, did not reveal any significant effects.

Summary – Attend 300 ms ISI, eMMN, Visit 1 to Visit 2: The planned mixed factors ANOVAs could not be conducted due to very limited data (TLD n=3, LI n=0). Simple effects comparisons for the TLD group did not reveal any significant differences in eMMN amplitude or latency between Visit 1 and Visit 2 during active listening to tones presented with a 300 ms ISI. These analyses lack power, and so no definitive conclusions can be drawn from this set of null results.

9.2.2.2 Attend 70 ms ISI - eMMN, Visit 1 to Visit 2

Attend 70 ms ISI - eMMN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a significant main effect of Hemisphere at bilateral frontal channels ($F=5.44$, $p<.05$) with lower amplitudes on the Left as compared to the Right side. There is also a significant Hemisphere x Group interaction at bilateral frontal channels ($F=5.78$, $p<.05$). Examination of the simple effects revealed that in both the TLD and LI groups, there are

no significant hemispheric differences in eMMN amplitude at either Visit 1 or Visit 2.

The Hemisphere x Group interaction showed that, across both Visits, eMMN amplitude is smaller at the left as compared to the right frontal channel (Left < Right) for the LI group only. There are no notable hemispheric differences in eMMN amplitude in the TLD group. However, these differences in the LI group do not reach significance in the paired t-test analyses. The simple effects for Group-related differences do not reveal any significant differences between TLD and LI children at Visit 1 or Visit 2.

Attend 70 ms ISI - eMMN Latency, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Visit at all channels examined: midline channels Fcz ($F=5.53$, $p<.05$) and Cz, ($F=8.57$, $p<.05$), and bilateral frontocentral ($F=5.89$, $p<.05$), frontal ($F=7.26$, $p<.05$) and central ($F=10.04$, $p<.01$) channels, with eMMN latencies longer at Visit 1 as compared to Visit 2. There are no other main effects or significant interactions. Examination of the within-groups simple effects show that in the TLD group there is no significant difference in eMMN latency between Visit 1 and Visit 2, while the LI group show a significant decrease in latency from Visit 1 to Visit 2 (Visit 1 > Visit 2; $t_9 = 1.57 - 3.10$, $p = .150 - .013$). Additionally, examination of the between-groups simple effects do not reveal any significant differences in eMMN latency between TLD and LI children at Visit 1 or Visit 2 in the Attend 70 ms ISI condition. In sum, only LI children show a decrement in eMMN latency during active listening to tones presented with a 70 ms ISI.

Summary – Attend 70 ms ISI, eMMN, Visit 1 to Visit 2: The Mixed factors ANOVAs revealed a significant main effect of Hemisphere and a significant Hemisphere x Group interaction in analyses of eMMN amplitude, but the simple effects failed to show any Hemisphere-related differences in either the TLD or LI group. The analyses of

latency revealed that *only* LI children show a decrement in eMMN latency during active listening to tones presented with a 70 ms ISI.

9.2.2.3 Attend 10 ms ISI – eMMN, Visit 1 to Visit 2

The mixed factors ANOVAs planned for the Attend 10 ms ISI condition could not be run because there were only 3 participants in the TLD group, and 2 participants in the LI group with sufficient data for analyses. So, simple effects comparisons were conducted only for the TLD group, and are interpreted with great caution give the extremely small sample size.

Attend 10 ms ISI - eMMN Amplitude, Visit 1 to Visit 2: The paired samples t-tests conducted for the TLD children only, comparing eMMN amplitude at Visit 1 and Visit 2 did not reveal any significant effects.

Attend 10 ms ISI – eMMN Latency, Visit 1 to Visit 2: The paired samples t-tests conducted for the TLD children only, comparing eMMN latency at Visit 1 and Visit 2, did not reveal any significant effects.

Summary – Attend 10 ms ISI, eMMN, Visit 1 to Visit 2: The planned mixed factors ANOVAs could not be conducted due to very limited data (TLD n=3, LI n=2). Simple effects comparisons, cautiously interpreted for the TLD group did not reveal any significant differences in eMMN amplitude or latency between Visit 1 and Visit 2 during active listening to tones presented with a 10 ms ISI. These analyses lack power, and so no conclusions can be drawn from this set of null results.

9.2.3 IMM/LDN analyses for the Ignore Condition, Visit 1 to Visit 2

Descriptive statistics are shown in Tables 9.2.3a – c for the IMMN/LDN in the Ignore condition.

9.2.3.1 Ignore 300 ms ISI – IMMN/LDN, Visit 1 to Visit 2

Ignore 300 ms ISI – IMMN/LDN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a significant Visit x Hemisphere interaction at bilateral frontal channels ($F=7.22$, $p<.05$). Examination of the simple effects of Hemisphere revealed no significant differences in IMMN/LDN amplitude between the Left and Right sides for the TLD or LI groups. Examination of the simple effects of Visit revealed no significant differences in IMMN/LDN amplitude from Visit 1 to Visit 2 for the TLD children, but in the LI group IMMN/LDN amplitude is significantly smaller at Visit 1 as compared to Visit 2 ($t_8 = 0.56 - 5.15$, $p = .590 - .001$).

Mixed factors ANOVAs also revealed a significant Visit x Group interaction at bilateral central channels ($F=5.77$, $p<.05$). As described above, the simple effects of Visit showed that only the LI children exhibit a significant change in IMMN/LDN amplitude from Visit 1 to Visit 2 (Visit 1 > Visit 2). There are no significant Visit-related differences in the TLD group. Examination of the simple effects of Group revealed no differences between the TLD and LI children at Visit 1 or Visit 2.

Overall, in frontal and central regions, in LI children IMMN/LDN amplitude significantly increases from Visit 1 to Visit 2, while TLD children do not show such changes in the Ignore 300 ms ISI condition.

Ignore 300 ms ISI – IMMN/LDN Latency, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a significant main effect of Visit at midline channels Fcz ($F=22.62$, $p<.001$) and Cz, ($F=8.01$, $p<.05$), and bilateral frontocentral ($F=16.07$, $p<.01$), frontal

($F=21.85$, $p<.01$) and central ($F=75.32$, $p<.001$) channels, with IMMN/LDN latencies longer at Visit 1 as compared to Visit 2. Examination of the simple effects revealed that in both the TLD and LI groups, IMMN/LDN latency significantly decreases from Visit 1 to Visit 2 (Visit 1 > Visit 2; TLD: $t_4 = 0.91 - 4.60$, $p = .415 - .010$; LI: $t_8 = 1.04 - 4.85$, $p = .327 - .001$).

Mixed factors ANOVAs also revealed a significant Hemisphere x Group interaction at bilateral frontal channels ($F=8.97$, $p<.05$). Examination of the simple effects of Hemisphere showed that neither group exhibited significantly different IMMN/LDN latencies on the Left as compared to the Right sides. Examination of the simple effects of Group showed that there are no significant differences between the TLD and LI children's IMMN/LDN latencies at Visit 1 or Visit 2. Thus, the Hemisphere x Group interaction results from combining data from Visits 1 and 2, and does not address the main research question of how IMMN/LDN latencies change from Visit 1 to Visit 2 in TLD and LI children.

Summary – Ignore 300 ms ISI, IMMN/LDN, Visit 1 to Visit 2: Overall, in LI children IMMN/LDN amplitude significantly increases from Visit 1 to Visit 2, while TLD children do not show such changes. In both the TLD and LI groups, IMMN/LDN latency significantly decreases from Visit 1 to Visit 2 (Visit 1 > Visit 2).

9.2.3.2 Ignore 70 ms ISI – IMMN/LDN, Visit 1 to Visit 2

Ignore 70 ms ISI – IMMN/LDN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Group at midline channel Cz ($F=5.40$, $p<.05$), with TLD children exhibiting smaller amplitudes than LI children (TLD < LI). There is also a

main effect of Visit at bilateral frontocentral ($F=4.36$, $p<.05$) and central ($F=4.66$, $p<.05$) channels, reflecting smaller amplitudes at Visit 1 as compared to Visit 2 (Visit 1 < Visit 2).

Examination of the simple effects for Group showed no significant group differences in IMMN/LDN amplitudes at Visit 1 or Visit 2. Further, examination of the simple effects for Visit also failed to reveal any significant differences in IMMN/LDN amplitude between Visit 1 and Visit 2 for both TLD and LI children. Thus, the main effects revealed in the ANOVAs result from the combination of data and do not reflect pre- to post-intervention changes in IMMN/LDN amplitude specific to either group of participants.

Ignore 70 ms ISI – IMMN/LDN Latency, Visit 1 to Visit 2: Mixed factors
ANOVAs revealed a significant Visit x Group interaction at bilateral frontal channels ($F=4.60$, $p<.05$), and a Hemisphere x Group interaction also at bilateral frontal channels ($F=4.97$, $p<.05$). Examination of the simple effects did not reveal any significant differences between each Group (TLD vs. LI within Visit), Visit (Visit 1 vs. Visit 2 within Group), or Hemisphere (Left vs. Right within Group and within Visit).

So, even in the absence of significant simple effects, the Visit x Group interaction illustrates that TLD and LI children exhibit different patterns of change in IMMN/LDN latency, with TLD children decreasing and LI children increasing from Visit 1 to Visit 2. Additionally, the Hemisphere x Group interaction suggests that over both visits, LI children show a Left > Right pattern for IMMN/LDN latency, while TLD children show a Left < Right pattern.

Summary – Ignore 70 ms ISI, IMMN/LDN, Visit 1 to Visit 2: Analyses of IMMN/LDN amplitudes elicited by pairs of tones separated by a 70 ms ISI during passive listening did not reveal any significant interactions that addressed the research question of how TLD and LI children's auditory discrimination processing may change from Visit 1 to Visit 2. However, the analyses of IMMN/LDN latency revealed a Visit x Group interaction demonstrating that TLD and LI children showed different patterns of change: IMMN/LDN latency from Visit 1 to Visit 2 decreases in TLD children and increases in LI children. There was also a Hemisphere x Group interaction, but this did not elucidate any changes between Visits 1 and 2 in the two groups.

9.2.3.3 Ignore 10 ms ISI – IMMN/LDN, Visit 1 to Visit 2

Ignore 10 ms ISI – IMMN/LDN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a significant main effect of Group at bilateral frontocentral ($F=5.55$, $p<.05$) and frontal ($F=18.19$, $p<.01$) channels. There are several significant interactions: at midline channel Cz there is a Visit x Group interaction ($F=4.60$, $p\leq.05$); at bilateral frontal channels there is a Hemisphere x Group interaction ($F=6.77$, $p<.05$) and a Visit x Hemisphere interaction ($F=7.01$, $p<.05$). Given the rather small and disparate sample sizes (TLD $n=5$, LI $n=9$), these findings are interpreted with caution.

Examination of the simple effects did not reveal any group differences in IMMN/LDN amplitude between TLD and LI children at Visit 1 or Visit 2 (Group), nor between Visit 1 and Visit 2 within each group (Visit). Also, no Hemispheric differences were found in the simple effects analyses. In sum, since the sample sizes are small and unequal, the results of the ANOVAs are interpreted with caution. Further, because there

are no significant finding in the simple effects analyses, it is difficult to formulate any definitive conclusions from these analyses of IMMN/LDN amplitude elicited by pairs of tones separated by a 10 ms ISI.

Ignore 10 ms ISI – IMMN/LDN Latency, Visit 1 to Visit 2: Mixed factors

ANOVAs revealed a significant main effect of Group at bilateral central channels ($F=10.29$, $p<.01$), with TLD children exhibiting shorter latencies than LI children. There is a main effect Visit at midline channel Fcz ($F=11.01$, $p<.01$), and bilateral frontocentral ($F=11.87$, $p<.01$), frontal ($F=4.78$, $p<.05$) and central ($F=19.46$, $p<.01$) channels, with latencies at Visit 1 longer than those at Visit 2. There is also a significant Visit x Group interaction in all regions analyzed: midline channels Fcz ($F=7.21$, $p<.05$) and Cz ($F=4.70$, $p<.05$), and bilateral frontocentral ($F=8.61$, $p<.05$), frontal ($F=5.26$, $p<.05$) and central ($F=10.83$, $p<.01$) channels. In all cases, the interaction reflects a decrease in TLD IMMN/LDN latency from Visit 1 to Visit 2, but relatively little change in the LI group.

Examination of the simple effects for Group revealed that TLD children have significantly shorter latencies than LI children at Visit 2 only ($t_{14} = -3.61$ - -1.70 , $p = .003$ - $.111$). There are no significant differences at Visit 1. Additionally, in the TLD group only, IMMN/LDN latencies are longer at Visit 1 as compared to Visit 2 ($t_4 = 0.93$ - 4.11 , $p = .406$ - $.015$). There are no Visit related changes in the LI group. Taken together, these findings suggest that IMMN/LDN latency decreases only in TLD children from Visit 1 to Visit 2.

9.2.4 IMMN/LDN analyses for the Attend Condition, Visit 1 to Visit 2

Descriptive statistics are shown in Tables 9.2.4a – b for the IMMN/LDN in the Attend condition.

9.2.4.1 Attend 300 ms ISI – IMMN/LDN, Visit 1 to Visit 2

Attend 300 ms ISI – IMMN/LDN Amplitude, Visit 1 to Visit 2: The mixed factors ANOVAs planned for the Attend 300 ms ISI condition were not able to be run because there were only 3 participants in the TLD group, and zero participants in the LI group with sufficient data for analyses. So, simple effects comparisons were conducted only for the TLD group. The paired samples t-tests conducted for the TLD children only, comparing IMMN/LDN amplitude at Visit 1 and Visit 2 did not reveal any significant effects.

Attend 300 ms ISI – IMMN/LDN Latency, Visit 1 to Visit 2: The paired samples t-tests conducted for the TLD children only, comparing IMMN/LDN latency at Visit 1 and Visit 2, did not reveal any significant effects.

9.2.4.2 Attend 70 ms ISI – IMMN/LDN, Visit 1 to Visit 2

Attend 70 ms ISI – IMMN/LDN Amplitude, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Visit at bilateral central channels ($F= 10.33, p<.01$) with IMMN/LDN amplitudes smaller at Visit 1 as compared to Visit 2. There is a main effect of Hemisphere at bilateral frontocentral channels ($F=6.28, p<.05$) with larger amplitudes on the Left as compared to the Right side. There is also a Hemisphere x Group interaction at bilateral frontocentral channels ($F=6.41, p<.05$).

Examination of the simple effects for Visit did not reveal any significant changes in IMMN/LDN amplitude from Visit 1 to Visit 2 in either the TLD or LI group, and

similarly examination of the simple effects of Hemisphere failed to show any significant differences in IMMN/LDN amplitude between the Left and Right sides within each group and within each Visit. However, the simple effects analyses of Group revealed that while there are no group differences in IMMN/LDN amplitude at Visit 1, at Visit 2 TLD children have significantly smaller amplitudes than LI children ($TLD < LI$), but only in two channels (Cz: $t_{22} = 2.34$, $p = .029$; and Ch. 54/Fc4: $t_{22} = 3.16$, $p = .005$). Considering all the results together, coupled with the relatively small sample sizes in the ANOVAs ($TLD n=6$, $LI n=8$), these findings are not very robust and do not seem sufficient to support any conclusions regarding group differences across the two visits.

Attend 70 ms ISI – IMMN/LDN Latency, Visit 1 to Visit 2: Mixed factors ANOVAs revealed a main effect of Visit at midline channel Cz ($F=8.00$, $p<.05$), with latencies at Visit 1 shorter than at Visit 2. There is a Visit x Group interaction at bilateral frontocentral channels ($F=4.82$, $p<.05$). Examination of the simple effects did not reveal any group differences in IMMN/LDN latency between TLD and LI children at Visit 1 or Visit 2 (Group), nor between Visit 1 and Visit 2 within each group (Visit). In sum, because the sample sizes in the ANOVAs are quite small, and there are no significant finding in the simple effects analyses, no definitive conclusions can be drawn from these analyses of IMMN/LDN latency elicited by pairs of tones separated by a 70 ms ISI during active listening.

Attend 70 ms ISI – IMMN/LDN Summary, Visit 1 to Visit 2: In the analyses of IMMN/LDN amplitude and latency, all findings are considered, noting the relatively small sample sizes in the ANOVAs ($TLD n=6$, $LI n=8$). Overall, the results are not robust enough to support any conclusions regarding group differences across the two visits in

IMMN/LDN amplitude or latency elicited by paired tones separated by a 70 ms ISI during active listening.

9.2.4.3 Attend 10 ms ISI – IMM/NDN, Visit 1 to Visit 2

Attend 10 ms ISI – IMM/NDN Amplitude, Visit 1 to Visit 2: The mixed factors ANOVAs planned for the Attend 10 ms ISI condition were not able to be run because there were only 3 participants in the TLD group, and 5 participants in the LI group with sufficient data for analyses. So, simple effects comparisons were conducted and interpreted with caution give the very small sample sizes.

Attend 10 ms ISI – IMM/NDN Amplitude, Visit 1 to Visit 2: The paired samples t-tests conducted comparing IMM/NDN amplitude at Visit 1 vs. Visit 2 did not reveal any significant effects for either the TLD or LI group (Visit), and nor any hemispheric differences (Left vs. Right) in either group at either Visit (Hemisphere). Similarly, the independent samples t-tests comparing the two Groups (within each Visit) failed to show any significant differences between TLD and LI children.

Attend 10 ms ISI – IMM/NDN Latency, Visit 1 to Visit 2: As in the simple effects analyses of amplitude, there are no significant findings in IMM/NDN latency. The paired samples t-tests conducted comparing IMM/NDN latency at Visit 1 vs. Visit 2 did not reveal any significant effects for either the TLD or LI group (Visit), nor any hemispheric differences (Left vs. Right) in either group at either Visit (Hemisphere). Similarly, the independent samples t-tests comparing the two Groups (within each Visit) failed to show any significant differences between TLD and LI children.

Attend 10 ms ISI – IMM/LDN Summary, Visit 1 to Visit 2: The planned mixed factors ANOVAs could not be conducted due to very limited data (TLD n=3, LI n=5). All simple effects comparisons failed to reveal any significant differences in IMM/LDN amplitude or latency between Visits, Hemispheres, or Groups during active listening to tone pairs presented with a 10 ms ISI. These analyses lack power, and so no conclusions can be drawn from this set of null results.

9.2.5 Summary of Event Related Potentials – Statistical Analyses

In the analyses of the eMMN, in the LI group, the only changes from Visit 1 to Visit 2 are seen in the 70 ms ISI conditions. These consist of an increase in eMMN latency in the Ignore condition, and a decrease in eMMN latency in the Attend condition, reflecting changes in rapid auditory processing (see Figure 9.2.5). The increase in the Ignore condition may be explained by a “time cost” related to extended processing following the FFWD intervention. FFWD aims to improve auditory discrimination abilities through active behavioral exercises. Once faster RAP achieved through active intervention, over time these improved abilities are likely to be incorporated into involuntary, automatic processing (Gomes et al., 2000, Kraus et al., 1995a). Since the LI children in the present study completed the follow-up ERP session shortly after completing the intervention, there may not have been sufficient time for these improvements in RAP to become completely automatic, and longer eMMN latencies may reflect extended processing of the stimuli during a phase of compensatory brain activation, before being integrated and streamlined into more efficient mechanisms (Meyler et al., 2008). In contrast, in the Attend condition improved RAP abilities in the

LI children are revealed in the form of shorter eMMN latencies, perhaps due to an enhanced benefit of attention on RAP at rates that are more salient following FFWD training (Tallal, 2004) and/or overall improvements in selective attention and vigilance (Stevens et al., 2008). In the TLD children, there are no changes in eMMN measures from Visit 1 to Visit 2 in the 70 ms ISI conditions, demonstrating the stability of the eMMN in children with typical language development. The noteworthy limitation on the interpretation of these findings is the small number of children who received the 300 and 10 ms ISI rates of presentation, especially in the Attend condition, and so changes in the eMMN at these rates of presentation cannot be completely ruled out. However, it is interesting that pre- to post- intervention changes in the eMMN are observed at the rate of presentation that is critical for speech processing (70 ms ISI) (Tallal & Gaab, 2006) during both passive and active listening, a rate that is therefore likely to be extremely salient and most experienced.

The IMMN/LDN appears to capture different aspects of auditory processing across the two visits. The functional mechanisms underlying the IMMN/LDN component are still poorly understood, as it has only recently been described and investigated (Ceponiene et al., 1998; Korpilahti et al., 2001; Shestakova et al., 2003). The IMMN/LDN has been proposed to be involved in further processing of auditory stimuli (Hämäläinen et al., 2008), and linked to the development of attention mechanisms (Ceponiene et al., 2002). In the present experiment, in the Ignore condition, TLD children exhibit IMMN/LDN latency decreases from Visit 1 to Visit 2 for all three rates of presentation, but no changes in amplitude. This consistent pattern of results may suggest short-term changes in the IMMN/LDN due to previous exposure to the stimuli (both

passive and active). These findings demonstrate that the IMMN/LDN component may not be a sensitive index of discrimination difficulty, at least for the rates of presentation tested here, in a group of normally developing children. In the LI children, however, pre- to post- intervention changes are seen in both IMMN/LDN amplitudes and latencies. Thus, under passive listening conditions, the IMMN/LDN appears to reflect differences in auditory processing across various rates of presentation in the LI group that may not be present in the TLD children. Recent investigations reported in the literature have demonstrated changes in the IMMN/LDN during and after the acquisition of new skills, including second language learning (Shestakova et al., 2003), and reading remediation in a group of poor readers (Alonso-Bua et al., 2006). The IMMN/LDN may therefore be a useful candidate component for investigating RAP abilities in groups of children with language difficulties, providing additional or different information than the eMMN alone.

No changes in IMMN/LDN amplitude and latency are observed in the Attend condition in either group, but it should be noted that the sample sizes were quite small (TLD $n \leq 6$, LI $n \leq 8$), and not all comparisons could be conducted (not enough data for ANOVA in the 300 and 10 ms ISI conditions), so no firm conclusions can be drawn from these null results.

9.3 Statistical Analyses of Behavioral Measures

9.3.1. Comparison of TLD and LI groups on CELF-4 Language Measures – Core, Receptive and Expressive Language

The main research question addressed in this set of analyses is: **Do language and reading abilities change from Visit 1 to Visit 2 differently in TLD (no intervention) as compared to LI children (FFWD intervention)?** To examine potential differences in

language and reading scores from Visit 1 to Visit 2 in both the TLD and LI children, a series of 2 (Group) x 2 (Visit) ANOVAs were performed with outcome variables CELF-4 Core Language Standard Score (Core), CELF-4 Receptive Language Standard Score (Receptive), CELF-4 Expressive Language Standard Score (Expressive), WRMT Word Identification Standard Score (Word ID), WRMT Word Attack Standard Score (Word Attack), and WRMT Passage Comprehension Standard Score (Passage Comprehension). It was hypothesized that significant improvements in language measures would be observed in the LI group since the FFWD intervention specifically targets auditory processing skills important for oral language processing, and significant improvements in LI children's language abilities have been reported in the literature (Tallal et al., 1996; Merzenich et al., 1996; Temple et al., 2003; Gaab et al., 2007; Stevens et al., 2008). We predicted that there would not be significant changes in the language and reading measures of TLD children with the possible exception of practice effects, as TLD children did not participate in an intervention.

The results of 2 x 2 ANOVAs revealed main effects of Group and Visit for all CELF-4 measures (Visit: Core, $F_{1,31} = 27.9$, $p < .001$; Receptive, $F_{1,31} = 15.1$, $p = .001$; Expressive, $F_{1,31} = 16.9$, $p < .001$, Group: Core, $F_{1,31} = 40.9$, $p < .001$; Receptive, $F_{1,31} = 36.1$, $p < .001$; Expressive, $F_{1,31} = 41.9$, $p < .001$), and significant Group x Visit interactions for CELF-4 Core ($F_{1,31} = 12.0$, $p < .01$) and CELF-4 Receptive ($F_{1,31} = 9.6$, $p < .01$). Overall, TLD children had higher CELF-4 language scores than LI children, and overall scores at Visit 2 were higher than at Visit 1. The significant Group x Visit interactions resulted from a considerable increases in standard scores in the LI group, and

little to no change in standard scores in the TLD group as illustrated in Figures 9.3.1a and b below. The statistical results are summarized in Tables 9.3.1a and b.

There was not a significant Group x Visit interaction for CELF-4 Expressive ($F_{1,31} = 3.7, p = 0.06$), so, as planned, paired samples t-tests were performed within each group to investigate changes in standard scores from Visit 1 to Visit 2 (Table 9.3.1b). These analyses address the question of whether TLD and LI children's scores changed in a similar manner from Visit 1 to Visit 2, or if there was a different pattern of change in one group as compared to the other. In the TLD group, there was no significant change in CELF-4 Expressive standard score from Visit 1 to Visit 2 ($t_{11} = -1.9, p = .082$), but in the LI group CELF-4 Expressive language standard score increased significantly from Visit 1 to Visit 2 ($t_{20} = -4.4, p < .001$). Thus, although a significant Group x Visit interaction was not seen in the multivariate analysis, further investigation revealed that the LI children indeed show improvements in expressive language, while no significant change is seen in the TLD children's expressive language scores from Visit 1 to Visit 2 [(Figure 9.3.1b, panels (c) and (f)].

9.3.2 Comparison of TLD and LI groups on Woodcock Reading Mastery Test (WRMT) – Word Identification, Word Attack and Passage Comprehension Subtests

For the reading measures (WRMT), 2 (Group) x 2 (Visit) ANOVAs revealed only a significant main effect of Group in the three subtests examined (Word ID, $F_{1,31} = 14.3, p = .001$; Word Attack, $F_{1,31} = 9.65, p = .004$; Passage Comprehension, $F_{1,30} = 23.7, p < .001$) with TLD children having higher scores than the LI children. There are no significant main effects of Visit (Word ID, $F_{1,31} = 0.73, p = .40$; Word Attack, $F_{1,31} =$

0.31, $p = 0.58$; Passage Comprehension, $F_{1,30} = 0.21$, $p = 0.65$), and no significant Group x Visit interactions (Word ID, $F_{1,31} = 0.24$, ns; Word Attack, $F_{1,31} = 0.003$, ns; Passage Comprehension, $F_{1,30} = 0.355$, ns). In sum, there are no significant changes in WRMT scores in either group from Visit 1 to Visit 2.

9.3.3 Investigating LI Subgroups: Receptive, Expressive and Mixed

Given that the LI classification includes a heterogeneous group of children with different patterns of language deficits (Bishop, 1997; Bishop, 2004), the 28 LI children who participated in Experiment 4 (Visit 1) were classified as having LI subtype **Mixed** (no significant difference between receptive and expressive language performance), **Receptive** (Receptive < Expressive), or **Expressive** (Expressive < Receptive) according to the CELF-4 standardized procedure (Semel et al., 2003, pp. 112 – 118). The resulting classifications are shown in Table 9.3.3. There were 18 children in the **Mixed LI subgroup**, 5 in the **Expressive LI subgroup**, and 5 in the **Receptive LI subgroup**. At Visit 2 (Experiment 5, after FFWD) there were 14 Mixed, 3 Expressive, and 4 Receptive LI participants. Due to the very small sample sizes in the Expressive and Receptive LI subgroups, the planned multivariate statistical analyses (mixed factors ANOVAs) were not carried out. Rather, a descriptive account of the LI subgroups' changes in language and reading performance at Visit 1 to Visit 2 are reported, followed by the results of a series of one-way ANOVAs designed to address the question of whether or not the three LI subgroups differed from each other in language and reading measures at Visit 1 and Visit 2. One-way ANOVAs are adequate to address the questions posed above, and can be conducted with smaller sample sizes as compared to multivariate, mixed factors ANOVAs

9.3.3.1 Description of Changes in CELF-4 Language Measures in LI Subgroups

In the **Mixed LI subgroup**, changes in Core Language ranged from -1 to 19 points, with a mean of an 8.86 point increase from Visit 1 to Visit 2. Eight children had increases between 6 - 9 points, and 4 children had increases between 12 – 19 points. These increases exceed potential practice effects that may occur as a result of re-administering the CELF-4 within a short period of time. The CELF-4 reports an average increase of 4 points on index scores (Core, Receptive, Expressive) when the test is re-administered within 1 to 4 weeks of the initial administration (Semel et al., 2003). In the present study, 12 out of 14 children had increases greater than 4 points, and the mean test-retest interval was 16.6 weeks (116 days), so it is unlikely that increases in these Mixed LI children's Visit 2 scores are due to practice effects. For the two remaining Mixed LI children, one child's Core language score decreased by 1 point, and the other child had only a 2-point increase. These differences are very small and likely reflect no changes (gains or losses) in language skills from Visit 1 to Visit 2. The differences between Visit 1 and Visit 2 scores are shown in Table 9.3.3.1. Changes in Expressive Language standard score ranged from -4 to 26 points (mean 7.7 points). Eight children had increases greater than 7 points, while the other 6 children had changes within or below the range of potential practice effects. In two children, decreases of 4 points from Visit 1 to Visit 2 most likely reflect the child's poor state during testing rather than a decrease in language ability³³. Changes in Receptive Language standard scores from Visit 1 to Visit 2 ranged from -2 to 23 points. Overall, the greatest gains were seen in

³³ It was noted in the data that for LI child 09013, "state was not optimal. Noted that this may not have been an accurate assessment", and for 09040 the child "...was quick to say when something was too hard (I don't know - this one's hard, etc). . . made comments about wanting to be done".

Receptive Language skills (mean 9.6 points), though only 8 of 14 children made significant gains. The other six children showed changes less than or equal to the conservatively estimated potential practice effect.

Of the 5 children in the **Expressive LI subgroup**, 3 returned for Visit 2. One child made very large gains (+15, +20, and +12 points on Core, Expressive, and Receptive Language, respectively), while the other 2 children had moderate changes (both gains and losses in standard scores).

Of the 5 children in the **Receptive LI subgroup**, 4 returned for Visit 2. One child (09039) made large gains in all area scores (Core +14 points, Expressive +9 points, Receptive +19 points), and one child (09051) made moderate gains in all area scores (Core +4, Expressive +7, Receptive +7). The other two children made small gains in Core (+2, +2) and Expressive (-1, +4) area scores, but showed large increases in Receptive language scores (+13, +16). For all children in the Receptive LI subgroup, the largest increases in scores were seen in Receptive language³⁴.

Overall, in the **Mixed** and **Receptive LI subgroups**, the largest gains occurred in Receptive language skills. This was the predicted result as FFWD most directly targets skills important for receptive language processing. In the **Receptive LI subgroup**, all 4 children made the largest gains in Receptive language. However, in the **Mixed LI subgroup**, 6 children made the greatest gains in Receptive language (as compared to Core or Expressive language area scores), and 3 children made the greatest gains in Expressive language. One Mixed LI child achieved the greatest increase in Core (+19; Expressive +16, Receptive +3), and another made a 12-point gain in both Expressive and

³⁴ For LI child 09051, there was an equal increase in Expressive and Receptive area scores from Visit 1 to Visit 2 (+7).

Receptive scores. The remaining 3 children had small changes in all area scores (both increases and decreases). The children in the **Expressive LI subgroup** did not follow any discernable pattern. One child made very significant improvements in Core, Receptive and Expressive, while the other two children showed inconsistent patterns of change. In sum, these results indicate that LI subgroup classification as Mixed, Expressive, or Receptive is not sufficient to capture or explain different patterns of improvements in language skills following FFWD.

9.3.3.2 Description of Changes in WRMT Reading Measures in LI Subgroups

Overall, in all LI subgroups, there seemed to be no consistent pattern of change from Visit 1 to Visit 2 in any of the WRMT subtests examined. The WRMT generates age-standardized scores at one-month intervals, and does not have reported test – re-test effects on standardized scores. For the **Mixed LI subgroup**, the mean difference in scores from Visit 1 to Visit 2 was less than 1 point for Word ID, Word Attack, and Passage Comprehension. There were increases as well as decreases in individual scores. Since the WRMT has age-normed scores at one-month intervals, a child with the same raw score at Visit 1 and Visit 2 (same number of correct responses) would have a lower score at Visit 2 because of an increase in age. Thus, many children had lower scores at Visit 2 as compared to Visit 1. In the **Expressive LI subgroup** and the **Receptive LI subgroup**, the same profile of increases and decreases were observed. Only one child in the **Receptive LI subgroup** made a substantial gain on the Word Attack subtest at Visit 2 (+18 points). Overall, within each LI subgroup, changes in reading subtest scores were neither remarkable nor consistent from Visit 1 to Visit 2.

9.3.3.3 Results of Statistical Analyses of LI Subgroups Language and Reading Measures

One-way ANOVAs were conducted to examine whether the three LI subgroups differed significantly from one another in language (CELF-4 Core, Receptive and Expressive) and reading (WRMT Word ID, Word Attack, Passage Comprehension) standard scores at Visit 1 and Visit 2. The ANOVAs revealed no significant effect of LI subgroup on any language or reading measure, except for Expressive Language at Visit 1 [$F(2, 27) = 4.10, p = .029$]. These results are summarized in Table 9.3.3.3. Planned post hoc tests (Tukey HSD) revealed that the **Expressive LI subgroup** had significantly lower Expressive language standard scores than the Receptive LI subgroup (mean difference - 21.4, $p = .023$). This was a predicted result, as lower Expressive relative to higher Receptive language scores comprise the classification criteria for the Expressive LI subgroup, and the reverse is true for the Receptive LI subgroup (lower Receptive relative to higher Expressive language scores). Based on these findings, all analyses will include all three LI subgroups combined as one LI group.

9.3.4 Results of Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

The main research question addressed in this set of analyses is: **Do auditory temporal processing abilities assessed using the ART-C change from Visit 1 to Visit 2 differently in TLD (no intervention) as compared to LI children (FFWD intervention)?** For children in Experiments 2, 3, 4, and 5, performance on the ART-C

was indexed by calculating the Percent of Correct Trials. For **2-tone sequences**, the Percent of Correct Trials was calculated for *each ISI* (500, 150, 70, 10 ms) ([number of correct trials at ISI / number of trials presented at ISI] * 100). For **3-tone sequences**, the Percent of Correct Trials was calculated for the *entire block* of trials 3-Slow and 3-Fast since there were only 10 trials in each block ([number of correct trials (Slow or Fast) / number of trials presented (Slow or Fast)] * 100). Between and within group comparisons were then carried out and these results are described below.

9.3.4.1 Between group Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

A Pearson Chi-Square test was conducted to see if children from the TLD and LI groups were able to learn the ART-C (achieve criterion following one full training phase) at the same rates at Visit 1 and Visit 2. Children who achieved criterion on Association and Sequencing during a single administration of training (Detection and Association phases of the ART-C) were classified as “1-Training”, and children who required a second training (repetition of Detection and/or Association) were classified as “2-Training”.

At **Visit 1**, all children in the TLD group were classified as 1-Training. In the LI group there were 21 children classified as 1-Training, and 7 children classified as 2-Training. Of these 7 children, 5 were not able to achieve criterion even after the second training and ART-C testing was discontinued. At **Visit 2**, again all children in the TLD group were classified as 1-Training. In the LI group there were 20 children classified as 1-Training, and only one child classified as 2-Training. This child was not able to pass

criterion after the second training and the ART-C testing was discontinued. The results of the Pearson Chi-Square tests are shown in Table 9.3.4.1a.

At **Visit 1**, the Pearson Chi-Square test showed a significant difference in the distributions of children classified as 1-Training and 2-Training in the TLD and LI groups, with the LI group having more children classified as 2-Training. These results indicate that the LI children often have more difficulty acquiring the skills (discrimination and sequencing) necessary to complete the ART-C. At **Visit 2**, however, the Pearson Chi-Square test showed that there was no difference in the distribution of the training classifications between the TLD and LI groups. This suggests that TLD and LI children were similarly able to achieve criterion on the ART-C with one training phase at Visit 2.

To further investigate potential differences in the training phase of the ART-C, the Number of Training Trials (NTT) (total number of trials administered during Association and Sequencing) was compared between the TLD and LI groups at Visit 1 and Visit 2 with independent samples t-tests. During the training phase of the ART-C, when a participant makes a mistake, the examiner re-presents the trial (a maximum of 3 times) so the child can correct his/her mistake. Additionally, if a child does not reach criterion on Association and/or Sequencing, the entire training phase is repeated. Analysis of the NTT required by the TLD and LI participants yields further insight into group differences that may not be reflected in the analysis of the ART-C testing phases only. The descriptive statistics are shown in Table 9.3.4.1b, and results of the independent samples t-tests comparing the NTT in TLD vs. LI children are shown in

Table 9.3.4.1c. The results showed that LI children received significantly more training trials on the ART-C as compared to TLD children at both Visit 1 and Visit 2.

For children who were able to achieve criterion and thus complete the testing phase of the ART-C (blocks 2-Fast, 3-Slow, 3-Fast), descriptive statistics were generated by Group (TLD or LI) for the Percent of Correct Trials at each ISI for 2-tone sequences (500, 150, 70, 10 ms), and for 3-Slow and 3-Fast at Visit 1 and Visit 2. Descriptive statistics are shown in Table 9.3.4.1d. Independent samples t-tests were conducted to compare the Percent of Correct Trials between groups for each 2-tone sequence ISI, and 3-Slow and 3-Fast at Visit 1 and Visit 2. The results of these analyses are shown in Table 9.3.4.1e.

There are no significant group differences at any ISI for the 2-tone sequences at Visit 1 and Visit 2, thus the planned Group (TLD, LI) x ISI x Visit (1, 2) Mixed Factors ANOVA was not conducted. Similarly, there are no significant group differences in the Percent of Correct Trials for the 3-Slow and 3-Fast blocks, so the planned Group (TLD, LI) x Rate (Slow, Fast) x Visit (1, 2) Mixed Factors ANOVA was not conducted. These findings suggest that for children who were successfully trained on the ART-C, the TLD and LI children performed similarly at all 2-tone sequence ISIs, and in the 3-Slow and 3-Fast blocks.

9.3.4.2 Results of Within group Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

To investigate potential changes in the training phase of the ART-C from Visit 1 to Visit 2, the Number of Training Trials (NTT) were compared between Visit 1 and Visit

2 within each group using paired samples t-tests. The paired samples t-test statistics are shown in Table 9.3.4.2a. Results show that there is no significant difference in the NTT for TLD children at Visit 1 (mean NTT 36.25) as compared to Visit 2 (mean NTT 36.00) ($t = 1.000$, *ns*). In the LI group there is a decrease in the NTT from Visit 1 (mean NTT 44.15) to Visit 2 (mean NTT 37.45) ($t = 2.055$, $p \leq .05$).

For children who achieved criterion on the ART-C and completed the testing phases, paired samples t-tests were conducted to compare the Percent of Correct Trials at Visit 1 vs. Visit 2 at each ISI for 2-tone sequences, and 3-Slow and 3-Fast for the TLD and LI groups. The paired samples t-test statistics are shown in Table 9.3.4.2b. For **2-tone sequences**, significant differences in the Percent of Correct Trials at Visit 1 vs. Visit 2 were found at 150 and 10 ms for the TLD group, and at 70 and 10 ms for the LI group. For the **3-tone sequences**, significant differences in the Percent of Correct Trials at Visit 1 vs. Visit 2 were found for 3-Slow in the TLD group only, and 3-Fast for the LI group only.

As planned, for **2-tone sequences**, variables that significantly differed ($p \leq .05$) in the paired samples t-tests for either or both groups were entered into a Group (TLD, LI) x ISI (150, 70, 10 ms) x Visit (1, 2) Mixed Factors ANOVA to investigate ART-C performance between groups and rates of presentation from Visit 1 to Visit 2. There were significant main effects of ISI ($F = 17.66$, $p = .00$) and Visit ($F = 22.97$, $p = .00$), but not Group ($F = .14$, $p = .71$). There was one significant interaction: ISI x Visit ($F = 4.76$, $p = .01$) suggesting that over both groups there was an improvement in ART-C performance from Visit 1 to Visit 2 as a function of ISI with the smallest increase seen for the 150 ms ISI, followed by a moderate increase in performance at the 70 ms ISI, and the greatest

increase in performance for the 10 ms ISI. All other interactions were not significant at the $p \leq .05$ level. The statistics for the mixed factors ANOVA are shown in Table 9.3.4.2c, and the results are illustrated in Figure 9.3.4.2a.

As planned, for **3-tone sequences**, variables that significantly differed ($p \leq .05$) in the paired samples t-tests for either or both groups were entered into a Group (TLD, LI) x Rate (Slow, Fast) x Visit (1, 2) Mixed Factors ANOVA to investigate ART-C performance between groups and rates of presentation from Visit 1 to Visit 2. Significant differences in the Percent of Correct Trials at Visit 1 vs. Visit 2 were found for 3-Slow in the TLD group only, and 3-Fast for the LI group only. There were significant main effects of Rate ($F = 54.59, p = .00$) and Visit ($F = 13.42, p = .001$), but not Group ($F = .09, p = .76$). There were no significant interactions at the $p \leq .05$ level. The results suggest that over both groups, performance on 3-tone sequences is better at slow as compared to fast rates, and the Percent of Correct Trials for 3-tone sequences increases from Visit 1 to Visit 2 (see Figure 9.3.4.2b). The statistics for the mixed factors ANOVA are shown in Table 9.3.4.2d.

9.3.4.3 Summary of Statistical Analyses of the Auditory Repetition Test – Child Version (ART-C)

Analyses of performance by TLD and LI children on the ART-C revealed significant differences in children's ability to learn the task depending on group classification at Visit 1, before intervention in the LI group. A greater number of LI children as compared to TLD children could not achieve criterion on the ART-C even though the LI children received more training trials on average. However, at Visit 2 there

was no difference in the numbers of TLD and LI children who achieved ART-C criterion, and the LI group showed a decrease in the amount of training trials needed to reach criterion from Visit 1 to Visit 2. There was no change in the TLD group's number of training trials across visits. These results demonstrate significant improvements in the LI group's ability to successfully complete the training phase of the ART-C from Visit 1 to Visit 2.

Of the children who did achieve criterion, performance on ART-C test phases at the group level was not significantly different between TLD and LI children regardless of the rate of presentation (500, 150, 70 or 10 ms in the case of 2-tone sequences and “slow” vs. “fast” in the case of 3-tone sequences) at either Visit 1 or Visit 2. These findings may have important implications for the ART-C, a task that is often used in the study of children with LI, SLI, or auditory processing impairments. The present findings suggest that analysis of the ART-C testing phases alone may not be sufficient to fully characterize different experimental groups. Differences in training (examining the number of children who fail to learn the task, the amount of training necessary for a child to learn the task, patterns of errors in training, etc.) may be very important variables to consider since serious difficulties with sequencing and/or discriminating tones may prevent a child with an auditory processing impairment from reaching training criterion. Analyzing the training phase of a task prevents the loss of data from “drop outs”, children who could not be tested with the ART-C due to impairments perhaps in the very skills the task aims to investigate.

Additionally, analyses of performance of the ART-C test phases showed that over both groups, performance improved from Visit 1 to Visit 2, with the greatest increases at

the shortest ISIs (for 2-tone sequences only), and that in general children, like adults in Experiment 1, made more errors as ISI decreased and rapid processing demands were greater.

9.4 Results of Correlation Analyses Between Behavioral and ERP Measures: All Participants

A series of Pearson correlation matrices (2-tailed, alpha value = .05) were generated to examine relations between Behavioral measures and ERP indices of auditory discrimination (early MMN and late MMN/LDN amplitude and latency at frontocentral channels at both Visit 1 and Visit 2). The Behavioral variables chosen for analyses are shown in Table 9.4. Correlations between Behavioral variables and MMN (eMMN and IMMN/LDN) amplitude and latency at each Rate of presentation (300, 70, and 10 ms ISI) in both Conditions (Ignore, Attend³⁵) were examined at Visit 1 and Visit 2. The data were examined for patterns of associations between Behavioral and ERP measures across all participants to address the question of how patterns persisting from Visit 1 to Visit 2 may change in the TLD as compared to the LI group.

A significant association was reported if the following minimum criterion was met: two or more variables within a behavioral domain were significantly correlated ($p \leq .05$) with an ERP variable at a single channel, OR a single behavioral variable was significantly correlated with an ERP variable at 2 or more channels. Before these analyses were conducted, preliminary data analyses were carried out examining demographic variables and intercorrelations (correlations among sets of variables within

³⁵ The Attend 300 ms ISI condition was not included in these analyses because there was a small sample size at Visit 1 ($n=9$), and only 3 participants at Visit 2, and all 3 were TLD children. Thus, it was not possible to look at potential changes in patterns of associations between Visits 1 and 2 across the two groups of children.

and across Visits). This was done to insure that there were no significant associations with demographic variables that would confound interpretation of the Behavioral and ERP data, and that the data followed a predictable pattern of intercorrelation.

First, correlations between Gender and Behavioral and ERP variables at Visit 1 were investigated given the higher percentage of males in the LI group (69% males) as compared to the TLD group (50% males). Note that preliminary analyses (pp. 95 – 96) showed that there were no significant differences between the TLD and LI groups on any other demographic variables (age at tests, birthweight, gestational age, socioeconomic status, maternal age, and maternal education level). Analyses here revealed that there were no associations between Gender and any of the Behavioral or ERP variables. Thus, there were no demographic variables that would affect interpretation of the planned correlation analyses.

Next, patterns of intercorrelations were examined among Behavioral variables (between and within each domain) and ERP variables (within each Rate and Condition) at Visit 1 and Visit 2 across all participants. Examining correlations *between* Behavioral variables, as expected, it was found that oral language and reading measures were all highly correlated at both Visit 1 (range .49 - .70) and Visit 2 (range .52 - .73). At Visit 1, there were no significant correlation patterns between auditory temporal processing and oral language, or between auditory temporal processing and reading. At Visit 2, there were still no significant correlation patterns between auditory temporal processing and oral language, but there were some significant correlations between reading measures and auditory temporal processing variables. To summarize, better reading performance (WID

and PC) was associated with better auditory temporal processing (higher percentage of correct trials for 3-Slow, and fewer NTT) at Visit 2 (range $|.35| - .53|^{36}$).

Examining correlations *within* each domain of Behavioral variables, as expected it was found that oral language measures from Visit 1 to Visit 2 were highly correlated (range $.86 - .96$), as were reading measures (range $.75 - .94$). There were also significant patterns of correlations among all auditory temporal processing variables (range $|.38| - .89|$).

Finally, examining correlations *within* each group of ERP variables (within Rate and Condition) for the eMMM and IMM/LDN revealed significant patterns of correlations within each group of ERP variables, as expected, for both amplitude and latency at Visits 1 and 2 (range $.36 - 1.0$). Given the topographical distribution of MMN component amplitudes observed at Visit 1 and Visit 2 in both the TLD and LI children, correlations among the frontocentral channels, where the MMN components are the most robust, were predicted.

Turning to the main correlation analyses, at Visit 1, patterns of relations were first examined between behavioral measures and eMMN amplitude and latency, followed by the same analysis of IMM/LDN amplitude and latency.

9.4.1 Visit 1 Correlation Analyses Between Behavioral and ERP Measures

9.4.1.1 Visit 1 - eMMN Amplitude Correlation Analyses

³⁶ The absolute values of Pearson correlations are shown because there were negative correlations between NNT and reading measures (i.e. fewer NTT correlated with higher reading scores), but all other intercorrelations were positive (e.g. higher percentage of correct trials for 3-slow correlated with higher reading scores).

In general, there were fewer significant associations between behavioral measures and eMMN amplitude as compared to latency. In significant correlations between eMMN amplitude and language and reading measures, the pattern was the same: **better behavioral performance is associated with lower amplitudes**. This is consistent with previous observations that TLD children, who have higher performance on language and reading measures, generally have lower eMMN amplitude fluctuations than LI children (PO300 and TO70) (See 8.0 Results of Experiment 4). Interestingly, in the Ignore 10 ms ISI condition, better performance on the ART-C was associated with higher eMMN amplitude. For this condition, TLD and LI children were observed to have eMMN amplitudes of similar magnitude, and so lower amplitudes are not associated with the TLD group. Also, there are no significant differences between TLD and LI children on the ART-C (for statistical comparison of TLD and LI ART-C performance, see pp. 198 - 200). Thus, eMMN amplitude correlations with ART-C measures in the Ignore 10 ms ISI condition do not contribute to understanding potential group differences between TLD and LI children, but show an association among behavioral and ERP measures generalized across all participants. All significant associations for eMMN amplitude are shown in Table 9.4.1.1.

9.4.1.2 Visit 1 - eMMN Latency Correlation Analyses

In all significant correlations between eMMN latency and behavioral measures, the pattern is the same: **better behavioral performance (language, reading, and auditory temporal processing) is associated with shorter eMMN latencies**. This is consistent with previous observations that TLD children have significantly shorter

eMMN latencies than LI children in the conditions that yielded significant correlations (PO300 and PO70) (See 8.0 Results of Experiment 4). All significant associations for eMMN latency are shown in Table 9.4.1.2.

9.4.1.3 Summary of Visit 1 eMMN Correlation Analyses

Overall, correlation analyses revealed significant associations **between better behavioral performance and lower eMMN amplitudes and shorter eMMN latencies** across all participants at Visit 1. In the descriptive reports of TLD and LI children's grand averaged waveforms, it was found that TLD children tend to have lower eMMN amplitudes accompanied by shorter eMMN latencies as compared to LI children. The one exception to this pattern of results occurred in the Ignore 10 ms ISI condition, where better performance on the ART-C was associated with larger eMMN amplitudes. This finding is explained by the fact that TLD and LI children performed similarly on the ART-C, except in terms of how much training was required. LI children needed more training trials to learn the task and also were more likely to fail to learn the task at all.

9.4.1.4 Visit 1 – IMM/LDN Amplitude Correlation Analyses

In nearly all of the significant correlations between IMM/LDN amplitude and behavioral measures, the pattern is the same: **better behavioral performance (language and auditory temporal processing) is associated with lower IMM/LDN amplitudes**. This is consistent with previous observations that TLD children more often exhibit lower IMM/LDN amplitude fluctuations than LI children (PO300, PO70, PO10) (See 8.0: Results of Experiment 4). The one exception to this pattern of findings occurred in the

Ignore 300 ms ISI condition where higher reading scores (WID, PC) are associated with higher amplitudes (Ch. 21). In this case, at Ch. 21 (C5, left hemisphere) where this association is seen, TLD children actually exhibit *higher* IMMN/LDN amplitudes as compared to LI children. This is also true at Ch. 53 (C6), the right hemisphere correlate of Ch. 21. This appears to explain this apparent contrasting finding. With this in mind, the significant correlation found here at Ch. 21 indicates that, as expected, better reading performance occurs in the TLD children. All significant associations for IMMN/LDN amplitude are shown in Table 9.4.1.4.

9.4.1.5 Visit 1 – IMMN/LDN Latency Correlation Analyses

In the significant correlations between IMMN/LDN latency and language measures, **better language performance is associated with shorter IMMN/LDN latencies**. These relations were found in the Attend 70 ms ISI condition. In this condition, TLD children generally exhibit shorter latencies as compared to LI children.

Interestingly, significant associations with reading (PC) in the Ignore 300 ISI condition (Ch. 53, 54), and auditory temporal processing (2-150, 2-70, and 3-Slow) in the Ignore 10 ms condition (Ch. 62) showed that better performance was associated with *longer* latencies. In the Ignore 300 ms ISI condition, examining TLD and LI latencies at Ch. 53 and 54 revealed that in these channels TLD children's latencies tended to be longer than those of LI children in contrast to the usual pattern. However, in the Ignore 10 ms ISI condition at Ch. 62, TLD children's latencies did not follow this pattern. TLD children had shorter latencies than LI children. So, scatterplots were generated to look at the distribution of TLD and LI participants IMMN/LDN latencies and ART-C

performance. One statistical outlier with extremely poor ART-C performance was identified (Subject ID 09010 from the LI group). Additionally, the scatterplots showed that LI children, who tend to have longer latencies, often perform as well as TLD children on the ART-C. Indeed, the ART-C analyses reported in the preceding section show that there are no significant group differences in Percentage of Correct Trials in this task. Correlation analyses were run again for the Ignore 10 ms ISI condition, excluding the statistical outlier, and a different pattern of results emerged showing that at faster rates of presentation in the ART-C (2-70, 2-10), **better performance is associated with shorter IMMN/LDN latencies**. This was the expected relation, suggesting that children who tend to have shorter IMMN/LDN latencies perform better on the ART-C at fast rates of presentation. All significant correlations between behavioral measures and IMMN/LDN latency are shown in Table 9.4.1.5.

9.4.1.6 Summary of Visit 1 IMMN/LDN Correlation Analyses

Most of the significant associations revealed in the correlation analyses between behavioral measures and the IMMN/LDN at Visit 1 follow the same pattern as those found in the eMMN analyses: **better behavioral performance is associated with smaller IMMN/LDN amplitudes and shorter IMMN/LDN latencies**. Exceptions to these patterns were further investigated and in all cases it was found that TLD children, who have higher behavioral scores than LI children, sometimes exhibit IMMN/LDN components with higher amplitudes and/or longer latencies.

9.4.2 Summary of Visit 1 Correlation Analyses between Behavioral and ERP Measures

Overall, at Visit 1, **better performance** on behavioral measures of language, reading and auditory temporal processing are associated with **lower amplitudes** and **shorter latencies** in the eMMN and IMMN/LDN components with few exceptions (see summaries of Visit 1 eMMN and IMMN/LDN Correlation Analyses). These are the expected results since TLD children, who perform better on behavioral measures, tend to have lower amplitude fluctuations accompanied by shorter latencies (reported in Results – Experiment 4). The majority of significant associations occur at channels located along the midline (Ch. 4, Cz) and in the right hemisphere (Ch. 62. 53. 54).

9.4.3 Visit 2 Correlation Analyses Between Behavioral and ERP Measures

At Visit 2, we did not expect to observe the same pattern of associations that were found at Visit 1 due to the fact that between the two visits, LI children completed an intensive intervention program that significantly affected their oral language performance and may therefore have impacted the morphology of their MMN components, reflecting underlying neurophysiological changes in auditory processing. For example, recall that in the Ignore 70 ms ISI condition, only LI children exhibited a significant increase in eMMN amplitude from Visit 1 to Visit 2. TLD children showed no such changes. Thus, in this case correlations at Visit 2 for the Ignore 70 ms ISI condition that differ from those at Visit 1 may reflect these changes that took place in the LI children.

Additionally, previous experience with the ERP stimuli and setting at Visit 1 could affect the MMN components in both TLD and LI children. In this set of analyses,

all significant associations between Behavioral and ERP measures at Visit 2 are reported, and ERP conditions that showed significant associations at *both* Visit 1 and Visit 2 are noted, as these conditions are the most likely to provide insight as to how the eMMN and IMMN/LDN components may change from Visit 1 to Visit 2 in TLD as compared to LI children.

9.4.3.1 Visit 2 – eMMN Amplitude Correlation Analyses

Correlation analyses revealed a number of significant associations between eMMN amplitude and behavioral measures, however not all associations follow the same pattern. As shown in Table 9.4.3.1, in some cases better behavioral performance is associated with *lower* eMMN amplitudes (black text), while in other cases better behavioral performance is associated with *higher* eMMN amplitudes (blue text). These apparently contrasting findings can be explained when each group of associations is considered separately within each ERP condition.

For the Ignore 300 ms ISI condition, **better auditory temporal processing performance (2-10 and 3-Fast) is associated with *higher* eMMN amplitudes**. Recall that only TLD children showed an increase in eMMN amplitude from Visit 1 to Visit 2 for Ignore 300 ms ISI condition (LI children did not change), so the significant correlations here likely reflect this change in the TLD participants. Thus, the correlations suggest that TLD children, who have higher eMMN amplitudes, tend to perform better on the ART-C for the 2-10 and 3-Fast trials.

Next, in the Ignore 70 ms ISI condition, **higher reading performance (WID, WA) is associated with *higher* eMMN amplitude**. Recall that there were no significant

changes in reading performance within each group from Visit 1 to Visit 2, and TLD children continued to earn higher reading scores than LI children at Visit 2. Examining mean eMMN amplitudes at each channel (Table 9.2.1b), it was found that at Ch. 53, where the significant correlations are observed, TLD children tend to have higher amplitudes than LI children (at all other channels examined, LI children have higher amplitudes as compared to TLD children). So, this association reflects the fact that TLD children, who have better reading performance, exhibit higher eMMN amplitudes at Ch. 53 in the Ignore 70 ms ISI condition.

Also in the Ignore 70 ms ISI condition, **better auditory temporal processing is associated with *lower* eMMN amplitudes**. In the channels where this association is observed (Ch. 17, 54), TLD children have lower amplitudes as compared to LI children. TLD children improved significantly on 3-Slow trials (LI children did not show a change for these ART-C trials). Thus, this association reflects that TLD children, who have better ART-C performance, exhibit lower eMMN amplitudes at Ch. 17 and 54 in the Ignore 70 ms ISI condition.

In the Ignore 10 ms ISI condition, **better language and reading performance is associated with *higher* eMMN amplitudes**. TLD children at Visit 2 exhibit higher amplitudes than LI children in all frontocentral channels. Neither TLD nor LI children showed a significant change in eMMN amplitude from Visit 1 to Visit 2 for this condition. In sum, the significant correlation here reflects that TLD children, who have higher language and reading scores, exhibit higher eMMN amplitudes in the Ignore 10 ms ISI condition.

In the Attend 70 ms ISI condition, **better language performance is associated with lower eMMN amplitudes**. In this condition, TLD children exhibit smaller amplitudes than LI children in all frontocentral channels. Thus, this association reflects the fact that TLD children, who have better language scores, exhibit lower eMMN amplitudes in the Attend 70 ms ISI condition.

Also in the Attend 70 ms ISI condition, **better auditory temporal processing is associated with higher eMMN amplitudes**. Although TLD children exhibit smaller amplitudes than LI children in all frontocentral channels, only LI children showed a significant improvement in 3-Fast from Visit 1 to Visit 2, while both groups significantly improved in the 2-10 trials from Visit 1 to Visit 2. Even with these changes, at Visit 1 and Visit 2 there were no differences *between* the two groups on ART-C performance for 2-10 or 3-Fast. Thus, due to the fact that LI children's scores improve and are indiscernible from those of TLD children, the association here may reflect that LI children, who have higher eMMN amplitudes in the Attend 70 ms ISI condition, display improved ART-C performance that is equivalent to that of TLD children.

In sum, as shown in the statistical analyses of behavioral performance, TLD children achieve higher scores on measures of language and reading. All correlations reflect the fact that better behavioral performance is associated with TLD children whether they exhibit larger or smaller eMMN amplitudes within the different ERP conditions.

9.4.3.2 Visit 2 – eMMN Latency Correlation Analyses

Correlation analyses revealed a number of significant associations between eMMN latency and behavioral measures, however not all associations followed the same pattern. As shown in Table 9.4.3.2, during passive listening (Ignore Condition), better behavioral performance is associated with *shorter* eMMN latencies (black text), while during active listening (Attend Condition) better behavioral performance is associated with *longer* eMMN latencies (blue text). These findings are explained as each group of associations is considered separately within each ERP condition, and ultimately a consistent result emerges from the data.

In the Ignore 70 ms ISI condition, **better language and reading performance is associated with shorter eMMN latencies**. This is the pattern typically associated with TLD children, who have higher language and reading scores and exhibit shorter latencies. Indeed, TLD children have significantly shorter eMMN latencies than LI children in the Ignore 70 ms ISI condition (Table 9.2.1b, p. 257). Additionally, the increased magnitude of these associations at Visit 2 as compared to Visit 1 (more channels, larger *r* values) are likely influenced by the fact that eMMN latencies increased significantly from Visit 1 to Visit 2 in the LI children only, therefore contributing greater variability to the data.

In the Ignore 10 ms ISI condition, **better language performance is associated with shorter eMMN latencies**, which are typically associated with TLD children. TLD children have significantly shorter eMMN latencies than LI children (Table 9.2.1c, pp. 257 - 258). Also, it was found that only TLD children show a decrease in latency from Visit 1 to Visit 2 for Ignore 10 ms ISI condition, so this created additional variability in the data (increasing range of eMMN latencies across all participants).

In the Attend 70 ms ISI condition, **better language performance is associated with longer eMMN latencies**. In this condition at channel Cz, where this association is seen, TLD children tend to have longer eMMN latencies than LI children. Thus, this association reflects the fact that TLD children, who have better language performance, exhibit longer eMMN latencies.

Similarly, in the Attend 10 ms ISI condition, **better language and reading performance is associated with longer eMMN latencies**. In this condition, TLD children tend to exhibit longer eMMN latencies as compared to LI children. Thus, this association reflects the fact that TLD children, who have better language performance, exhibit longer eMMN latencies in the Attend 10ms ISI condition.

In sum, as shown in the statistical analyses of behavioral performance, TLD children achieve higher scores on measures of language and reading (pp. 275 - 279). All correlations reflect the fact that better behavioral performance is associated with TLD children whether they exhibit longer or shorter eMMN latencies within the different ERP conditions.

9.4.3.3 Summary of Visit 2 – eMMN Correlation Analyses

Overall, better behavioral performance is associated with the TLD group, and the correlations observed follow this pattern whether TLD children show higher or lower amplitudes, or shorter or longer latencies. The change in magnitude of many associations may be due to changes in behavioral performance, especially in the LI group, that adds a higher degree of variability in the data, resulting in significant correlations between a greater number of variables with higher r values (Visit 1 range $|.383 - .641|$; Visit 2 range

|.352 - .943|) and a higher number of channels (maximum of 3 channels at Visit 1, and 6 channels at Visit 2).

9.4.3.4 Visit 2 – IMMN/LDN Amplitude Correlation Analyses

Initial correlation analyses revealed that in nearly all of the significant associations, **better behavioral performance (language, reading, and auditory temporal processing) is associated with lower IMMN/LDN amplitudes**. The one exception to this occurs in the Ignore 300 ms ISI with ART-C measures (2-150, 2-70) where better performance is associated with higher IMMN/LDN amplitudes at channels 53 and 54. Recall that there are no significant differences between TLD and LI children in ART-C performance for 2-150 and 2-70. Scatter plots were generated to look at the relations between ART-C performance at 2-150 (Ch. 53) and 2-70 (Ch. 53 and 54) and IMMN/LDN amplitude in both groups of children. In all of the scatter plots, one TLD child with very low ART performance and low IMMN/LDN amplitude was identified (Subject ID 09076). This child was removed from the analyses and the correlations for the Ignore 300 ms ISI condition were run again. This time no significant associations emerged between IMMN/LDN latency and ART-C performance at 2-150 and 2-70. In sum, this single outlier in the TLD group “pulled” the correlation, but after excluding this participant, no significant associations were present in the data. Thus, in the final analyses, in all significant associations between behavioral measures and IMMN/LDN amplitude at Visit 2, including the Ignore 300 ms ISI condition, **better behavioral performance is associated with lower IMMN/LDN amplitude** (see Table 9.4.3.4).

9.4.3.5 Visit 2 – IMMN/LDN Latency Correlation Analyses

In the significant associations found in the Ignore 70 and Ignore 10 ms ISI conditions, **better behavioral performance (language and auditory temporal processing) is associated with shorter IMMN/LDN latencies**. This was the expected result, since TLD children, who generally exhibit better language and ART-C scores, tend to have shorter IMMN/LDN latencies as compared to LI children. However, in the Attend 10 ms ISI condition, better performance on the ART-C (2-150, 2-70, NTT) was associated with longer IMMN/LDN latencies. There was a very small sample size for this condition (n=9), so the results should be interpreted with caution. To further investigate this association, scatter plots were generated which revealed that TLD children and most of the LI children have the same NTT (the minimum, 36 training trials), while there are two LI children who required more training. These two LI participants also had shorter IMMN/LDN latencies, and so it appears that the correlation was influenced by these two data points, the only ones that introduced any variability into the analyses. Additionally, one LI child (Subject ID 09010) was identified who had very poor ART-C performance (at or below chance levels and significantly lower than any other participant). Notably, this child was one of the two participants that required more than the minimum number of training trials on the ART-C. This outlier was removed from the data and the correlation analyses were run again for the ART-C variables. This time no significant relations were found between ART-C performance and IMMN/LDN latency in the Attend 10 ms ISI condition. Therefore, in the final analyses, in all significant associations **better behavioral performance is associated with shorter IMMN/LDN latencies** (see Table 9.4.3.5).

9.4.3.6 Summary of Visit 2 – IMMN/DLN Correlation Analyses

Overall, across all participants it was found that better behavioral performance is associated with lower IMMN/DLN amplitudes and shorter IMMN/DLN latencies. Notably, there are many more significant associations of greater magnitude between behavioral performance and IMMN/DLN measures at Visit 2 as compared to Visit 1. At Visit 1 significant correlations between behavioral variables and IMMN/DLN amplitude ranged from $r = .333 - .616$ at a maximum of 2 channels, while at Visit 2 the correlations ranged from $r = .350 - .862$ at a maximum of 4 channels. This was also true for correlations with IMMN/DLN latency. At Visit 1 the correlations ranged from $r = .383 - .589$ at a maximum of 2 channels, while at Visit 2 the correlations ranged from $r = .413 - .744$ at a maximum of 5 channels.

9.4.4 Summary of Visit 2 Correlation Analyses between Behavioral and ERP Measures

Correlation analyses between behavioral and ERP measures at Visit 2 revealed that overall **there are many more significant associations at Visit 2 as compared to Visit 1, and these are of higher magnitude (higher r value) and often occur at more channels**. Analyses of the eMMN component at Visit 2 revealed that better behavioral performance is associated with the TLD group, and all significant associations follow this pattern whether TLD children exhibit higher or lower amplitudes, or shorter or longer latencies. In the IMMN/DLN analyses at Visit 2, better behavioral performance is

associated with lower amplitudes and shorter latencies, characteristics more often observed in the TLD group.

The data were examined to see what ERP conditions yielded consistent significant associations between behavioral and ERP measures at Visit 1 *and* Visit 2 so these could be further investigated. In the eMMN analyses, the Ignore and Attend 70 ms ISI conditions are the only conditions that have significant persistent associations at Visit 1 and Visit 2. In the IMMN/LDN analyses, the majority of significant associations present at both visits are in the Ignore and Attend 70 ms ISI conditions. There are also significant relations within the Ignore 10 ms ISI and the Ignore 300 ms ISI. It was decided that the Ignore and Attend 70 ms ISI conditions were the best candidates for further investigation because consistent significant relations emerged for these conditions for *both* the eMMN and IMMN/LDN, and these conditions also have the largest number of participants. The sample sizes for the Ignore 300 and 10 ms ISI conditions, especially at Visit 2, are quite small, as noted in previous sections.

So, correlation analyses were conducted comparing behavioral and ERP measures for the Ignore and Attend 70 ms ISI conditions separately for TLD and LI children at both Visit 1 and Visit 2. The results were examined for patterns of significant associations, and how these patterns may differ across groups and across visits. The findings are reported below.

9.5 Correlation Analyses Between Behavioral and ERP Measures in TLD and LI Children

The main research question addressed in this final set of correlation analyses was: **Do TLD and LI children show different patterns of correlations between behavioral and ERP measures from Visit 1 to Visit 2?** It was predicted that LI children would show a greater degree of change in patterns of significant associations as compared to TLD children due to the intensive intervention program completed by the LI children between Visits 1 and 2, which led to significant changes in oral language skills. A smaller degree of change in patterns of associations was expected for the TLD children who did not participate in any intervention program, but effects of previous experience with the ERP stimuli and behavioral assessments may have had an effect on these repeated measures. Below, the results of these analyses are summarized.

9.5.1 Correlation Analyses for TLD and LI children - eMMN at Visit 1 and Visit 2

Significant associations found in the correlation analyses between Behavioral and eMMN measures for TLD and LI children are shown in Tables 9.5.1a (TLD children) and 9.5.1b (LI children). Overall, TLD children have more associations than LI children at Visit 1. In nearly all of the significant relations found in the TLD group at Visit 1, better behavioral performance is associated with larger eMMN amplitudes and longer eMMN latencies. The one exception to this was in the Attend 70 ms ISI condition where better ART-C performance (2-10) is associated with shorter eMMN latencies. The only significant association found in the analysis of LI children at Visit 1 is in the Ignore 70 ms ISI condition where better language performance is associated with longer eMMN latencies. This is the same relation that is found in the TLD group.

Examining changes from Visit 1 to Visit 2, for the shared correlation in the TLD and LI groups in the Ignore 70 ms ISI condition, the association in each group changes in the same way. At Visit 1 better behavioral performance is associated with *longer* eMMN latencies, while at Visit 2 better behavioral performance is associated with *shorter* eMMN latencies. Additionally, both TLD and LI children show a similar pattern of change for eMMN amplitude in the Attend 70 ms ISI condition where there are no significant associations at Visit 1, but at Visit 2 better behavioral performance is associated with *lower* eMMN amplitude.

In the TLD group, changes in patterns of correlations appear to result from changes in eMMN amplitude and latency rather than any change in behavioral performance. Such eMMN changes may be due to previous exposure to and experience with the stimuli at Visit 1, and/or very short term maturational changes. Interestingly, in the LI group similar changes in significant associations from Visit 1 to Visit 2 appear to result from increased scores on behavioral measures, specifically oral language, as well as changes in eMMN measures. The significant gains in language abilities in the LI group are attributed to the FFWD intervention, and changes seen in ERPs that may underlie language skills have probably also been affected, in addition to influences of previous experience with the ERP stimuli. An example is shown in Figure 9.5.1 in the Attend 70 ms ISI condition, where in the TLD group the change in correlation patterns from Visit 1 to Visit 2 are due to increases in eMMN amplitude, whereas in the LI group the same pattern of change is more attributable to increases in language performance.

Notably, **the number of significant associations between Behavioral and eMMN measures exhibited by LI children at Visit 2 are similar to those found in the**

TLD group at Visit 1. This suggests that in LI children *after* intervention and in naïve TLD children, eMMNs elicited by stimuli requiring rapid auditory processing correlate with behavioral performance in some similar ways. Although these associations apparently do not result from underlying mechanisms that operate in an identical fashion in these two groups of children, these findings are relevant to the potential clinical and further research applications of the eMMN response as an index of auditory discrimination and relations with behavioral performance. When comparing language impaired and normally developing groups of children, interpretation of eMMN responses should not be limited to variations on a single continuum, but the possibility of underlying mechanisms that operate in different ways should be considered. In sum, the eMMN is a reliable index of automatic auditory discrimination that relates to behavioral measures of language, reading, and auditory temporal processing in both TLD and LI children, and is useful for investigating relations between behavioral and underlying auditory processing abilities.

9.5.2 Correlation Analyses for TLD and LI children – IMM/LDN at Visit 1 and Visit 2

Significant associations found in the correlation analyses between Behavioral and IMM/LDN measures for TLD and LI children are shown in Tables 9.5.2a (TLD children) and 9.5.2b (LI children). At Visit 1 there are very few significant associations between behavior and IMM/LDN measures in both groups of children. At Visit 2, however, LI children have many more associations than TLD children. More specifically, at Visit 2, TLD children have no significant correlations between behavior and

IMMN/LDN amplitude (latency only), while LI children exhibit significant associations between behavior and IMMN/LDN amplitude *and* latency in both the Ignore and Attend conditions.

In the TLD group at Visit 2, associations between behavioral and IMMN/LDN latency show that in the Ignore 70 ms ISI condition, better language is associated with *longer* latencies, and in the Attend 70 ms ISI, better language and reading scores are associated with *shorter* latencies. Interestingly, in the LI group at Visit 2, in all but one of the significant associations between behavioral and IMMN/LDN measures, better behavioral performance is associated with *smaller* amplitudes and *shorter* latencies. Thus, the patterns of associations between behavioral and IMMN/LDN measures change from Visit 1 to Visit 2 in different ways for TLD and LI children. The main finding is that **LI children have many more significant associations at Visit 2 as compared to TLD children**. In nearly every case, better behavioral performance is associated with lower amplitudes and shorter latencies. In sum, the IMMN/LDN may be a better index of ERP changes associated with the FFWD intervention in LI children, but may not be as informative for a group of children with typical language development.

9.5.3 Summary of Correlation Analyses Between Behavioral and ERP Measures in TLD and LI Children

In the correlation analyses, **significant associations were found between children's MMN components and oral language, reading, and auditory temporal processing measures**. This shows that both the eMMN and IMMN/LDN are useful indexes of auditory processing that are related to behavioral abilities indexed by more

traditional auditory psychophysical and standardized language assessments. TLD children, in general, tend to have smaller amplitudes and shorter latencies as compared to LI children for both the eMMN and IMMN/LDN. It was found that the **ERP stimuli that correlate with behavioral measures across *both* visits are those with a 70 ms ISI.** This an interesting finding since these 70 ms ISI stimuli tap into rapid auditory processing and are in the range that are important for speech processing.

Examination of the TLD and LI groups separately showed that there are different patterns of associations between behavioral measures and eMMN and IMMN/LDN elicited by stimuli with a 70 ms ISI. **The eMMN analyses showed that the number of significant associations exhibited by LI children at Visit 2 is similar to that exhibited by TLD children at Visit 1.** Changes in patterns of correlations from Visits 1 to 2 in the two groups appear to result from differential shifts in the data (e.g. greater shift in LI language measures, as compared to a greater shift in TLD eMMN amplitude), suggesting that eMMN changes may index early, automatic auditory discrimination processes that operate differently in these two groups of children at two time points, with the LI group participating in the FFWD intervention between visits. **The IMMN/LDN analyses showed that LI children have many more significant associations at Visit 2 as compared to TLD children,** suggesting that the IMMN/LDN may be a more informative component when investigating immediate intervention outcomes in LI children. The IMMN/LDN is thought to be involved in extended processing of more complex auditory events in addition to early automatic processing reflected in the eMMN (Cheour et al., 2001), and so may be a less sensitive measure for TLD children who have normal, automatic auditory discrimination skills in the RAP time range examined here. However,

LI children may benefit from prolonged processing reflected in the IMMN/LDN as improved RAP skills resulting from FFWD intervention may not yet be incorporated into early automatic change detection processes indexed by the eMMN. In sum, correlations between ERP and behavioral measures revealed significant patterns of associations that differed in the TLD and LI groups for the eMMN and IMMN/LDN components, suggesting that these two components capture different aspects of auditory discrimination processing in these two groups of children.

9.6 Overall Summary of Experiment 5 Results

The research questions addressed in the present experiment are **What types of changes occur following an intensive auditory intervention program aimed at improving RAP abilities in LI children in (i) behavioral measures of language, reading and auditory temporal processing, (ii) in the eMMN and IMMN/LDN components, and (iii) how might such changes in behavioral and electrophysiological measures be related?** The results here show that FFWD resulted in significant improvements in oral language and measures of auditory temporal processing, replicating previous reports of positive outcomes following appropriate implementation of FFWD (Stevens et al., 2008; Krumpe & Harlow, 2008; Gaab et al., 2007; Temple et al., 2003; Tallal & Merzenich, 1996). LI children in the present study displayed significant gains in all language areas (receptive, expressive, and overall language ability), and significantly improved in both the ability to learn and perform well on aspects of an auditory temporal processing task. Changes in the eMMN and IMMN/LDN components were also observed following FFWD in LI children that differed from results

observed in control children across visits. In LI children, pre- to post- intervention changes in eMMN latency are observed that may reflect compensatory changes in RAP mechanisms (Ignore condition), as well as improvements due to enhanced selective attention (Attend condition). Changes in the IMMN/LDN across visits appear to reflect differences in auditory processing across various rates of presentation in the LI group. This variability is not seen in the TLD children, suggesting that the IMMN/LDN is not a very sensitive index of auditory processing (at least for the rates tested here) in a group of children with normal language development, but may be informative for children with abnormal or impaired auditory abilities.

Relations between these behavioral and electrophysiological indices were investigated through correlation analyses and it was found that the the eMMN and IMMN/LDN are associated with behavioral performance in both LI and TLD children, supporting the idea that MMN components elicited by stimuli that tap into RAP reliably relate to traditional measures of language and auditory processing across normally developing and language impaired populations. Of the three different rates of presentation tested in the present study, the one that showed the most reliable associations between behavior and *both* the eMMN and IMMN/LDN across visits and conditions (Ignore and Attend) was the 70 ms ISI, which is within the time range that is critical for speech processing (Tallal & Gaab, 2006). When the association between behavioral measures and mismatch components elicited by tone pairs separated by 70 ms were further investigated, it was found that LI and TLD children exhibited different patterns of significant associations within and across visits.

The eMMN analyses show that the number of significant associations exhibited by LI children *after* intervention are similar to those exhibited by naïve TLD children (Visit 1). Although it is unlikely that these associations result from underlying mechanisms that operate in an identical fashion, these findings demonstrate that improvements following FFWD training in LI children are manifest as increased significant relations between behavioral measures and the eMMN. Overall the results show that the eMMN, an index of early automatic auditory discrimination, relates to behavioral indices of language, reading, and auditory temporal processing in both TLD and LI children, and is therefore useful for investigating relations between electrophysiological and behavioral measures. The IMMN/LDN analyses show that after completing FFWD, LI children have many more significant associations between the IMMN/LDN and behavioral measures as compared to TLD children (at both visits). The IMMN/LDN is thought reflect extended processing of more complex auditory events (Hämäläinen et al., 2008; Cheour et al., 2001), and LI children may benefit from prolonged processing time as improved RAP skills resulting from FFWD intervention are not yet fully incorporated into early automatic change detection processes indexed by the eMMN. Thus, the IMMN/LDN may be useful for investigating immediate or short-term follow-up intervention outcomes in LI children, but may be a less sensitive measure for TLD children who have normal, auditory discrimination skills and do not require additional processing time. In sum, correlations between ERP and behavioral measures revealed significant patterns of associations that differed in the TLD and LI groups for the eMMN and IMMN/LDN components, suggesting that these two components capture different aspects of auditory processing in these two groups of children.

Taken together, the present findings demonstrate that completion of the FFWD intervention program in LI children results in immediate and significant gains in oral language and auditory temporal processing abilities, as well as changes in electrophysiological measures of auditory discrimination. Changes in ERP measures differ depending upon the rate of presentation of complex, non-verbal stimuli as well as the attention state of the child. Further, significant associations are found between behavioral and ERP measures, with the most robust and persistent relations found between behavior and paired complex tones presented at a rate within the time range that is essential for accurate speech processing (70 ms). The eMMN and IMMN/LDN components, thought to reflect separate aspects of automatic auditory discrimination processes, capture differences in TLD and LI children at both visits, demonstrating that these components together contribute to understanding auditory processing abilities that underlie complex behaviors, including language and reading, in both impaired and normally developing groups of school-age children.

10.0 General Discussion

The series of experiments reported here investigate relations among rapid auditory processing (RAP), attention, and language ability, and specifically address three main questions: (1) How are these factors related when development proceeds normally and language is *intact*? (2) How are these factors related when development is abnormal and language is *impaired*? (3) How are these factors related when abnormal language development is *intervened* and language and the underlying auditory system are altered? To address these questions, five experiments were conducted utilizing converging electrophysiological and behavioral techniques. The ERP analyses focused on examination of the mismatch negativity (MMN) response elicited by paired complex tones separated by a gap of 300, 70 or 10 ms during passive and active listening. Behavioral measures were traditional standardized and psychophysical assessments of language, reading, and auditory temporal processing. In all experiments, the electrophysiological techniques and auditory stimuli were identical, allowing for rigorous inspection of how the brain responds to rapidly presented, compound auditory stimuli across several populations: adults who experienced normal language development, 6 - 9 year old children with typical language development (TLD), and 6 - 9 year old children diagnosed with a language impairment (LI) both before and after completing the intervention program Fast ForWord-Language® (FFWD).

Overall, this body of work shows that automatic auditory processing, reflected in the MMN components, is modulated by the rate of presentation of auditory stimuli as a function of the attentional state of the listener over the course of development, supporting the idea that attention is an important component in the development of normal, mature

RAP abilities (Gomes et al., 2000). Further, it is shown that automatic auditory discrimination processes are atypical when language development is impaired, and the two developmental MMN components, the early MMN (eMMN) and late MMN, also called the Late Discriminative Negativity (lMMN/LDN), provide different insights into these difficulties. This work also demonstrates that in a group of LI children, the completion of the intervention program FFWD results in significant improvements in oral language and measures of auditory temporal processing, replicating previous reports of positive outcomes following appropriate implementation of FFWD (e.g. Stevens et al., 2008; Gaab et al., 2007). Such changes are related to automatic auditory discrimination processes, reflected in MMN components, specifically those that tap into RAP and are in the temporal range that is critical for decoding the rapidly changing features of spoken language.

Below, the present findings are discussed in the context of the three main research questions addressed in this dissertation, followed by the overall implications of this body of work and anticipated future directions.

10.1 *The Intact System: Rapid Auditory Processing and Attention in the context of Normal Development*

The auditory mismatch negativity (MMN), reflecting the brain's automatic response to any detectable change in the auditory environment, has been widely applied to investigations of central auditory processing in adults over the last 30 years (for a review, see Näätänen et al., 2007), but the developmental progression of the MMN and its underlying mechanisms are still poorly understood (Cheour et al., 2001). Maturational changes in ERPs are generally characterized by decreases in latency and amplitude

fluctuations with increasing age, and are attributed to increases in synaptic density in the auditory cortex, increases in myelination, as well as changes in the location and orientation of component generators (Thomas and Crow, 1994; Morr, et al., 2002; Martin et al., 2003; Shafer et al., 2000; Gomot et al., 2000; Eggermont 1998, 1992, 1988; Huttenlocher et al., 1982). Developmental changes in ERPs, and specifically the MMN, are of interest to both basic research and clinical investigations of auditory acuity since the MMN, which can be elicited passively without a behavioral response, is suitable for many populations, including pre-verbal infants, and individuals with motor and language impairments. The present examination of maturational differences in the MMN between adults and young school-age children experiencing normal development contributes to a better understanding of the development of RAP abilities that underlie language abilities. Additionally, the role of attention in early, automatic auditory discrimination was investigated, specifically how the MMN is modulated by selective attention directed toward the auditory modality.

Attention, shown to be a critical component of learning, may function to (i) recruit more neural resources during the processing of a sensory event, or (ii) increase synchrony among neural ensembles responding to a stimulus, or (iii) both (Näätänen et al., 1993b; Gomes et al., 2000). This drives plasticity so that a neural response to a sensory event that is initially voluntary (requiring attention to induce synchrony and/or recruit additional neural coalitions) eventually becomes automatic or involuntary. At the physiological level, it has been demonstrated that paired cortical and neuromodulatory mechanisms are necessary for such plastic changes to occur (Kilgard & Merzenich, 1998; Bao et al., 2003). A better understanding of how attention affects the modification of

neural representations in the auditory system will help elucidate the mechanisms of normal language acquisition, and be beneficial to the development and revision of intervention strategies for children with impaired language abilities. In adults and, to a lesser extent, children, attention has been shown to enhance the MMN, especially when the discrimination between two auditory stimuli is near the perceptual threshold, however the literature contains conflicting reports (e.g. Alho et al., 1989; Näätänen et al., 1993a; Gomes et al., 2000). Here, the MMN was examined in adults and young school-age children who experienced normal development (children with typical language development, TLD) in order to investigate potential maturational differences in the MMN, particularly with respect to the modulatory effects of rate of presentation and attention.

The present findings show that peak amplitudes and latencies of the mature MMN are similar for the three rates of presentation investigated (300, 70, and 10 ms ISI) during passive listening. This supports the idea that passively-elicited automatic auditory discrimination processes are equally efficient for these three rates of presentation in the adult brain. However, attending to the stimuli results in longer latencies at all three rates of presentation, and larger amplitudes are observed for the 300 and 70 ms ISI, but not the 10 ms ISI. These findings suggest that in normal adults, attention to paired tones separated by 300 and 70 ms gaps initiates the recruitment of additional neural resources, and/or induces greater neural synchrony, as reflected in higher MMN amplitudes (Näätänen et al., 1993a; Gomes et al., 2000). However, for tones separated by 10 ms, the MMN does not appear to be modulated by attention, indicating that the auditory system may be functioning at maximum efficiency to process such rapidly presented stimuli, and

thus attention does not confer a measurable advantage for discrimination indexed by the MMN. Although simple gap detection paradigms (i.e. detecting the presence of a silent gap within an otherwise continuous frequency band) show that adult thresholds are less than 10 ms, with more complex stimuli, like those used in the present study (e.g. different frequencies before and after the silent gap), the limits of auditory acuity are markedly elevated, and thresholds are closer to the range of 10 to 20 ms (Phillips, 1999; Phillips et al., 1998). This disparity is due to a more complex “between channel comparison” when two stimuli with different spectral compositions flank a silent gap, as opposed to a simple “discontinuity detection” process where a silent period is detected within an otherwise continuous sound (Phillips, 1999; Phillips & Hall, 2002). Such “between channel” stimuli, like those used in the present study, better mimic acoustic cues in speech perception (e.g. voice onset times), and thus tap into auditory temporal processing mechanisms that are important for language. Overall, the present findings suggest that in the mature adult, automatic auditory discrimination may be modulated by rate as a function of attention, and that such modulation is indexed by changes in the MMN.

With the same stimuli and paradigm, it was found that, overall and as expected, 6 - 9 year old TLD children exhibit larger amplitude fluctuations and longer latencies as compared to adults (Shafer et al., 2000; Thomas and Crow, 1994). Two developing MMN components were identified in the difference waveforms: the eMMN and IMM/NDN. These two mismatch components have been previously described in the literature in children, although the underlying mechanisms, especially those related to the IMM/NDN, are not well characterized (for a review, see Cheour et al., 2001). The eMMN is thought to be an immature version of the adult MMN, reflecting a pre-attentive

auditory change detection process, while the IMMN/LDN is believed to be involved in further discrimination of complex stimuli following an involuntary orienting response, and may be linked to attentional mechanisms within the context of the general maturation of the central nervous system (Hämäläinen et al., 2008; Ceponiene et al., 2002).

In TLD children, the amplitudes of passively elicited eMMN and IMMN/LDN do not differ across the three rates of presentation, suggesting that similar neuronal populations or levels of neuronal synchrony are engaged for all rates investigated. However, analysis of latency reveals rate modulation of both the eMMN and IMMN/LDN, though the pattern of modulation differs for these two components. The eMMN exhibits longer latencies at faster rates of presentation (70 and 10 ms ISI), while the IMMN/LDN exhibits longer latencies at slower rates of presentation (300 ms ISI). We speculate that these findings are related to maturing RAP abilities as they are reflected in the developing temporal window of integration (TWI) in 6 – 9 year old children. Temporal integration is the process by which two acoustic elements occurring in close temporal proximity are processed as a single auditory event (Bregman, 1990). This ability is critical for extracting sound structure from the auditory environment, and is an essential component in the translation of acoustic cues into meaningful neural representations (Wang et al., 2005). The TWI refers to the time range within which temporal integration occurs, and the TWI has been shown to decrease over the course of development (Oceak et al., 2008, Wang et al., 2005). The upper limit of the TWI is estimated to be approximately 200 ms in adults, 300 ms in 9 to 11 year old children, and 350 ms in 5 to 8 year old children (Wang et al., 2005). The TLD children in the present

experiment are between 6 and 9 years of age, and so the length of the TWI for this sample is estimated to be less than 300 - 350 ms.

It is proposed that in TLD children, eMMN peak latency elicited by tone pairs separated by shorter gaps may be somewhat lengthened due to the processing of two stimuli that fall within the TWI as a unitary event. The 300 ms ISI stimuli appear to just exceed the TWI in this sample of children, and so integration does not occur. The IMMN/LDN on the other hand, may exhibit shorter latencies for stimuli that tap into RAP (70 and 10 ms) and are processed as a single event. Such integrated stimuli may trigger further inspection of the acoustic event following a rapid, involuntary attention switch toward the auditory modality, while the IMMN/LDN in the 300 ms ISI condition may reflect a “second look” only at the second (deviant) tone in the pair. Indeed, in the 300 ms ISI waveform there is an obligatory N2 response to the second tone that is not elicited by the 70 or 10 ms ISI stimuli, indicating that the two tones are not processed as a single auditory event. Thus, during passive listening, the eMMN and IMMN/LDN categorically vary as a function of rate dependent upon whether two stimuli fall inside or outside the TWI, rather than on a “slow to fast” continuum.

Turning to the question of attention modulation in TLD children, it was found that attending to the auditory modality results in larger eMMN amplitudes for tone pairs with a 300 and 70 ms, but not the 10 ms ISI. This is the same pattern of results reported in adults, and suggests that for the slower rates of presentation, attending to the stimuli may confer a benefit in automatic discrimination due to increases in active neural populations and/or an increase in neuronal synchrony. The lack of an effect in the 10 ms ISI may indicate that the automatic discrimination processes are functioning at maximum

efficiency, and so attending to the tone pairs does not result in a measurable increase in eMMN amplitude. Examination of attention effects on the IMMN/LDN revealed no significant modulation of IMMN/LDN amplitude, but IMMN/LDN latency was significantly longer when attending to stimuli presented with 70 ms ISI. Since the IMMN/LDN is thought to be involved in further processing of complex (often linguistic) stimuli (Cheour et al., 2001; Hämäläinen et al., 2008), it is interesting to note that an attention effect is observed in children only for the ISI that falls in the time range (tens of milliseconds) that is critical for processing the rapidly changing elements of speech (Tallal & Gaab, 2006). These findings show that young school age children with typical language development exhibit both rate and attention modulation of the two developmental mismatch components, with the eMMN and IMMN/LDN reflecting somewhat different aspects of auditory discrimination.

Direct comparison of the adult MMN and child eMMN³⁷ reveals that during passive listening, adults and TLD children have comparable MMN amplitudes when tone pairs are separated by a 300 or 70 ms gap. However, for tones separated by only 10 ms, adults have significantly larger MMNs as compared to TLD children, indicating that in 6 – 9 year old TLD children, RAP abilities have not yet reached adult levels. However, when participants actively listen to the stimuli, MMN amplitudes of adults and TLD children are not significantly different at any of the rates of presentation examined. These findings suggest that while RAP abilities are still developing and are not yet under automatic control in young children, attention enhances discrimination of very rapidly

³⁷ The eMMN is thought to reflect pre-attentive, automatic change detection processes associated with the mature MMN, whereas the IMMN/LDN may represent a separate process involving further inspection of a deviant stimulus, possibly following an involuntary attention shift (Hämäläinen et al., 2008). The IMMN/LDN has also been found to rapidly attenuate with age making it largely unsuitable for study in adults (Cheour et al., 2001; Korpilahti et al., 2001).

presented sounds and this is reflected in an adult-like MMN (Gomes et al., 2000). In terms of MMN latency, as expected, during passive listening, adults exhibit shorter latencies than TLD children at all rates of presentation (Thomas and Crow, 1994; Shafer et al., 2000), but, during active listening, adults and TLD children have similar MMN latencies elicited by tones separated by a 300 ms gap. More rapid maturational changes in MMN amplitude and more gradual changes in latency have been reported (Ponton et al., 2000), and the present results are consistent with this literature. In contrast to MMN amplitudes, which appear to be at adult levels even in passive listening for the slower rates of presentation, this “lag” in developing adult-like MMN latencies may be attributed to neurobiological changes in the auditory cortex, especially myelination, that have a protracted period of development, extending well into adolescence (Eggermont, 1988). So, although the neuronal assemblies involved in auditory discrimination processes may be in place due to developmental increases in synaptic density, resulting in comparable MMN amplitudes for adults and 6 – 9 year old children, the speed of transmission that is dependent upon myelination and synaptic refinement, may follow a longer developmental trajectory (Huttenlocher & Dabholkar, 1997).

Overall, the present findings contribute to a better understanding of developmental RAP abilities in young school-age children and how these are reflected in the MMN. We show that when sounds are ignored, developmental differences in adult and children’s RAP abilities are apparent, but attention enhances RAP in children, “boosting” MMN responses to mature levels. This attention enhancement is more striking in measures of MMN amplitude, and is less robust for latency. This variable “attention effect” on MMN amplitude and latency may be explained by the maturational time

courses of neurobiological events, including changes in synaptic density and myelination (Ponton et al., 2000; Huttenlocher & Dabholkar, 1997). This should be taken into account when designing and conducting investigations of developmental changes in the MMN, so that both amplitude and latency measures can be examined together in order to fully understand the effects of stimulus and/or context variations on the MMN.

10.2 *The Impaired System: Rapid Auditory Processing and Attention in Children with a Language Impairment*

One of the main goals of this dissertation was to examine RAP in a group of children with a diagnosed language impairment (LI) in order to better understand the auditory processing deficits, remediation potential, and intervention outcomes in such a population. Intact RAP skills are believed to be essential for normal language development, and there is strong, accumulating evidence that poor RAP abilities are a basic impairment underlying developmental language disorders (Tallal & Gaab, 2006; Benasich & Tallal, 2002). It is estimated that 6 to 8 percent of all children entering kindergarten can be classified as language impaired despite adequate intelligence and otherwise normal development (Leonard, 1998; Tomblin et al., 1997). Given that LI affects so many children, understanding the etiology of this disorder and implementing effective interventions is a significant goal of the research and educational communities. In the present body of work, RAP abilities were investigated, as indexed by the MMN components, in 6 – 9 year old children with a LI as compared to those with typical language development (TLD). Specifically, modulation of the eMMN and IMM/LDN components as a function of rate of presentation and attention were explored.

Initial visual inspection of the grand averaged waveforms revealed that, as expected, LI children exhibit the same waveform morphology as TLD children (see pp. 140 – 158). Major auditory evoked components include a prominent P1 and N2 in both the standard and deviant waves, and an eMMN and IMMN/LDN in the difference wave. Further analyses revealed that in TLD and LI children, eMMN and IMMN/LDN amplitude does not vary as a function of rate of presentation during either passive or active listening. All significant findings were apparent in the analyses of latency. This again underscores the idea that measures of MMN amplitude should not be interpreted in isolation, but should be considered together with the temporal properties of the component of interest and within the context of underlying neurobiological changes (Ponton et al., 2000; Eggermont, 1988; Huttenlocher & Dabholkar, 1997).

As previously described, TLD children exhibit longer eMMN latencies when two tones are presented at faster (70 and 10 ms ISI) as compared to slower (300 ms ISI) rates during both passive and active listening. These findings are taken to suggest that, for TLD children, when two complex tones are presented within the temporal window of integration (TWI c.a. < 300 – 350 ms, Wang et al., 2005), peak latency might be prolonged due to the processing of two stimuli as a single auditory event. Additionally, TLD children have significantly shorter eMMN latencies than LI children overall, and here we show that within the LI group, eMMN latencies are similar across all three rates of presentation. Difficulty resolving two brief auditory stimuli presented in rapid succession is a well-documented deficit in children with LI (for a review, see Tallal, 2004) that may be related to underlying neuroanatomical anomalies, such as ectopias and microgyria (Galaburda & Kemper, 1979; Galaburda et al., 1985; Humphreys et al., 1990),

linked to early neurobiological events, including neuronal migration (Galaburda et al., 2006; Threlkeld et al., 2007; Burbridge et al., 2008; Denenberg et al., 1991). Here, we suggest that LI children may fail to show rate modulation of eMMN latency because even the slowest rate of presentation examined (300 ms) falls outside of an abnormal TWI, reflecting impaired RAP abilities in this group of LI children. Indeed, in the seminal studies demonstrating impaired RAP in LI children, Tallal & Piercy (1973) found that LI children required a gap of ≥ 305 ms in order to accurately sequence two successive tones.

Analyses of the late mismatch component reveals that a slower rate of presentation (300 ms ISI) results in longer IMMN/LDN latencies when the stimuli are ignored in both LI and TLD children. This may be taken to suggest that in both groups of children, faster rates of presentation trigger IMMN/LDN mechanisms to perform further processing of such stimuli (Hämäläinen et al., 2008). However, during active listening, only LI children continue to show this pattern of rate modulation; there are no IMMN/LDN latency differences across the three rates of presentation in TLD children. We speculate that for LI children, even during active listening, early automatic processing reflected in the eMMN may not be sufficient to accurately or fully discriminate the compound stimuli used here, even at the slowest rate of presentation. Thus, in LI children the mechanisms indexed by the IMMN/LDN are engaged so that further processing or discrimination of the sounds can occur.

Furthermore, in general, attention leads to larger eMMN amplitudes in both LI and TLD children, reflecting possible increases in neural synchrony and/or neural recruitment (Näätänen et al., 1993b; Gomes et al., 2000). In contrast, analyses of the IMMN/LDN fail to reveal any effects of attention on IMMN/LDN amplitude in both LI

and TLD children, but attention increases IMMN/LDN latency in the 70 ms ISI only. Given the proposed involvement of the IMMN/LDN in further processing of complex (often linguistic) stimuli (Cheour et al., 2001), it is interesting to note that an attention effect observed in *both* LI and TLD children occurs only for the ISI that is in the time range (tens of milliseconds) that is important for speech processing (Tallal & Gaab, 2006).

Overall, these results are consistent with the theory of slowed RAP as an underlying deficit in language impairments, and highlight differences of the effects of attention on the early and late mismatch components. An attention effect is observed in TLD and LI children only for the rate of presentation (70 ms) that is within the time range that is important for decoding rapid transitions in speech (Tallal, 2004). It is interesting that even though this rate of 70 ms ISI presentation rate appears to be too rapid for fully automatic processing in LI children, stimuli presented in this time frame still engage the auditory system to “tune in”, suggesting that this is a critical time range for auditory processing. Finally, the different patterns of findings for the eMMN and IMMN/LDN together contribute to better characterization of RAP impairments in a group of children with a LI better than either component could alone.

10.3 *The Intervened System: Rapid Auditory Processing and Attention Following Auditory Discrimination Training in Children with a Language Impairment*

The third aim of this series of experiments was to examine relations between rapid auditory processing (RAP), attention, and language ability in LI children following an intensive intervention program that specifically targets auditory processing skills

(Tallal et al, 1996; Merzenich et al., 1996). The effects of learning-dependent plasticity have been documented in a growing number of studies using various intervention programs for children with language disorders (Myler et al., 2008; Stevens et al., 2008; Krumpe & Harlow, 2008; Gaab et al., 2007; Temple et al., 2003; Simos et al., 2002a, 2002b; Kujala et al., 2001; Heim, Eulitz, & Elbert, in press; Merzenich et al., 1996; Tallal et al., 1996), and here we investigated the FFWD intervention program that was designed to improve RAP skills that underlie language difficulties in LI children (Merzenich et al., 1996; Tallal et al., 1996). We hypothesized that changes in both RAP and language would be evident in post-training assessments and that such changes would be reflected in the mismatch negativity components of the ERP waveforms.

Our findings show that completing the FFWD intervention program results in significant and immediate improvements in oral language and measures of auditory temporal processing in children with a LI, replicating previous reports of positive outcomes following proper implementation of FFWD (Stevens et al., 2008; Krumpe & Harlow, 2008; Gaab et al., 2007; Temple et al., 2003; Tallal & Merzenich, 1996). LI children in the present study displayed marked gains in all language areas (receptive, expressive, and overall language ability), and significantly improved in both the ability to learn and perform well on aspects of an auditory temporal processing task. Significant changes in reading scores were not observed. Given that all of the LI children in the present study received FFWD intervention during the summer months when school was not in session, it is likely that such secondary improvements in reading are not seen because children did not have sufficient time and/or customary or supplementary educational instruction necessary to incorporate their enhanced auditory discrimination

abilities into improvements in reading. FFWD does not directly address reading skills, and so it is not surprising that in the short-term follow-up assessment (1 to 4 weeks following completion of FFWD) no changes in reading were apparent. Changes in reading following FFWD have been reported, and this may be due in part to the timing of the administration and post-training assessments (Temple et al., 2003; Gaab et al., 2007). Future studies with additional follow-up time points noting the amount of educational instruction received during and after the intervention period are needed to comprehensively address this issue in 6 – 9 year old LI children.

Examining pre- to post- intervention changes in the eMMN and IMM/LDN components revealed different patterns of results for LI and TLD children. In the analyses of the eMMN, in the LI group, the only changes following FFWD are seen in the 70 ms ISI conditions, specifically an increase in eMMN latency during passive listening, and a decrease in eMMN latency during active listening, reflecting changes in RAP. The increase in eMMN latency may be explained by a “time cost” related to extended processing following the FFWD intervention. FFWD aims to improve auditory discrimination abilities through active behavioral exercises. Once faster RAP achieved through active intervention, over time these improved abilities are likely to be incorporated into involuntary, automatic processing (Gomes et al., 2000, Kraus et al., 1995a). Since the LI children in the present study completed the follow-up ERP session shortly after the end of the FFWD intervention, there may not have been sufficient time for these improvements in RAP to become completely automatic. Moreover, longer passively-elicited eMMN latencies may reflect extended processing of the stimuli during a phase of compensatory brain activation, before being integrated and streamlined into

more efficient mechanisms (Meyler et al., 2008). In contrast, during active listening, improved RAP abilities in the LI children are evident in the form of shorter eMMN latencies, perhaps due to an enhanced benefit of attention on RAP at rates that are more salient following FFWD training (Tallal, 2004) and/or overall improvements in selective attention and vigilance (Stevens et al., 2008). In the TLD children, there are no changes in eMMN measures across visits in the 70 ms ISI conditions, demonstrating the short-term stability of the eMMN in children with typical language development. The noteworthy limitation on the interpretation of these findings is the small number of children who received the 300 and 10 ms ISI rates of presentation, especially during active listening, and so changes in the eMMN at these rates of presentation cannot be completely ruled out. However, it is interesting that robust pre- to post- intervention changes in the eMMN are observed at a rate of presentation that is most critical for speech processing (70 ms ISI) (Tallal & Gaab, 2006) during both passive and active listening, a rate that is therefore likely to be extremely salient.

The IMM/LDN appears to capture different aspects of auditory processing across the two visits. The functional mechanisms underlying the IMM/LDN component are still poorly understood, as it has only recently been identified and begun to be investigated (Ceponiene et al., 1998; Korpilahti et al., 2001; Shestakova et al., 2003). The IMM/LDN has been proposed to be involved in extended discrimination processing of auditory stimuli (Hämäläinen et al., 2008), and has been linked to the maturation of attention mechanisms (Ceponiene et al., 2002). In the present experiment, during passive listening, TLD children exhibit IMM/LDN latency decreases across the visits for all three rates of presentation, but no changes in amplitude. This consistent pattern of results

may be taken to suggest short-term changes in the IMMN/LDN due to previous exposure to the stimuli (both passive and active). These findings demonstrate that the IMMN/LDN component may not be a sensitive index of discrimination difficulty in a group or normally developing children, at least for the rates of presentation tested here,. In the LI children, however, pre- to post- intervention changes are seen in both IMMN/LDN amplitudes and latencies. Thus, under passive listening conditions, the IMMN/LDN appears to reflect differences in auditory processing across various rates of presentation in the LI group that may not be present in the TLD children. Recent investigations reported in the literature have reported changes in the IMMN/LDN during and after the acquisition of new skills, including second language learning (Shestakova et al., 2003), and reading remediation in a group of poor readers (Alonso-Bua et al., 2006). The IMMN/LDN may therefore be a useful candidate component for investigating RAP abilities in groups of children with language difficulties, providing additional or different information than the eMMN alone³⁸.

Finally, relations between behavioral and electrophysiological indices were investigated and results show that both the eMMN and IMMN/LDN are significantly correlated with behavioral performance in LI and TLD children, supporting the idea that MMN components elicited by stimuli that tap into RAP relate to traditional measures of language and auditory processing across normally developing and language impaired populations. Of the three rates of presentation tested in the present study, the one that showed the most reliable associations between behavior and *both* the eMMN and

³⁸ No changes in the IMMN/LDN were observed during active listening in either group, although the sample sizes were quite small (TLD $n \leq 6$, LI $n \leq 8$), and not all comparisons could be conducted (not enough data for ANOVA in the 300 and 10 ms ISI conditions), so no firm conclusions can be drawn from these null results.

IMMN/LDN across visits and conditions (passive and active listening) was the 70 ms ISI, which is within the time range that is critical for decoding rapid transitions in spoken language (Tallal & Gaab, 2006). When the association between behavioral measures and mismatch components elicited by tone pairs separated by 70 ms were further investigated, it was found that LI and TLD children exhibit different patterns of associations within and across visits.

The number of significant associations between the eMMN and behavioral measures exhibited by LI children *after* intervention are similar to those exhibited by naïve TLD children (at visit 1). Although it is unlikely that these associations result from underlying mechanisms that operate in an identical fashion, these findings demonstrate that improvements following FFWD training in LI children are manifest as increased significant relations between the eMMN and behavioral measures of language, reading and auditory temporal processing. The eMMN, an index of early automatic auditory discrimination, is therefore useful for investigating relations between electrophysiological and behavioral measures in both TLD and LI children. Additionally, after completing FFWD, LI children have many more significant associations between the IMMUN/LDN and behavioral measures as compared to TLD children (at both visits). LI children may benefit from prolonged processing time, as reflected in the IMMUN/LDN, because improved RAP skills resulting from FFWD intervention are not yet fully incorporated into early automatic change detection processes indexed by the eMMN. Thus, the IMMUN/LDN may be a valuable marker for investigating immediate or short-term follow-up intervention outcomes in LI children, but may be a less sensitive measure for TLD children who have normal auditory discrimination skills and do not require additional

processing time. In sum, correlations between ERP and behavioral measures revealed significant patterns of associations that differed in the TLD and LI groups for the eMMN and IMMN/LDN, suggesting that these two components capture different aspects of auditory processing in these two groups of children.

Taken together, the present findings demonstrate that completion of the FFWD intervention program in LI children results in immediate and significant gains in oral language and auditory temporal processing abilities, as well as changes in electrophysiological measures of auditory discrimination. Changes in ERP measures differed depending upon the rate of presentation of complex, non-verbal stimuli as well as the attentional state of the child. Further, significant associations were found between behavioral and ERP measures, with the most robust and persistent relations found between behavior and paired complex tones presented at a rate within the time range that is essential for accurate speech processing (70 ms). The eMMN and IMMN/LDN components, thought to reflect separate aspects of automatic auditory discrimination processes, captured differences in TLD and LI children at both visits, demonstrating that these components contribute collaboratively to understanding auditory processing abilities that underlie complex behaviors, including language and reading, in both impaired and normally developing groups of school-age children.

10.4 Concluding Remarks and Future Directions

In sum, this body of work directly contributes to the understanding of RAP as it is influenced by attention in the mature adult, children experiencing typical development, and children with a language impairment. Further, the behavioral and

electrophysiological changes following the targeted intervention program, FFWD, in LI children link improvements in language abilities to underlying neurophysiological changes in auditory processing mechanisms. As in all empirical research, however, there are limitations to the design and interpretation of every experiment, and new questions naturally arise leading to ideas for future studies. Here, the two main limitations were small sample sizes in some of the stimulus conditions (particularly, the 300 and 10 ms ISI Attend conditions), and the lack of a non-intervened group of LI children. These factors constrained some of the secondary research questions in the present body of work, and lay the groundwork for future investigations.

Small sample sizes limited the ability to carry out multivariate statistical comparisons in every condition. Fatigue and restlessness in 6 – 9 year old children is not an unexpected or unprecedented complication in relatively long ERP sessions, and was the main cause of loss of data in the present studies. A future aim would include additional participants in the 300 and 10 ms ISI conditions to increase statistical power. Additionally, the present dissertation focused on traditional peak analysis methods making this series of studies comparable to a large body of existing ERP/MMN literature. While these analyses directly addressed the present research questions, more sophisticated statistical methods examining power band and single trial analyses would provide valuable insights into differences between normal and impaired groups, as well as characterize changes in auditory processing as a result of exposure to auditory stimuli in conjunction with development and plasticity. Indeed, examination of gamma band power spectrums revealed differences between infants at an elevated risk of developing a language impairment due to a positive family history and a group of infants with no such

history (Benasich et al., in press). This, and other prospective longitudinal studies directly address the overarching goal of early identification and remediation of RAP impairments that may underlie abnormal language development in very young children. The research reported here examines these issues in older children who have experienced impaired language development, and insights from power band analyses will contribute to understanding the etiology and intervention outcomes of developmental language disorders. Collaborations investigating power band spectra in the present data set are already underway (Hollander & Harris, CMBN, Rutgers University; Heim, University of Konstanz), and the findings are eagerly anticipated. Also, other objective ERP analyses methods including principal and independent components analyses (PCA, ICA) (Kalyakin et al., 2008; Kayser & Tenke, 2005) and fitting power-band measurements to general linear models (GLM) (Montgomery & Buzsaki, 2007; Jacobs et al., 2006) will be extremely valuable in further understanding the way in which brain responses change as a result of both maturation and training-induced plasticity. Continuing analyses of the present data set will include these types of statistical methods.

In addition to the data-driven statistical methods described above, further investigation of other traditionally identified ERP components in this data set, including the P3/P3a and the N1, also have the potential to be extremely informative. The P3, which peaks over parietal areas approximately 300 ms after the onset of a deviant stimulus, is believed to reflect a voluntary orienting response, or switching of focused attention, that involves response selection and/ or context updating (e.g. Buchwald, Guthrie, & Schwabe, 1994; Dehaene-Lambertz, 1997). The amplitude of the P3 is thought to reflect a number of factors involved in attentional processing, including the amount of

perceptual-cognitive resources required for stimulus discrimination (Näätänen, 1992; Johnson, 1986; 1993). The P3 is elicited during oddball presentations when the subject is actively attending to the auditory stimuli and has been instructed to respond to a deviant (infrequent) stimulus. In passive oddball conditions, however, where the participant has been explicitly instructed *not* to attend to the auditory stimuli and/or is engaged in a distracting (primary) task, a P3a component following the MMN is observed. The P3a is thought to represent an involuntary and transient attention shift to novel (Alho, Escera, Diaz, Yago, & Serra, 1997; Escera, Alho, Schroger, & Winkler, 2000) or deviant (Picton 1992; Baudena, Halgren, Heit, & Clarke, 1995) stimuli. It has been proposed that automatic analyses of the physical features of acoustic stimuli (reflected in the MMN) may lead to the switching of attention to salient events (reflected in the P3a), such that passive attention leads to conscious perception. Thus the P3 and the P3a may be interesting components for future analyses in the present data, and may further elucidate changes following the FFWD intervention, reflecting differences in auditory and attentional processing in the present sample of LI children.

The N1 is an exogenous sensory response that is one of the first cortically generated ERP components. The N1, a major negative deflection occurring approximately 100 ms after stimulus onset, is believed to reflect afferent activation elicited by ‘new’ stimulus features, and is typically elicited by abrupt changes in the auditory environment, including stimulus onsets and offsets (Näätänen, 1992). The N1 has been shown to discriminate between individuals with language impairment and controls, with LI children exhibiting longer N1 latencies than children with typical language development (Jirsa & Clontz, 1990; Mason & Mellor, 1984). Also, in an

analyses of a sub-set of the LI children in the present series of studies, it was found that the N1 component began to emerge in the standard and deviant waves as part of the P1-N1-P2 complex only *after* the completion of the FFWD program, making the waveforms of LI children appear similar to those of children with typical language development (Friedman et al., 2007, 2005). Thus, it may be very informative to examine the emergence of the N1 as a marker of rapid auditory processing in the full sample of LI and TLD children included in the present dissertation.

Another logical extension of the present work involving the FFWD intervention strategy would include a group of non-intervened LI children, perhaps on a delayed start schedule, thus allowing for short-term developmental and experience-related factors to be investigated. Additional follow-up assessments at 6 months, 1 year and even 2 years following the initial intervention would provide information about long-term behavioral outcomes as well as trace the course of potential early compensatory to later normalized neural activation during RAP.

In conclusion, this body of research demonstrates that automatic auditory discrimination, reflected in the Mismatch Negativity, is differentially modulated by the rate of auditory stimulus presentation as a function attention in the mature brain, the normally developing system, and in the impaired developing system. The findings support the idea that attention is a critical component in the normal development of mature RAP abilities, and in auditory learning resulting from an intensive auditory intervention designed to aid children with language impairments. The two developmental MMN components, the eMMN and IMMN/LDN, provide different insights into normal and disordered RAP in children allowing an opportunity to better understand relations

between basic auditory processing skills and language abilities. This work also demonstrates that in a group of LI children, the completion of the intervention program FFWD results in significant improvements in oral language and measures of auditory temporal processing, replicating and extending previous findings. Such changes are related to automatic auditory discrimination processes, reflected in MMN components, specifically those that tap into RAP and are in the temporal range that is critical for decoding the rapidly changing features of spoken language.

11.0 References

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12.0 Curriculum Vitae

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- 1992 Graduated from Westlake High School, Austin, Texas, U.S.A.
- 1996 Bachelor of Arts from Colgate University, Hamilton, New York, U.S.A.
Major: Biology
- 1996 – 1998 Employed as Laboratory Coordinator at the Infancy Studies Laboratory,
Rutgers University, Newark, New Jersey
- 1998 Admitted to Graduate Program in Behavioral and Neural Sciences,
Rutgers University, Newark, New Jersey
- 1998 – 1999 Received Johnson & Johnson Fellowship Award, Rutgers University,
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- 2001 Article: “Developmental disorders of language” in Encyclopedia of
Cognitive Science, London, UK: Nature Publishing Group, Macmillan
Reference Limited.
- 2002 Article: The importance of rapid auditory processing abilities to early
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Developmental Psychobiology, 40, 278-292.
- 2004 Article: Age and experience-related improvements in gap detection in the
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- Article: Impaired gap detection in juvenile microgyric rats.
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- Article: Timing errors in event-related potentials. Journal of Neuroscience
Methods, 138 (1-2), 1-6.
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Neuropsychologia, 44 3, 396-411.
- Article: Development of structure and function in the infant brain:
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