DEVELOPMENT OF PITCH PERCEPTION

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INDEXED BY
INFANT MISMATCH RESPONSES

By

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A Thesis
Submitted to the School of Graduate Studies
in Partial Fulfillment of the Requirements
for the Degree
Doctor of Philosophy

McMaster University

DOCTOR OF PHILOSOPHY (2005)
(Psychology)

McMaster University
Hamilton, Ontario

TITLE: Development of Pitch Perception Indexed by infant Mismatch Responses

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NUMBER OF PAGES: viii, 160

ABSTRACT

Hearing provides a vital means for infants to discover their environment and communicate with their caregivers. Identifying and discriminating the pitch of sounds is critical for infants in order to acquire information from speech and music. Therefore, how infants process pitch is a fundamental question in research on auditory development. The focus of this dissertation is the use of auditory event related potentials (ERPs) derived from electroencephalogram (EEG) recordings to examine the maturation of pitch perception in early infancy.

Pitch perception in adults has been extensively studied, but little is known about the development of pitch perception during early infancy. Infant mismatch responses (MMRs) are ERP components that are elicited by infrequent changes in auditory stimuli. MMR is a promising tool to study infant pitch perception because it can be elicited without attention or a behavioural response. However, previous studies on MMRs in infants have reported inconsistent results, some reporting frontally positive responses while others report frontally negative mismatch responses. In Chapter 2, we examined MMRs to simple pitch changes in infants between 2 and 4 months of age and found both types of infant MMRs are present, but the morphological distributions and developmental trajectories are different. In Chapter 3, we reported that both types of infant MMRs are affected similarly by the amplitude of pitch change but only the positive MMR becomes stronger when stimulus presentation rate increases, which suggests different neural mechanisms for the two types of infant MMRs. The studies reported in Chapter 4 found that only the negative MMR can be elicited readily by changes in pitch patterns, suggesting that it may be functionally similar to mismatch negativity (MMN) in adults.

The experiments in Chapter 5 used MMR as the indication of whether infants automatically integrate the frequency components of a complex tone into a single pitch percept, even when the fundamental frequency component (corresponding to the pitch) is removed. Previous studies show that adult MMN is elicited by a pitch change in such tones missing the fundamental. Previous behavioural studies using a conditioned head turn method show that 7-month-olds also perceive pitch with tones missing the fundamental. The results of the present study indicate that infants as young as 4 months of age integrate components into a single pitch percept, but evidence for this in younger infants could not be found.

In conclusion, the current dissertation established a promising procedure utilizing infant MMR to study infant pitch perception and contributed to the knowledge of early development of pitch perception by demonstrating dramatic changes in brain response to pitch in harmonic tones in infants between 2 and 4 months old, and to pitch in tones in infants missing the fundamental between 3 and 4 months old.

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Chapter 1:

GENERAL INTRODUCTION

Pitch and Pitch Processing in Auditory System

Pitch is one of four fundamental perceptual dimensions of sound, the others being duration, loudness, and timbre (Ward, 1929). Pitch is a subjective percept related to the frequency of vibration, and can be defined as an "attribute of auditory sensation in terms of which sounds may be ordered on a musical scale" (American Standards Association, 1960). Research on pitch can be traced back 2500 years, when Pythagoras studied the nature of pitch in musical tones.

Pitch is a very important cue for grouping and segmenting simultaneous sounds from different sound sources (Bregman, 1994), as sounds with similar pitches are likely to have been generated by the same sound source in the natural environment; sounds with very different pitches are likely to have been generated from different sound sources. In addition, pitch contributes to our ability to identify individual speakers and their characteristics (e.g., gender, age, size) and to perceive prosodic features (e.g., stress, intonation) in speech. In music, recognizing melodies would be very difficult, if not impossible, without pitch processing, as melodies consist of patterns of tones with different pitches and durations. Furthermore, both music and speech rely on pitch patterns or relations between successive pitches to convey meaning. Developmentally, learning to link different pitch patterns to different meanings is likely one of the first steps for infants to make sense of sounds (Fernald, 1989). Due to the vital role of pitch perception for auditory experience, the study of pitch perception is critical for an understanding of human auditory processing.

Sounds that elicit the sensation of pitch are called tones. The simplest tone, called a pure tone, is composed of a single sine wave. Frequency describes the numbers of times that a sound waveform repeats itself in one second. A pure tone only has one frequency that is equal to the repetition rate of the sine wave. (In fact, a tone can only approach pure tone status, as it would have to be infinitely long to be completely pure.) The pitch that is perceived when listening to a pure tone corresponds to the frequency of the pure tone. The complex tones that we hear in music and speech are composed of a combination of pure tones called partials, components or harmonics. The partial that has the lowest frequency is called the fundamental, and all the other partials are called harmonics. Harmonics have frequencies that are typically integer multiples of the fundamental frequency. For example, a complex tone with a fundamental at 220 Hz has harmonics at 440 Hz, 660 Hz, 880 Hz, 1100 Hz, 1320 Hz, and so on. A complex tone is perceived as a single auditory object having a single pitch, which corresponds to the repetition rate of the complex waveform or the frequency of its fundamental. The higher harmonics do contribute substantially to the sensation of pitch, however, as complex tones elicit a stronger sensation of pitch than pure tones. (For a review of the physical nature of pitch, see Moore, 2003). People are sensitive to a wide range of sound frequencies from about 20 to 20,000 Hz, but are maximally sensitive (i.e., have lowest detection threshold for) frequencies between 1.5 KHz and 6 KHz (for absolute sensitivity measurement data, see

ISO 389-7, 1996). For pitch discrimination sensitivity, the most common measure is the difference limen for frequency (DLF), which is the smallest detectable change in the frequency of pure tones or in the pitch of complex tones. The DLF in normal adults is smallest for middle frequencies (between 25 to 4,000 Hz), where less than a 1% change in frequency is detectable. The DLF becomes larger for very high and very low frequencies. (For a review of pitch perception performance in human adults, see Moore, 2003.)

When we hear a sound, the sound wave first reaches our outer ear (pinna), which acts as a filter (selectively attenuates frequency components dependent on the location of the source relative to the ear). Once the sound waves reach the end of the ear canal, they vibrate the eardrum, which connects the ear canal and the middle ear. When the eardrum is vibrating, the vibrations pass to the three tiny bones called ossicles that are attached to the center of the eardrum. The ossicles match the impedance of the eardrum to that of the fluid in the cochlea in the inner ear. The cochlea contains the basilar membrane, which vibrates in response to the sound wave. Attached to the basilar membrane are thousands of fibers called hair cells that move up and down as the basilar membrane vibrates. The inner hair cells act as auditory receptors that convert the vibratory movement into electrochemical impulses in the auditory nerve fibers. The auditory nerve fibers connect to the cochlear nucleus in the brainstem, which connects to the superior olivary nucleus, then to the inferior colliculus, then to the medial geniculate body, with the information eventually arriving at the auditory cortex (for a review, see Moore, 2003).

Auditory frequency information is coded in two distinct physiological processes in the human auditory system. The first process is spatial coding. Near the apex of the cochlea, the basilar membrane vibrates with maximal displacement in response to low frequency tones, and near the base of the cochlea it vibrates maximally to high frequency tones. Thus different frequencies maximally enervate different populations of hair cells residing on the membrane. In this way, a spatial map of frequency is formed in the cochlea. Similar tonotopic maps have been found at all subcortical levels of the auditory pathway, including the inferior colliculus (Stierbler & Ehret, 1985) and the thalamus (Bigalke-kunz et al., 1987). Primary auditory cortex also contains several frequency maps (for reviews, see Griffiths 2003; Ozaki & Hashimoto, 2007).

The second process involves coding sound frequency information through the temporal pattern of neural firing. Because hair cells fire at the time of maximal displacement of the basilar membrane, the timings of the discharge patterns across neurons reflect the periodicities and phase information of the sounds. Through patterns of firing in populations of neurons, temporal information can be encoded up to about 5 kHz, which corresponds roughly to the upper limit for the sensation of pitch (for a review, see Cariani, 1999). A temporal representation of frequency has been found in the central auditory system from the auditory brainstem (e.g., Greenberg & Rhode, 1987; Rhode, 1995) to the primary auditory cortex (e.g., Griffiths et al., 1998, Patterson et al., 2002, Warren & Griffiths, 2003) in studies using stimuli containing only temporal cues to pitch (see Chapter 5 for details of such stimuli; for a review, see Yost et al., 1996).

Development of Pitch Perception in Infants

Pitch perception plays a vital role in speech recognition, music perception, and the identification of sounding objects in the environment as discussed at the beginning of this chapter. In order to better understand the processes of language acquisition, music learning, and general auditory development, it is therefore vital to learn about how pitch perception develops in infancy. Research on pitch development can also make a significant contribution to the understanding of human pitch perception mechanisms in general. For example, if spatial and temporal pitch mechanisms develop at different ages, they can potentially be studied in greater isolation during development. Studies on infant pitch perception may also provide information of relevance for screening young infants at potential risk for central hearing disorders by indentifying age norms for the development of various pitch processing abilities.

Considering the importance of pitch perception for auditory communication, and the importance of auditory communication between very young infants and caregivers who sing and talk to them, it is not surprising that even young infants are able to respond to pitch information. Fetuses at the gestational age of 35 weeks have been found to respond to pure tones at frequencies between 100 Hz to 3000 Hz (Hepper & Shahidullah, 1994). Furthermore, this study found that after habituation to a 500 Hz tone, fetuses show movement responses to tones of 250Hz, indicting some discrimination of frequency. Fetuses of 36-39 weeks gestational age react with a change in heart rate when a piano tone switches from note D4 (f_0= 292 Hz) to C5 (f_0=518 Hz). (Lecanuet et al ,2000). Hence some frequency information appears to be available at the onset of hearing around the sixth prenatal month. Even near birth, absolute thresholds and discrimination sensitivity for frequency and pitch in fetuses remains largely unknown.

Postnatally, infants' discrimination abilities have been studied by allowing them to control the presentation of sounds by their non-nutritive sucking: after habituation to one sound, infants increase their sucking when a discriminable novel sound is presented. Using this method, Nazzi et al. (1998) found that neonates respond to changes when the pitch contour of a word is changed. By at least as young as 2 months, infants are able to discriminate and remember relatively complex prosodic contours (pitch changes in the successive musical notes) in speech and music (Jusczyk & Thompson, 1978; Kuhl, 1979; Plantinga et al., 2007).

However, young infants are much poorer than adults in both absolute sensitivity and discrimination among pitches. For absolute sensitivity, infants require sounds to be louder in order to hear them. Most infant data comes from studies that used various behavioral responses (e.g., sucking rate, head turn, and other motor activity) as the indication of whether or not infants heard a sound. Results from these studies show that newborns have a relatively flat threshold curve across frequency and that their thresholds are about 50–60 dB higher than those of adults (e.g., Weir, 1979; Olsho et al., 1987). These thresholds rapidly decrease after birth and by 6 months of age thresholds for 2 and 4 kHz tones are much closer to those of adults (within 5–10 dB); for frequencies lower and higher than this range, thresholds remain farther from those of adults (10–20 dB) (Olsho et al., 1988). Absolute sensitivity continues to improve with age, but does not reach adult levels until well into childhood (e.g., Maxon & Hochberg, 1982.). Nevertheless, direct assessment of cochlear function with otoacoustic emissions and click-evoked cochlear responses in newborns suggests that the cochlea is largely mature at birth (e.g., Probst, 1990). Brainstem function matures somewhat later: auditory brainstem evoked responses (ABR) suggest that infants' threshold are adult-like at birth for low frequencies (e.g., 0.5 kHz), adult-like at 1 month of age for very high frequencies (e.g., 10 kHz), but continue to improve into childhood for middle frequency tones (e.g., 3 kHz) (e.g., Stockard-Pope et al., 1992). However, infant-adult differences in threshold assessed by ABR are not large enough to account for the behavioral performance gap between adults and infants, especially after 3 months of age. Studies indicate that the major mechanisms contributing to the development of auditory sensitivity in infancy are likely the maturation of the middle ear (giving rise to greater amplification) and the auditory cortex (e.g., Keefe et al.,1994; Stapells et al., 1988). It is also possible that other non-auditory factors such as the development of attention and motor control contribute to the behavioural differences found (for a review of mechanisms underlying the development of absolute pitch sensitivity in infancy, see Werner & Marean, 1996).

Given the uncertainty about the source of the immaturities, it is of importance to obtain an objective physiological indication of pitch perception at the level of auditory cortex.

Most of our knowledge of pitch discrimination in infants comes from psychophysical studies using either pure or complex tones. Infant performance as measured by DLF is generally much poorer than that of adults. However, high-frequency (e.g., 4 kHz) discrimination appears to mature earlier, with DLF of around 4% for 3-month-olds but only 2% for 6-month-olds compared to less than 1% for adults. High frequency discrimination is adult-like by 4 years of age. For low-frequency (e.g., 0.5 kHz or 1kHz) discrimination, the DLF remains around 3% for both 3- and 6-month-olds and does not reach the adult level of less than 1% until 8 to 10 years (e.g., Olsho et al., 1982, 1987; Sinnott & Aslin, 1985; Maxon & Hochberg, 1982). Infants younger than 3 months have not yet been studied, likely because of the limitations of behavioural testing in young infants.

Less is known about what infants hear when they listen to harmonic complex tones. However, Clarkson and colleagues studied this question in older infants and demonstrated that 7- and 8-month-olds are able to extract the pitch of complex tones even when there is no energy at the fundamental frequency (Clarkson & Clifton, 1985; Montgomery & Clarkson, 1997), as long as low harmonics other than the fundamental are represented (Clarkson & Rogers, 1995). However, the difficult requirements of this experimental design, in which infants learn to actively respond to pitch changes while ignoring salient timbre differences, make it difficult if not impossible to use it with younger infants.

Event Related Potential (ERP) and Mismatch Negativity (MMN)

One big challenge for studying infant pitch perception, and indeed infant auditory perception in general, is that the psychophysical procedures require infants to attend to auditory stimuli and make overt behavioural responses. This is not always easy to achieve, especially when using relatively complex stimuli or tasks, and when testing young infants who lack good motor control. Moreover, even for older infants who can perform psychophysical tasks, it is still extremely difficult, if not impossible, to separate perceptual abilities from the influence of attentional abilities, motivational factors, and motor control skills on the results. Hence, alternative approaches of studying infant pitch perception are greatly needed. The rapid advance of neuroimaging techniques offers opportunities in this field and the event related brain potential (ERP) is one of the promising approaches.

As discussed above, auditory events are coded as electrochemical impulses in neurons from the cochlea to the cortex. Electroencephalography (EEG) is a technique that monitors the neural electrical activity in the brain by recording electrical potentials from electrodes placed on the scalp. The EEG contains spontaneous electrical potentials as well as potentials evoked by external sensory stimuli such as sounds. The external event-evoked activity (ERP) is generally much smaller in amplitude than spontaneous endogenous potentials, but the former is time locked to the external stimulus whereas the latter is not. Thus the stimulus of interest is often presented repeatedly so that tens or hundreds of evoked potentials can be averaged together in order to maintain the evoked signal while reducing all other activity that is not time-locked to the stimulus.

Within the averaged ERP waveforms, several deflections can be observed. These deflections comprise underlying ERP components (which may overlap in time) and these ERP components are thought to reflect various stages of neural processing evoked by external stimuli. In auditory ERP waveforms in normal adults, the earliest components occur around 10 ms after the onset of a sound stimulus. These components form the aforementioned ABR and originate in the brainstem (for a review of ABR, see Stapells & Oates, 1997). Auditory middle latency responses (AMLR) are ERP components occurring between 20 ms and 70 ms post stimuli, and reflect early activity in primary auditory cortex. ERP components with latencies of 100 ms or more are thought to reflect perceptual and cognitive processes. (For a summary of common ERP components, see Luck, 2005).

One component of particular interest for the series of studies in the current dissertation is called mismatch negativity (MMN). MMN is elicited in response to occasional changes (deviants) in an ongoing repeating stream of sounds (standards). MMN in adults manifests as a negativity at frontal electrodes on the scalp and a concurrent positivity at occipital and parietal electrodes. Its latency is between 100 and 250 ms after stimulus onset. MMN can be elicited by various types of change, such as a change in a sound feature (e.g., pitch, timbre, loudness, duration, interstimulus interval, location, or a combination of these factors), by a change in a sequence pattern (e.g., occasional repeated tones in a train of alternating tones), or by a change in category (e.g., changing from exemplars of one speech sound category to another). MMN is thought to reflect a cortical change detection mechanism in sensory memory (for a review of MMN, see Näätänen et al., 2007; Näätänen & Winkler, 1999). It has been found to have multiple generators in cortex, as indicated by studies using ERP source localization, intracranial depth electrodes, and a combination of MMN with other neural imaging techniques, such as magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). The main generators appear to be located in the secondary auditory cortex (e.g., Mathiak et al., 2002; Liebenthal et al., 2003; Schall et al., 2003). Further evidence that the main generators are in secondary auditory cortex comes from lesion studies. For example, MMN to synthetic vowels was elicited in patients with predominantly anterior lesions but not in patients with more posterior lesions in auditory cortex (Aaltonen et al., 1993). Although attention does have an impact on the amplitude and latency of the MMN response, MMN can be elicited in adults without an overt behavioral response and even without conscious awareness (e.g., Sussman et al., 1998; Oades & Dittmann-Balcar, 1995). MMN can even be observed when adults are asleep, although the amplitude is greatly decreased in this case (e.g., Sallinen et al., 1994; Atienza et al., 2002). Therefore, MMN is of great interest for researchers studying auditory perception in special populations for whom attention is hard to engage or behavioral responses are hard to obtain in psychophysical tasks, such as patients with motor disorders and young infants.

ERP and Mismatch Responses (MMR) in infancy

Over the first months after birth, tremendous changes occur in the size of the infant's head, the shape and thickness of the skull, and overall characteristics of the brain such as weight, volume, and the amount of gray and white matter. The central neural system undergoes vast changes during infancy, with rapid progress in synapse proliferation, synaptic pruning and strengthening, and myelination of neural pathways (for a review of infant brain development that relates to the changes in the infant ERP, see Picton & Taylor, 2007). These changes have great impact on the ERPs recorded from infants. For example, in comparison to adults, the smaller head size and thinner skull of infants can lead to larger measured responses; the immature myelination can prolong the latencies of ERP components; the combination of synaptiogenesis and lack of synchronization can affect the amplitudes of ERP components; regional immaturity and open fontanelles in the skull can lead to different ERP morphologies and scalp distributions. As a result of these factors, infant ERP responses typically bare little resemblance to adult ERP waveforms, with the absence of most common ERP adult components (for a review of infant ERP responses, see Picton & Taylor, 2007).

In infant auditory evoked ERPs, the most prominent component is a large positive deflection[1] that is maximal over the frontal central regions of the scalp, peaking around 300 ms regardless of the type of stimulus (e.g., Barnet et al., 1975; Rotteveeel et al., 1987; Pasman et al., 1992; Shucard et al., 1987). This monophasic response may resemble the P1-N1-P2 response pattern in adults, although the clear adult-like N1 response is not seen until well into childhood (e.g., Bruneau et al., 1997; Pang & Taylor, 2000; Shahin et al., 2004).

The MMN component has been of particular interest in studies of infants, as outlined above, beginning with a study by Alho et al. (1990). However, at least two kinds of mismatch response (MMR) have been reported in response to infrequent auditory changes: an increase of the aforementioned infant slow positive wave[1] (e.g., Dahaene-Lambertz & Gliga, 2004; Leppänen et al., 1997, 2004; Trainor et al., 2001, 2003) and an adult MMN-like frontal negativity[1] (e.g., Alho et al., 1990; Pang et al., 1998; Cheour et al., 1996, 1998). The functional nature of these mismatch responses is largely unclear,. So is the reason for obtaining slow positive waves versus the frontal negativity, although several explanations have been proposed: different types of infant MMRs may reflect the state (sleep, awake) of infants during testing (e.g., Friedrich et al., 2004), methodological differences across studies such as stimulus presentation rate (Čeponiené et al., 2002), different underlying neural processes such as a change detection mechanism (as reflected in MMN in adults) versus refractory processes in neural circuits (Cheour et al.,1998), or maturational differences such as the transition from immature types of discrimination processes to adult like processes (e.g., Morr et al., 2002; Trainor et al., 2001, 2003). (For a detailed summary of previously proposed hypotheses for the infant MMR mechanisms, please see the introduction to Chapter 2 of the current dissertation.) In sum, more basic knowledge about infant MMRs is needed to facilitate and evaluate their use for studying more complex pitch perception phenomena, such as cortical pitch discrimination, melodic discrimination, and representation of the pitch of the missing fundamental. This is the goal of the studies comprising the present dissertation.

Overview of Empirical Chapters in Current Dissertation

In order to better understand the infant MMRs and evaluate the possibility of utilizing such responses to study development of infant pitch perception, we designed and conducted a series of studies on the infant MMR.

In Chapter 2, we examined MMRs to simple pitch changes in infants between 2 and 4 months of age and observed two types of distinct infant MMRs, with different morphological distributions and different developmental trajectories. Specifically, we found a frontally positive slow wave response that diminished in amplitude with increasing age, and a faster frontally negative response that increased in amplitude with increasing age. Chapter 3 continues with an examination of the factors that affect these two types of infant MMRs. The results demonstrated that the slow wave, but not the negativity, is affected by presentation rate. Given that a fast presentation rate can cause circuits to become refractory, this result suggests that the slow wave but not the fast negativity involves refractory neural processes. To further understand the neural mechanisms underlying infant MMRs, in Chapter 4, we studied infant responses to a change in pitch pattern that did not involve the introduction of new pitches. Results from this study showed that the positive MMR largely disappears for pattern changes whereas the negative MMR remains robust. The fact that the positive MMR reduces when novel tones are removed provides converging evidence that the positive MMR represents the release from a refractory state. The negative MMR, on the other hand, is elicited by both simple pitch changes and changes in the sequence of a pitch pattern. Therefore, it resembles the MMN in adults, which is thought to be an electrophysiological index of automatic auditory cortical discrimination processes (Näätänen & Winkler, 1999).

Since the experiments from Chapters 2 to 4 suggest that the frontally negative MMR in infants is functionally similar to MMN in adults, in Chapter 5 we used MMR responses to study more complex aspects of pitch perception in infants. Specifically, we used it to study infants' perception of pitch when the fundamental frequency is removed. Adults are able to automatically integrate the frequency components of harmonic complex sounds in such a way that even when the fundamental frequency is removed, the perception of pitch does not change. Our results indicated that infants as young as 4 months of age also hear the pitch of complex harmonic tones with missing fundamental frequencies.

In general, the studies in this dissertation extensively examined the MMRs to pitch changes in infants from 2 to 4 months of age and then utilized the negative MMR as a measure to study the development of pitch perception for harmonic complex tones.

Footnotes

[1] Because Chapter 2, 3, 4, and 5 were completed and submitted at different times and our understanding of infant mismatch responses also evolved with new results, the terms describing the infant mismatch responses are not completely consistent across these chapters. The detailed terminology of these infant ERP components in each chapter are clarified as follows:

1. The characteristic large positive deflection in both infant standard and deviant waves was called "broad positive slow wave" in Chapter 2, "prominent slow wave" in Chapter 3, and "slow positive wave" in Chapter 4.
2. The increase in the above characteristic large positive deflection that occurs in the deviant waves results in a positive MMR in the difference waves (deviant wave minus standard wave). This positive MMR was called "slow positive wave" or "positive slow wave" in difference waves in Chapter 2, "broad discriminative positivity" in Chapter 3, and "positive mismatch response" in Chapter 4
3. Another MMR prominent in 3-month-olds and older infants is a frontally negative deflection that is morphologically similar to adult MMN. This negative MMR was called "MMN-like negativity" or "negative mismatch response" in Chapters 2, 3 and 4, and "infant MMN" in chapter 5.

References

The references for this chapter can be found with those from Chapter 6, on page 188

Chapter 2:

MISMATCH RESPONSES TO PITCH CHANGES IN EARLY INFANCY

This chapter is reprinted from Journal of Cognitive Neuroscience, Vol.19, 2007, Pages 872-892, He, Hotson & Trainor, "*Mismatch Responses to Pitch Changes in Early Infancy*". Copyright (2007) with permission from Elsevier

Introduction to the Chapter 2

The previous literature reported inconsistent findings on the infant MMRs across various auditory stimuli. Without first understanding the forms of typical infant MMRs and their characteristics, it is impossible to utilize the component to study other perceptual phenomena about infants' pitch perception.

In this chapter, we investigated the infant MMRs to simple pitch changes at three different age (2, 3, and 4-month-olds).

In the results, we found two types of infant MMRs: A positive slow MMR and an adult MMN-like negative MMR. The two types of MMRs differ in their morphological distributions. Moreover, the positive MMR is found in 2 and 3-month-olds but disappears at 4 months of age, while the negative MMR is not significant at 2 months of age but becomes prominent in 3 and 4-month-olds. The coexistence of the two MMRs and the fact that they have different developmental trajectories suggest that they are functionally distinct.

Mismatch responses to pitch changes in early infancy

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Abstract

We investigated the emergence of discriminative responses to pitch by recording 2-, 3-, and 4-month-old infants' EEG responses to infrequent pitch changes in piano tones. In all age groups, infants' responses to deviant tones were significantly different from responses to standard tones. However, two types of mismatch responses were observed simultaneously in the difference waves. An increase in the left-lateralized positive slow wave was prominent in 2-month-olds, present in 3-month-olds, but insignificant in 4-month-olds. A faster adult-like mismatch negativity (MMN), lateralized to the right hemisphere, emerged at 2 months of age and became earlier and stronger as age increased. The coexistence and dissociation of two types of mismatch responses suggests different underlying neuromechanisms for the two responses. Furthermore, the earlier emergence of the MMN-like component to changes in pitch compared to other sound features implies that neural circuits involved in generating MMN-like responses have different maturational timetables for different sound features.

Introduction

In recent years, event-related potentials (ERPs) have started to become an alternative method for studying auditory perception in infants because they do not depend on any overt responses, which are hard to obtain in infants. One ERP component, the mismatch negativity (MMN), has been extensively analyzed in studies of auditory discrimination in adults (for reviews, see Näätänen & Alho 1995, 1997; Näätänen, Jacobsen, & Winkler, 2005; Picton, Alain, Otten, Ritter, & Achim, 2000; Schröger, 1998). MMN is elicited by infrequent changes (deviant stimuli) in an ongoing stream of sound events (standard stimuli). MMN is most clearly seen in the difference wave obtained by subtracting the average response to standard stimuli from the average response to deviant stimuli. MMN appears as a negativity that peaks between 130 and 250 ms after stimulus onset depending on the difficulty of the discrimination and whether the deviants represent a change in pitch, duration, loudness, category, pattern, or other abstract sound feature. MMN manifests at the scalp as a bilateral frontal negativity concurrent with an inverted polarity at posterior and mastoid sites, consistent with primary generators in the two auditory cortices, and is thought to reflect the operation of updating sensory memory traces (Näätänen & Alho, 1997). MMN is of particular interest in developmental studies because it does not require a behavioural response and, although affected by attention, attention is not required for its elicitation (e.g., Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993; Oades & Dittmann-Balcar, 1995; Sussman, Ritter, & Vaughan Jr., 1998). However, different studies reported different developmental trajectories for MMN in infants (e.g., Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990; Dehaene-Lambertz & Dehaene, 1994; Cheour-Luhtanen, Alho, & Sainio, 1996; Leppänen, Eklund, & Lyytinen, 1997; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Trainor, Samuel, Desjardins, & Sonnadara, 2001; Trainor et al., 2003). In the present study, we used high-resolution EEG recordings to examine the development of mismatch responses to pitch changes in infants between 2 and 4 months of age.

Pitch perception is essential for both language and music acquisition in infancy. In speech, before infants understand the meanings of words, they are particularly attentive to the pitch contours (e.g., Fernald & Kuhl, 1987; Fernald & Mazzi, 1991; Werker & McLeod, 1989), which convey emotional meaning. Pitch contours also provide cues that help infants to learn vowel categories (Trainor & Desjardins, 2002) and delineate stress patterns that provide cues to lexical and grammatical boundaries (Jusczyk & Derrah, 1987). In music, infants can remember the pitch patterns of melodies (Trehub, 2001) and recognize familiar melodies transposed in pitch (Plantinga & Trainor, 2005) before they understand words or are sensitive to the particular scales used in their music system of exposure (Trainor & Trehub, 1992). Behavioral studies have indicated that infants' frequency discrimination abilities improve rapidly over the first few months after birth (e.g., Kessen, Levine, & Wendrich, 1979; Maxon & Hochberg, 1982; Olsho, Schoon, Sakai, Turpin, & Sperduto, 1982; Olsho, Koch, Halpin, & Carter, 1987; Sinnott & Aslin, 1985): For frequencies above 2 KHz the thresholds of 6-month-olds approach those of adults for frequencies of 4 KHz. For frequencies below 2 KHz, infants can already detect changes of 3% at 3 months of age, although this is considerably above thresholds of adults (less than 1%), and adult levels are not reached until well into childhood.

Since the first work by Alho et al. (1990), a number of studies have tried to elicit an MMN-like response in newborns and young infants using pitch changes in pure or complex tones. Table 1 summarizes the methods and major findings of these studies. A negativity in the difference wave similar to the adult MMN has been reported in infants from preterm newborns to 1-year-olds (Alho et al., 1990; Čeponiené et al., 2000, 2002; Hirasawa, Kurihara, & Konishi, 2003). However, a number of studies instead report a slow positive component in the difference wave ranging from 200 to 450 ms (Leppänen et al., 1997; Leppänen, Guttorm, Pihko, Takkinen, & Lyytinen, 2004; Cheour et al., 1999; Morr, Shafer, Kreuzer, & Kurtzberg, 2002). A similar positive component has not been reported in the adult literature. Such conflicting results have also been reported in infant MMN studies using other sound features. For example, Cheour and her colleagues reported MMN-like negativity in newborns in response to vowel changes (Cheour-Luhtanen et al., 1996, Cheour et al., 1998) while Friederici, Friedrich and their colleagues reported a broad positivity using similar vowel sounds (Friederici, Friedrich, & Weber, 2002; Friedrich, Weber, & Friederici, 2004). Dehaene-Lambertz and colleagues (Dehaene-Lambertz & Dehaene, 1994, Dehaene-Lambertz, 2000, Dehaene-Lambertz & Pena, 2001) found a positivity for syllable changes in newborns, 3-month-olds and 4-month-olds. Trainor and colleagues reported a positive response in 2-month-old infants but a negative response in 6-month-old infants to fine temporal changes (Trainor et al., 2001, 2003). However, for occasional changes in sound location, a negative response is not seen until 8 months of age (Sonnadara, Hotson, & Trainor, submitted). To date, the question as to why two kinds of mismatch responses have been reported in infants is largely unresolved.

A number of hypotheses have been proposed for when positivities and when negativities will be seen. One possibility is that the state of the infant plays a role. For example, Friedrich et al. (2004) reported that negativities were more apparent in awake than in asleep infants. It has also been suggested that differences might reflect physiological characteristics of infants, but the findings are inconsistent across studies. Cheour et al. (1999) and Čeponiené et al. (2002) found a negativity in normal newborns but a positivity in cleft palate newborns. However, Pihko et al. (1999) reported a positivity in normal newborns and a negativity in newborns at risk for dyslexia. Leppänen et al. (2004) found a positivity for more mature newborns and a negativity for less mature newborns. It is possible that stimulus differences might be involved in these discrepancies, but this is unlikely because both Cheour et al. (1999) and Leppänen et al. (2004) used pure tones.

It is possible that methodological differences across studies may explain why some studies report negativities while others report positivities (Leppänen et al., 2004). For example, placement of reference electrodes above versus below the Sylvian fissure can cause the polarity of components generated in auditory cortex to invert when measured at the scalp. However, studies using the same reference channel have reported different polarities in infants (e.g., Leppänen et al., 1997, 1999; Cheour et al., 1998; Čeponiené et al., 2002), suggesting that reference differences are not responsible for the different mismatch polarities reported.

It is also possible that methodological differences across studies cause different neuro-mechanisms to be activated, leading to different observed responses. For example, inter-stimulus interval (ISI) can interact with the refractory periods of neural circuits. The negative response may reflect a non-refractory memory-comparison-based change detection process (Jacobsen & Schröger, 2001) whereas the positivity may reflect a release from a refractory state because the stimulus change activates new neural circuits. Since refractory periods in early infancy would be expected to be longer due to immature myelination and synaptic functioning (Moore, 2002), optimal ISIs for MMN elicitation could be different in infants and in adults. However, studies using comparable ISIs have reported both the negative and the positive mismatch response in infants (e.g., Leppänen et al., 1999; Čeponiené et al., 2002). Thus, the effect of ISI alone cannot explain the positive versus negative mismatch responses.

An alternative possibility is that the negative and positive responses to change might reflect different neural processes, perhaps taking place in different cortical layers (Trainor et al., 2003). Morr et al. (2002) reported the presence of a negative response to pitch changes in infants under 12 months of age to large, but not to small, pitch changes, suggesting that different processes may be used for easy and hard discriminations. It is also possible that the negative response might reflect a true mismatch process whereas the positive slow wave might represent an involuntary attention shift (Kushnerenko et al., 2002) or the automatic categorization of stimuli (Friedrich et al., 2004). Furthermore, if the two processes could occur at the same time, the positivity could potentially mask the negativity because of their overlapping latencies (Morr et al., 2002).

Because the positive mismatch response is reported as a broad slow wave, while the negative mismatch response is typically reported as an adult-like fast component, different filter settings may be able to distinguish these components. Most studies use a high pass filter with a cut off between 0.1 and 1.0 Hz (see Table 1), none of which will entirely filter out the slow wave if present. Even so, Weber, Hahne, Friedrich and Friederici (2003) found that the positive slow wave was reduced and a negativity was more clearly seen when a 1.0 Hz high-pass filter was used than when a 0.3 Hz high pass filter was used on the same data on word stress changes in 4- and 5-month-old infants, although the negativity was not significant in either case. Trainor et al. (2003) filtered more aggressively, comparing 0.1 and 3.0 Hz high pass filter settings, and were able to observe MMN-like negativities in some 3- and 4-month-old infants with the higher filter setting in a fine temporal discrimination task. These results suggest that filtering might serve as a useful tool for dissociating the two types of change responses.

Adults do not show the slow positive response to change, and previous work in our lab suggests that in a temporal gap-detection task there is a transition from a predominance of the positive response at 2 months to a predominance of the negative response at 6 months. To investigate further the idea that the positive response is seen predominantly in younger infants and the negative response predominantly in older infants, the present study examines responses to pitch change across age.

In adults, the neural circuits involved in generating the MMN differ somewhat depending on the specific feature change to be detected. For example, different sound features (e.g., intensity, frequency, or location) elicit MMN with different amplitudes and latencies (Deouell & Bentin, 1998), topographic maps (Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991), source dipole locations (Giard et al., 1995), source models in MMNm, the magnetic counterpart of the MMN, (Levänen, Ahonen, Hari, McEvoy, & Sams, 1996; Rosburg, 2003) and activation locations in event-related-fMRI studies (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005). Behavioral data also indicates that auditory discrimination for different sound features matures at different ages (for review, see Werner & Marean, 1996). Finding that the transition from a predominantly positive to a predominantly negative response matures at different ages for different sound features would add to the evidence that there are multiple MMN mechanisms specialized for different sound features.

Conducting a detailed study of how responses to pitch change develop across age would also be useful in that, despite the fact that this information is crucial for evaluating developmental theories of MMN development, it is not currently available. Most ERP studies of pitch change tested only newborns (see Table 1), the exceptions being Čeponiené et al. (2000; 6-month-olds), Morr et al. (2002; 2- to 47-month-olds), Kushnerenko et al. (2002; 2- to 4-day-olds, 3-, 6-, and 9-month-olds), and Fellman et al. (2004; 2- to 4-day-olds, 3-, 6-, 9-, and 12-month-olds). The Čeponiené et al. (2000) study showed that most infants exhibit MMN-like negativity at 6 months of age, but did not test younger infants. Morr et al. (2002) did test younger infants, but grouped the results from

2- to 7-month-olds together, precluding investigation of the brain correlates paralleling behavioural improvements in pitch discrimination during this period. Kushnerenko et al. (2002) found an MMN-like negativity followed by a positivity in 75% of infants at each age between newborn and 12 months with no significant age effect. However, in this study, individual infants showing MMN at one age did not consistently show it at another age, either older or younger. In addition, examination of the waveforms illustrated in the original paper shows clear changes across age, with MMN becoming more clear with increasing age, although these are not reported to be significant. These facts suggest a potential signal to noise problem, perhaps caused by the number of infants tested or the small number of epochs obtained in individual infants (not reported). The waveforms shown in Fellman et al. (2004) clearly show a prominent slow positive wave in newborns, and MMN appears to emerge at 3 months for full term infants, but not for pre-term infants corrected for gestational age.

In sum, the question as to how the mismatch response to pitch changes develops in early infancy remains largely unanswered. The present study investigated the development of positive and negative mismatch responses to pitch changes in infants between 2 and 4 months of age using natural complex tones (piano timbre). An oddball paradigm was employed in which one piano tone, C_5 (F0 = 523.25 Hz), acted as the standard and a different piano tone, $F\#_5$ (F0 = 740 Hz), acted as the deviant. Dense array EEG recordings were obtained, and different band pass filters were applied to investigate the characteristics of the two types of infant mismatch responses across age. The presence of both components at certain ages in the same infants would provide strong evidence that they represent two different neural mechanisms.

Methods

Participants

A total of 39 healthy, full term infants ranging in age from 2 to 4 months with no known hearing deficits were included in the present study. Written consents were obtained from parents for their infants' participation. The final sample consisted of 14 4-month-olds (9 female), 11 3-month-olds (6 female), and 14 2-month-olds (11 female). All infants were awake during the testing. An additional 3 2-month-olds were eliminated from the final sample because they fell asleep. Furthermore, 13 infants (6 2-month-olds, 3 3-month-olds, and 4 4-month-olds) were excluded from the final sample because for each of these infants, the mean number of artifact-free deviant trials across all 124 electrodes was less than 100.

Stimuli

Monaural piano tones were synthesized with Reason® 2.0 software (Propellerhead software). Standard and deviant stimuli were piano notes C5 and F5#, with fundamental frequencies of 523.25 and 740 Hz, respectively. The duration of both stimuli was 600 ms with a 200 ms inter-stimulus interval (ISI). During testing, recorded stimuli were played by E-prime® 1.1 software (Psychology Software tools, Inc.) on a Dell OptiPlex280 computer with an Audigy® 2 platinum sound card (Creative Labs). All stimuli were presented over a speaker (WestSun Jason sound® JS1P63) located one meter directly in front of the participant at a level of 70 dB (A) at the location of the infant's head, over a background noise level of 29 dB(A)

Procedure

The infant was seated on his or her parent's lap in a sound-attenuating room (Industrial Acoustics Co.) A silent video (Baby Einstein®) was played to keep infants happy and still. An oddball paradigm was used in which standard stimuli were presented on 80%, and deviant stimuli on 20%, of the trials. Stimulus order was randomized with the constraint that at least two standards occurred between successive deviants. A complete experiment consisted of 1600 trials, but testing was stopped early if infants became fussy, so the number of trials obtained in accepted subjects across all electrodes varied between 560 and 1600, with a mean of 1186 trials.

Data Acquisition and Analyses

EEG was recorded from 124 locations on the scalp using a Geodesic Sensor Net® (Electrical Geodesics, Inc). All electrode impedances were maintained below 50kΩ.

The electrical potential was digitized at 1000 Hz for the majority of participants (14 participants were digitized at 250 Hz). The online recording was referenced to the vertex (electrode Cz in the 10/20 system) with a band pass filter of 0.1–400 Hz.

To investigate the ERP components within different frequency bands, three different band pass filter settings were implemented offline: 0.5–20, 3–20, and 0.5–3 Hz. Roll-off for all filters was set to 24 dB/oct. The filtered continuous data was then segmented into 700 ms epochs, including a 100 ms prestimulus-onset baseline. EEG responses exceeding ± 120 μv in any epoch were considered artifact and omitted from averaging. The remaining standard and deviant trials were averaged separately, excluding the standard trials immediately following deviant trials. Because it is only possible to obtain a small number of trials from each infant, the above rejection process was carried out for each electrode individually in order to remove the trials contaminated by artifacts (mainly due to blinks, eye, or head movement) in electrodes near the noise source while preserving the trials in relatively unaffected electrodes. For each infant, for each electrode, the mean number of artifact-free deviant trials was counted; if the mean number across all 124 electrodes was less than 100, the data from that infant was excluded from further analysis. The mean numbers of accepted deviant trials across all infants and all electrodes were as follows: 2-month-olds: mean=197, SD=25; 3-month-olds: mean=213, SD=18; 4-month-olds: mean=231, SD=22. The averaged waveforms were then baseline corrected and referenced to an average reference. Difference waves were obtained by subtracting the standard from the deviant waveforms. Grand average difference waves were computed for each age group. Voltage maps were computed at the peak latency of the fast negative, fast positive, and slow positive waves based on the grand averaged difference waves for each age group.

For statistical analysis, 94 electrodes were selected to be divided into 5 groups for each hemisphere (Fig. 1), and the waveforms for all electrodes in each group were averaged together to represent scalp brain responses at the frontal (20 electrodes), central (20 electrodes), parietal (20 electrodes), occipital (16 electrodes), and temporal (18 electrodes) regions. Because we were primarily interested in the development of MMN, the temporal regions were not analyzed as they could potentially contain overlapping components such as the T-complex. Thirty electrodes were excluded from the above averages due to the following considerations: 9 electrodes in the forehead near the eyes in order to further reduce the contamination of eye movement artifacts; 12 electrodes at the edge of the Geodesic net to reduce contamination of face and neck muscle movement; 9 electrodes in the midline to enable comparison of the EEG response between hemispheres.

Insert Figure 1 here

In the 3–20 Hz band pass condition, in order to test which part of the difference wave was significantly different from zero in each age group, two-tailed t-tests were calculated at each time point of the difference wave across all infants in that age group. The peak latency and amplitude of the MMN-like negativity were measured in each infant at each of the 8 regions defined in Figure 1. The negativity was defined as the largest negative peak between 100 and 300 ms at frontal and central regions (and as the largest positive peak between 100 and 300 ms at parietal and occipital regions due to the polarity inversion) and the positivity following the negativity was defined as the largest positive peak between 200 and 400 ms following the negative peak at frontal and central regions (and as the largest negativity in this window at parietal and occipital regions). Separate 3-way ANOVAs were calculated for the peak latencies and absolute values of the amplitudes to test whether they varied significantly across age, hemisphere, and brain region.

For the 0.5–3 Hz band pass condition, the component of interest was the slow positive wave. In order to compare the standard and deviant waveforms under this filter setting, the amplitude and latency of the slow positive peak between 100 and 400 ms in each case was identified. This time window was chosen because the slow wave peaked around 250 ms and extended from about 100 to 400 ms. ANOVAs were used to test whether the slow positive wave differed significantly across age, hemisphere, and region.

The Greenhouse-Geisser correction was applied to all within-subjects measures with more than 2 levels in all of the above ANOVA tests. The Tukey HSD test was used for post hoc comparisons. The Bonferroni correction was used for within-subject comparisons.

Results

Description of Waveforms

Insert Figure 2 here

Group average ERP waveforms of the standard and deviant waves for each of the electrode groups (band-pass filter setting: 0.5–20 Hz) across all 2-, 3-, and 4-month-olds are shown in Figure 2. Two-month-old deviant and standard waveforms were dominated by a broad positive slow wave between 100 and 400 ms at frontal and central regions, which reversed polarity at the parietal, occipital, and temporal regions. The amplitude of the slow frontal positive component was larger in deviant than in standard waves during the period between about 200 to 400 ms (see difference waves, Figure 3). Similar broad positive components were also observed in the standard and deviant waves for 3-month-olds, but in this age group, the deviant waves were more negative than the standard waves between 150 to 250 ms at frontal sites and more positive between 250 and 350 ms. This gave rise to a difference wave pattern with a small MMN-like negativity around 200 ms followed by a positivity around 300 ms. Both components reversed polarity at posterior sites (Figure 3). For 4-month-olds, the positive component was less spread out in time in the standard waves and the deviant waves showed a double peak pattern with two overlapping positive peaks. Difference waves showed the same two fast components as in the 3-month-olds (Figure 3). Figure 3 (bottom) compares the difference waves across the three age groups at electrode FZ.

Insert Figures 3 and 4 about here

This transition of the infant mismatch response from a slow positive wave to a MMN-like negativity is similar to that reported by Trainor et al. (2003) for gap discrimination, although the transition appears to occur earlier for pitch discrimination (2 to 4 months of age) than for gap discrimination (4 to 6 months of age). Additionally, the present experiment found that the adult MMN-like negativity observed in 3- and 4-

month-olds and the slow positive difference wave in 2-month-olds, overlapped in latency range; thus the slow positive wave might potentially mask the fast negativity at some ages. Since it is clear that the slow positive wave and the faster MMN-like negativity differ in frequency characteristics (see also Trainor et al., 2003; Weber et al., 2003), different band pass filter settings were applied to isolate those two components and further study their developmental trajectories.

Development of MMN-like negativity and P3a-like positivity: Results under 3–20 Hz band pass filtering

When the zero phase shift band pass filter between 3-20 Hz was applied, the slow components were largely filtered out. In the obtained grand average difference waves (Figure 4), a negativity around 200 ms followed by a positivity can be observed in all three age groups.

Paired t-tests were employed to determine the latencies at which the amplitudes of deviant and standard waves were significantly different (see bars over difference waves in Figure 4). The MMN-like negativity around 200 ms was significant only at the FL (left frontal) and FR (right frontal) regions in 2-month-olds but it achieved significance at 6 out of 8 regions in the 3-month-olds and at all 8 regions in the 4-month-olds. The positivity following the negativity around 300 ms was also significant only at the FL and FR regions in 2-month-olds but was significant in 7 regions in 3-month-olds and in all regions in 4-month-olds.

To examine how the MMN-like negativity and the following positivity changed by age, region, and hemisphere, the peak latencies and absolute amplitudes of the MMN-like negativity (or the following positivity) in all 3 age groups were measured for each infant in all 8 regions and subjected to 3-way repeated measures analyses of variance (ANOVA). The dependent variable was peak latency or amplitude (separate ANOVAs for latency and amplitude). The within-subject factors were hemisphere (left, right) and brain region (frontal, central, parietal, occipital). The single between-subjects factor was age (2, 3, 4 months).

For the peak latency of the MMN-like component, the main effects of age [$F(2, 36)=6.08$, $p<.005$], hemisphere [$F(1, 36)=10.08$ $p<.003$], and region [$F(3,108)=3.32$, $p=.02$] were significant. Tukey Post hoc tests indicated that the peak latencies in 2-month-olds (mean=214 ms) and 3-month-olds (mean=212 ms) were significantly longer (2- vs. 4-month-olds, $p=.007$; 3- vs. 4-month-olds, $p=.03$) than in 4-month-olds (mean=199 ms). For hemisphere, latencies were shorter ($p<.003$) in the right hemisphere (mean=205 ms) than in the left hemisphere (mean=212 ms). Post hoc tests indicated significant regional differences only between the parietal (mean=214 ms) and central (mean=204 ms, $p=.04$) regions.

For the absolute peak amplitude of the MMN-like component, the ANOVA showed significant main effects for age [$F(2, 36)=10.85$, $p<.001$], hemisphere [$F(1, 36)=7.38$, $p=.01$], and region [$F(3,108)=3.55$, $p=.02$]. Post hoc tests indicated that the amplitudes of the MMN-like component in 3-month-olds (mean=1.06 μv) and 4-month-olds (mean=1.22 μv) were larger (3- vs. 2-month-olds, $p=.008$; 4- vs. 2-month-olds,

$p<.001$) than in 2-month-olds (mean=0.55 μv). The main effect of hemisphere reflected significantly larger ($p=.01$) amplitudes in the right (mean=1.03 μv) than left hemisphere (mean=0.86 μv). The main effect of region arose from the fact that the amplitude of MMN-like negativity was smaller in the parietal region (mean=0.82 μv) than in the frontal (mean=1.02 μv, $p=.02$) and occipital (mean=1.01 μv, $p=.01$) regions.

The positivity following the negativity showed nearly identical effects as with the MMN-like negativity. For the peak latency of the positivity following the negativity, the main effects of age [$F(2, 36)=15.62$, $p<.001$], hemisphere [$F(1, 36)=4.87$, $p=.03$], and region [$F(3, 108)=3.47$, $p=.02$] were significant. Post hoc tests indicated that the peak latencies in 2-month-olds (mean=322 ms) and 3-month-olds (mean=316 ms) were significantly earlier (2- vs. 4-month-olds, $p<.001$; 3- vs. 4-month-olds, $p<.001$) than in 4-month-olds (mean=293 ms). For the hemisphere effect, latencies were shorter ($p=.03$) in the right hemisphere (mean=308 ms) than in the left hemisphere (mean=313 ms). Post hoc pairwise comparison tests with Bonferroni correction found no significant regional differences.

For the absolute peak amplitude of the positivity following the negativity, there were significant main effects of age [$F(2, 36)=13.99$, $p<.001$], hemisphere [$F(1,36)=8.87$, $p=.005$], and region [$F(3,108)=8.40$, $p<.001$]. Post hoc tests indicated that the amplitudes of the positivity in 3-month-olds (mean=1.24 μv) and 4-month-olds (mean=1.33 μv) were larger (3- vs. 2-month-olds, $p=.001$; 4- vs. 2-month-olds, $p<.001$) than 2-month-olds (mean=0.575 μv). The peak amplitude in left hemisphere (mean=0.96 μv) was smaller ($p=.03$) than in the right hemisphere (mean=1.14 μv). Similar to the results for the MMN-like negative peak, the parietal region had a smaller peak amplitude (mean=0.859 μv) than the frontal (mean=1.14 μv, *p*=.004) and occipital (mean=1.19 μv, *p*<.001) regions. The topographic voltage maps at the mean peak latency of the MMN-like negative peak and at the peak of the following positivity are shown in Figure 6 for each age group (top and middle panels). Both the MMN-like negativity and the following positivity have larger amplitudes in the right than in the left hemisphere, especially for the 3- and 4-month groups. Several studies suggest that the positivity following the MMN-like negativity in infants may be related to involuntary shifts of attention (Čeponiené et al., 2002; Kushnerenko et al., 2002), and hence analogous to the P3a component in adults. Although the P3a only follows the MMN in adults when attention is captured, immature inhibitory attentional mechanisms in infants may result in attentional capture being the norm, and hence P3a-like processes may typically follow the MMN in infants.

Positive Slow Wave: Results under 0.5–3 Hz band pass filtering

The 0.5-3 Hz band pass filter was employed to isolate the slow positive wave as much as possible. The peak amplitudes and latencies of the positive peak in the standard and deviant waveforms (see Figure 5) in all three age groups were measured for each infant in all 8 regions, and subjected to two 4-way ANOVAs, one with peak amplitude and one with peak latency as the dependent variables. The between-subject factors were stimulus type (standard, deviant), region (frontal, central, parietal, occipital),and hemisphere (left, right). The single within-subjects factor was age (2, 3, 4 months).

Insert Figure 5 here

For amplitude, the main effects of stimulus type [*F*(1, 36)=18.47, *p*<.001], hemisphere [*F*(1, 36)=5.92, *p*=.02], and region [*F*(3,108)=31.52, *p*<.001], were significant, as well as interactions between stimulus type and age [*F*(2, 36)=7.10, *p*=.003] and between region and hemisphere [*F*(3, 108)=7.09, *p*<.001]. Post hoc tests indicated that the peak amplitude of the deviants (mean = 2.86 μv) was significantly larger (*p*<.001) than that of the standards (mean = 1.844 μv). As to the significant stimulus type by age interaction, post hoc tests revealed that the deviant peaks were significantly larger than standard peaks in both 2-month-olds ($\text{mean}_{\text{deviant}}$=2.10 μv, $\text{mean}_{\text{standard}}$= 1.12 μv, *p*<.001) and 3-month-olds ($\text{mean}_{\text{deviant}}$=2.63 μv, $\text{mean}_{\text{standard}}$= 1.93 μv, *p*=.005). However, no significant peak amplitude differences were found for 4-month-olds ($\text{mean}_{\text{deviant}}$=2.399 μv, $\text{mean}_{\text{standard}}$= 2.480 μv). The main effect of region arose from the fact that the peak amplitude was smaller in the central (mean=1.13 μv) than in the frontal (mean=2.54 μv, *p*<.001), parietal (mean=2.19 μv, *p*<.001), and occipital (mean=2.57 μv, *p*<.001) regions. Frontal peaks were also significantly larger (*p*=.029) than parietal peaks. For hemisphere, peak amplitudes were larger (*p*=.02) in the left hemisphere (mean=2.28 μv) than in the right hemisphere (mean=1.94 μv). Post hoc tests revealed that the larger amplitudes in the left hemisphere were significant for parietal (*p*<.001) and occipital (*p*=.002) regions but not for the other two regions.

For the peak latencies, the ANOVA showed significant main effects for age [*F*(1, 36)=4.63, *p*=.016] and stimulus type [*F*(1, 36)=12.95, *p*=.001], and a significant interaction between age and stimulus type [*F*(2, 36)=9.339, *p*=.001]. Post hoc tests indicated that the peak latencies in 2-month-olds (mean= 232 ms) and 3-month-olds (mean=236 ms) were longer (2- vs. 4-month-olds, *p*=.05; 3- vs. 4-month-olds, *p*=.03) than in 4-month-olds (mean=207 ms). Pairwise comparisons showed that the peak latency in standard waves was significantly shorter than those of deviants in 4-month-olds ($\text{mean}_{\text{deviant}}$=226 ms, $\text{mean}_{\text{standard}}$= 189 ms, *p*<.001) but there was no significant latency difference for 2- and 3-month-olds.

The analysis outlined above indicates that the slow positive wave was significantly increased in deviants compared to standards for 2- and 3-month-olds, but not for 4-month-olds. As can be seen in the whole head topographical voltage maps (Figure 6), the slow positive wave was larger in the left than in the right hemisphere, which is opposite to the MMN-like and P3a-like responses. It is possible that the .5 to 3 Hz filter setting did not entirely eliminate the faster MMN-like negativity and P3a-like responses. However, it is unlikely that the P3a-like response had much influence on the slow positive wave peaks. First, in 3-month-olds the 95% confidence interval for the latency of the slow positive wave was between 220 and 252 ms, which is much earlier than the P3a-like positivity which peaked at 316 ms. Similarly, in 4-month-olds, the 95% confidence interval for the slow positive wave was between 193 and 221 ms, which is much earlier than the P3a-like positivity, which peaked at 293 ms, although the later latency of the deviant compared to standard slow positive wave components in 4-month-olds might reflect some influence of the P3a-like component. However, if the waves under the .5 to 3 Hz filter were contaminated by the P3a-like positivity, the deviant positive peaks would be expected to be significantly larger than the standard positive peaks in the 4-month-olds, who had the largest P3a-like positivity, but no differences were found in this age group.

Insert Figure 6 here

In sum, while the MMN-like negativity increased in amplitude with age, the effect of occasional pitch changes on the amplitude of the slow positivity decreased with age, disappearing by 4 months. The fact that both the MMN-like negativity and the slow positivity were clearly present at 3 months of age further suggests that these components represent different processes in the developing brain.

Discussion

In the current experiment, we recorded 2-, 3-, and 4-month-old infants' EEG responses to infrequent pitch changes in piano tones. In all three age groups, infants' responses to deviant tones were significantly different from responses to standard tones. However, the difference waves in 2-month-olds were dominated by a slow positive wave while the two older groups showed a faster prominent adult-like MMN/P3a-like response pattern, although the slow positive wave also remained clear in the 3-month-old data. Two bandpass filter settings were applied to further investigate slow and fast mismatch responses. The results under the 3-20 Hz filter setting confirmed that the adult-like MMN/P3a-like responses were significant in only a few scalp regions at 2 months of age but achieved significance in most regions at 3 months of age and in all regions at 4 months of age. Both the MMN-like negativity and the following P3a-like positivity were stronger in the right than the left hemisphere. Moreover, with increasing age, both peaks increased in amplitude and decreased in latency. On the other hand, the results under the 0.5-3 Hz filter setting indicated that the peak amplitude difference between standard and deviant slow waves was significant in 2- and 3-month-olds but not in 4-month-olds. In addition, both deviant and standard slow waves were larger in the left than right hemisphere in 2- and 3-month-olds.

The present results demonstrate the existence of two types of infant mismatch responses. The MMN/P3a-like response pattern in older infants is similar to that reported by other studies in infants at comparable ages. (e.g., Cheour-Luhtanen et al., 1996; Cheour et al., 1998; Morr et al., 2002; Trainor et al., 2001, 2003; Kushnerenko et al., 2002; Fellman et al., 2004). The slow positive wave is also similar to that reported in several studies (e.g., Leppänen et al., 1999, 2004; Dehaene-Lambertz, 2000; Dehaene-Lambertz & Pena, 2001; Friederici et al., 2002; Trainor et al., 2003; Sonnadara et al., submitted; Friedrich et al., 2004). In addition, the current study confirmed the findings of Trainor et al. (2003) and Weber et al. (2003) that different types of mismatch responses can be separated by using different band pass filters.

As far as we are aware, the current study is among the first to report both a significant slow positive wave and a significant MMN/P3a-like response to the same stimulus in the same infants (the 3-month-old group) analyzed in the same data set, which demonstrates that the two types of mismatch responses can indeed coexist during a certain period in early infancy. We also show that although the two responses overlap in latency, they can be separated by using different filter settings because they differ in duration. Furthermore, the MMN/P3a-like response showed a right-hemisphere dominance, and increased in amplitude and decreased in latency with increasing age, whereas the slow positive wave was left-hemisphere dominant and decreased in amplitude with increasing age. This dissociation of the two mismatch responses in their developmental trajectories and topographical distribution patterns suggests even more strongly that they are very likely to be independent processes with independent underlying neuromechanisms.

The current results demonstrate that there is a developmental transition in infants' mismatch response from a slow positive wave to an MMN-like fast negativity in early infancy for infrequent pitch changes (Trainor et al., 2001, 2003) and is consistent with the Trainor et al. (2001, 2003) study of gap detection tasks and the study by Sonnadara et al. (submitted) on sound localization tasks. However, despite the similar developmental pattern, the transition found here for pitch takes place between 2 and 4 months of age, which is earlier than that found for gap detection (4 to 6 months of age) and localization tasks (after 8 months of age). These different maturational timetables confirm our hypothesis of feature-specific MMN development. Furthermore, earlier MMN maturation for pitch discrimination than for gap detection mirrors the earlier behavioral maturation of pitch discrimination (for review, see Werner & Marean, 1996) in comparison to gap detection (Irwin, Ball, Kay, Stillman, & Rosser, 1985).

A question that remains largely unanswered is the nature of the two types of mismatch responses in early infancy. In general, the characteristic slow wave component seen in early infancy is thought to result from the poorly myelinated connections between neurons in the immature brain (Vaughan & Kurtzberg, 1992; Paus et al., 2001). The slow wave may thus disappear as the process of myelination takes place. However, this does not indicate what the increased amplitude of the slow wave in response to occasional change actually represents. It has been hypothesized that the positive slow wave may reflect a release from a refractory state (Čeponiené et al., 2002) or an automatic categorization of stimuli (Friedrich et al., 2004) or an immature type of P3a response representing an involuntary attention shift (Kushnerenko et al., 2002). However, to date we do not have a definitive answer to this question.

Nor are the neural generators of the slow wave clear. Trainor et al. (2003) discuss several possibilities. Because anatomical data from human autopsies indicate that the neurofilaments necessary for fast, effective synaptic communication are only present in layer I of auditory cortex during the first months after birth (Moore & Guan, 2001), and layer I is not involved in discriminative processes in adults, one possibility is that the slow waves involve a subcortical sink (depolarization) with a passive circuit-completing source in layer 1. However, this seems unlikely because thalamic field potentials are not visible at the scalp in adults, and the input to layer I is non-specific in adults. A second possibility proposed by Trainor et al. (2003) is that neurons in layer IV are depolarizing even though they do not have functional synapses (Huttenlocker & Dabholkar, 1997), and these depolarizations are accompanied by passive returns located in layer I. The scalp potentials appear as slow waves because highly synchronized depolarization is not possible in layer IV because of the immaturity of their synaptic function.

Similarly, although several studies (e.g., Cheour-Luhtanen et al., 1996; Cheour et al.,1998; Čeponienė et al., 2000, 2002; Friedrich et al., 2004; Morr et al., 2002) suggest that the MMN-like response to change seen in infancy could represent discrimination processes in auditory cortex similar to those underlying the MMN response in adults, this interpretation also needs validation. The source of MMN is thought to be in the supragranular layers of A2, including layers II and upper III (Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994). However, according to Moore et al. (Moore & Guan, 2001; Moore, 2002), only layer I is fully functional before 4 months of age, with mature synapses beginning to develop in deeper layers (IV, V, VI) around 4 months of age, but not in layers II and upper III until after 5 years of age. Thus, the generators and underlying mechanisms of the MMN-like negativity seen in infants may in fact be quite different from that seen in adults in terms of neural mechanisms and function. More research is needed in order to investigate the nature of the mismatch response in infants and its underlying neural generators.

Overall, the current study demonstrated that there are two types of mismatch responses to infrequent pitch changes co-existing during a certain period in early infancy. The adult-like MMN/P3a-like response pattern becomes more prominent while the slow positive difference wave diminishes as age increases. Furthermore, the maturational timetables according to which these mismatch responses develop are different for different stimulus features, with early emergence of the MMN-like negativity for pitch discrimination compared to gap discrimination or sound localization. The co-existence of two types of responses and the dissociation of their developmental trajectories also suggests that they have separate underlying neuromechanisms.

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Acknowledgements

This research was funded by a grant to LJT from the Canadian Institutes for Health Research. We thank Dorcas Yung for help in testing the infants and Jingjiang Lei for technical support.

Table 1. Summary of infant mismatch studies with frequency changes in pure tone or complex tones

Study	Age and state	f0 of standards (S) and deviants (D)	Duration (d) and ISI	Filters	ERP response
Alho et al., 1990	Newborns in quiet sleep	Pure tone S: 1000 Hz D: 1200 Hz	d: 40 ms ISI: 570 ms	0.5 - 30 Hz	Negativity at 296 ms (FZ) and 270 ms (CZ)
Leppänen et al, 1997	Newborns in quiet sleep	Pure tone S: 1000 Hz D: 1100 Hz, 1300 Hz	d: 74 ms ISI: 351 ms	<30 Hz	Positivity, 250 - 300 ms, both conditions
Cheour et al., 1999	Newborns (healthy and cleft palate groups) in active sleep	Pure tone S: 1000 Hz D: 1100 Hz	d: 100 ms ISI: 700 ms	1- 30 Hz	Negativity, 200-500 ms in healthy group and 3 of 9 in cleft palate group; Positivity in rest of cleft palate newborns
Čeponiené et al., 2000	Newborns in active sleep and 6-month-olds mostly awake (healthy and cleft palate group)	Pure tone S: 1000 Hz D: 1100 Hz	d: 100 ms ISI: 700 ms	1- 30 Hz	Negativity, 80-300 ms in healthy newborns and all 6-month-olds No peak or smaller negativity (250- 450 ms) in cleft palate newborns
Čeponiené et al., 2002	Newborn in active sleep	Harmonic tones with 3 partials S: 500 Hz D: 750 Hz	d: 200 ms ISI: 600 ms	1- 15 Hz	Negativity, 80-300 ms in 81% of subjects.
Kushnerenko et al., 2002	Infants recorded every 3 months from newborn to 12 months old, kept awake except newborns in active sleep, others awake	Harmonic tones with 3 partials S: 500 Hz D: 750 Hz	d: 100 ms ISI: 700 ms	1 – 15 Hz	Negativity, 80-300 ms and positivity 250-450 ms in 75% of infants at each age, but MMN not consistent within subjects across age.

Morr et al., 2002	Infants 2- 47 months state unknown	Pure tone S: 1000 Hz D: 1200 Hz 2000 Hz	d: 150 ms ISI: 750ms	1-15 Hz	2000 Hz deviants: negativity 150-350 ms; 1200 Hz deviants: positivity only
Hirasawa et al., 2003	Newborn in quiet sleep, active sleep or awake	Pure tone S: 1000 Hz D: 1100 Hz	d: 100ms ISI 900m (exp 1), variable ISI 350,900,1400 ms (exp2)	0.1-40 Hz	Negativity150-450 in all groups and conditions
Leppänen et al., 2004	Newborns (more mature, less mature according to heart period and gestational age) in quiet sleep	Pure tone S: 1000 Hz D: 1100 Hz	d: 74 ms ISI: 351ms	<30 Hz	Negativity in less mature newborns; Positivity in more mature newborns
Fellman et al., 2004	Newborns, 3, 6, 9, 12, and 15 months (preterm and fullterm); newborns in active sleep, others awake	Harmonic tones with 3 partials S: 500 Hz D: 750 Hz	d: 100 ms ISI: 700 ms	1 – 15 Hz	Fullterm infants, negativity 50-150 ms in newborns and 150 -250 ms in 3, 12 and 15 months; not significant in 6 and 9 months, positivity 250-350 in all ages. Preterm infants: both components found to develop later than fullterm infants.

Figure Captions

Figure 1. The grouping of electrodes in the Geodesic net (see Methods section for details).

94 out of 124 electrodes were selected to be divided into 5 groups (frontal, central, parietal, occipital, and temporal) for each hemisphere. Each region included 16 to 20 channels. The waveforms for all channels in each region were averaged together to represent EEG responses from that scalp region. The other 30 out of 124 channels were excluded from further analysis to avoid artifacts and enable comparison between hemispheres. The temporal regions were not used in the analyses.

Figure 2. Grand average waveforms of the standard and deviant waves for each of the three age groups (left panel: 2-month-olds; middle panel: 3-month-olds; right panel: 4-month-olds) for all 8 scalp regions with band pass filtering between 0.5 and 20 Hz.

Figure 3. Grand average difference waves (deviant – standard wave) for each of the three age groups (left panel: 2-month-olds; middle panel: 3-month-olds; right panel: 4-month-olds) for all 8 scalp regions with band pass filtering between 0.5 and 20 Hz. Difference waves at electrode Fz are overlaid for the three age groups (bottom).

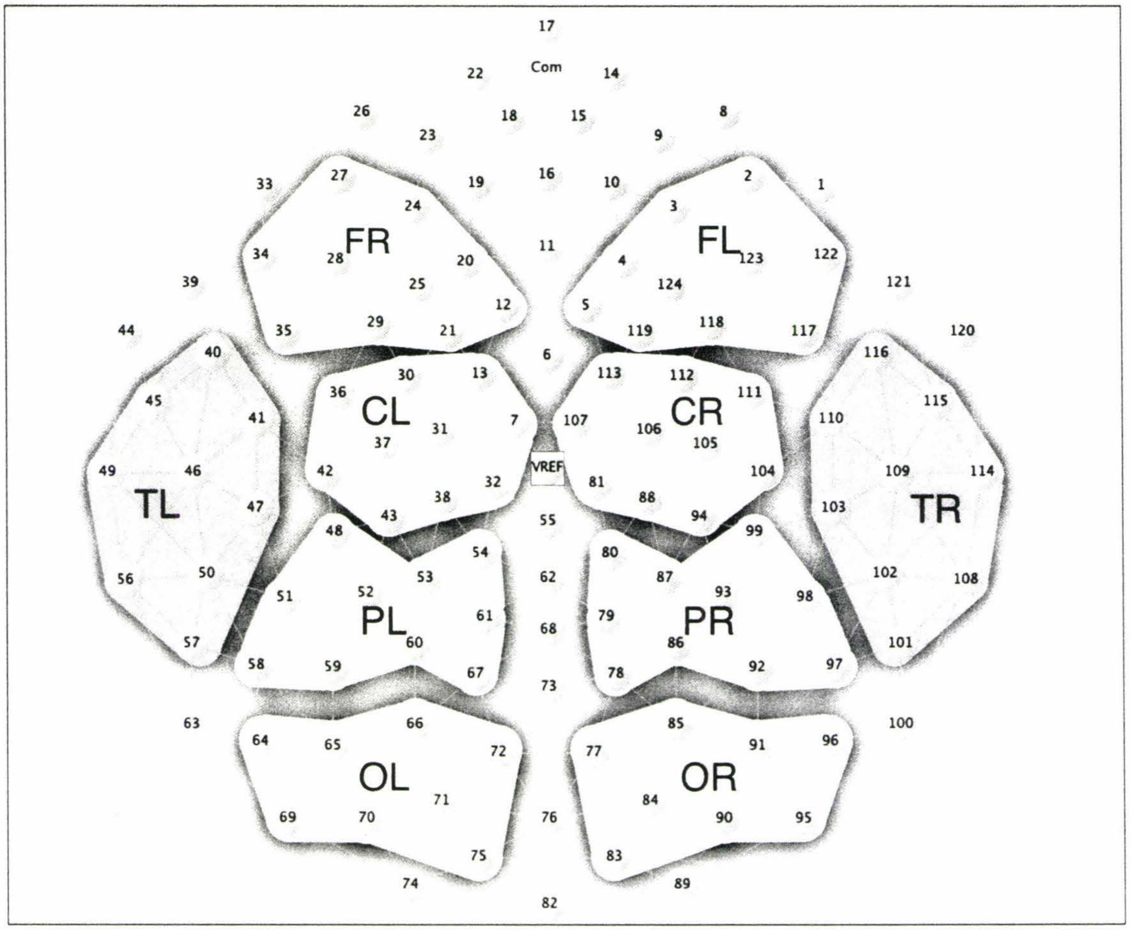
Figure 4. Grand average difference waves (deviant – standard wave) for each of the three age groups (left panel: 2-month-olds; middle panel: 3-month-olds; right panel: 4-month-

olds) for all 8 scalp regions with band pass filtering between 3 – 20 Hz. Bars indicate regions in which the waveforms are significantly different from zero. Difference waves at electrode Fz are overlaid for the three age groups (bottom).

Figure 5. Grand average standard and deviant waves for each of the three age groups (left panel: 2-month-olds; middle panel: 3-month-olds; right panel: 4-month-olds) for all 8 scalp regions with band pass filtering between .5 and 3 Hz.

Figure 6. Whole head topographical voltage maps for the MMN-like negativity, P3a-like positivity, and slow positive wave (not shown for 4-month-olds because the component was not significant) for each of the three age groups.

Figures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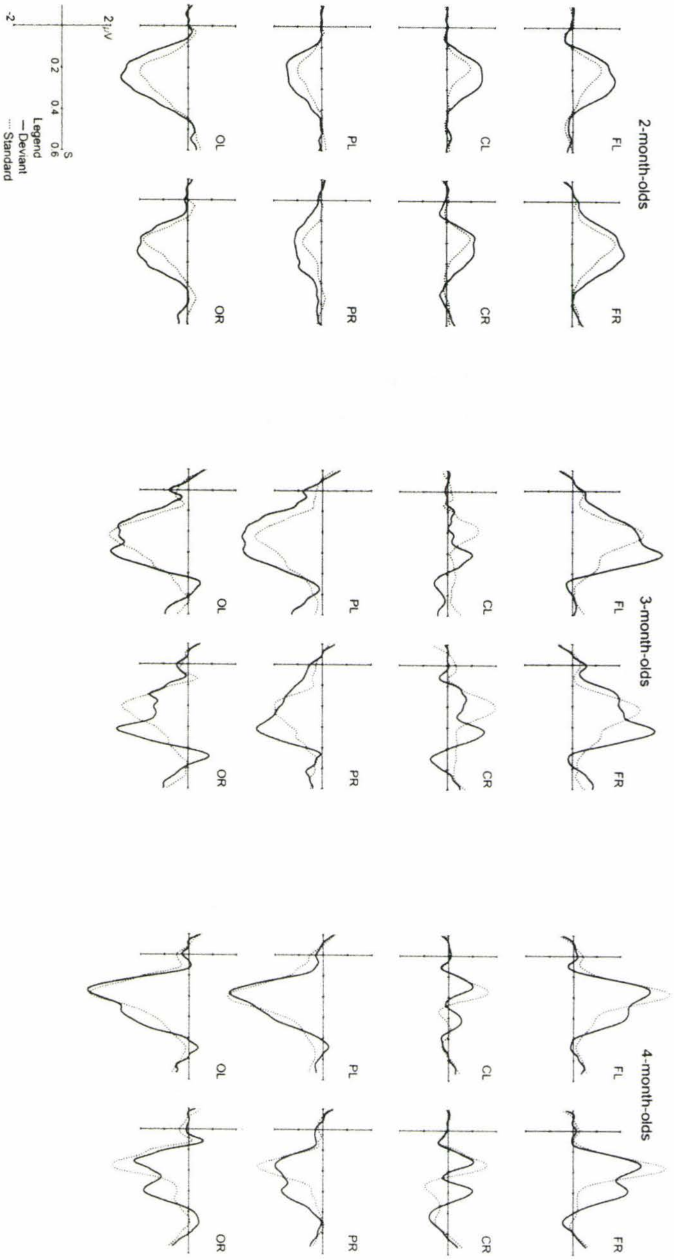
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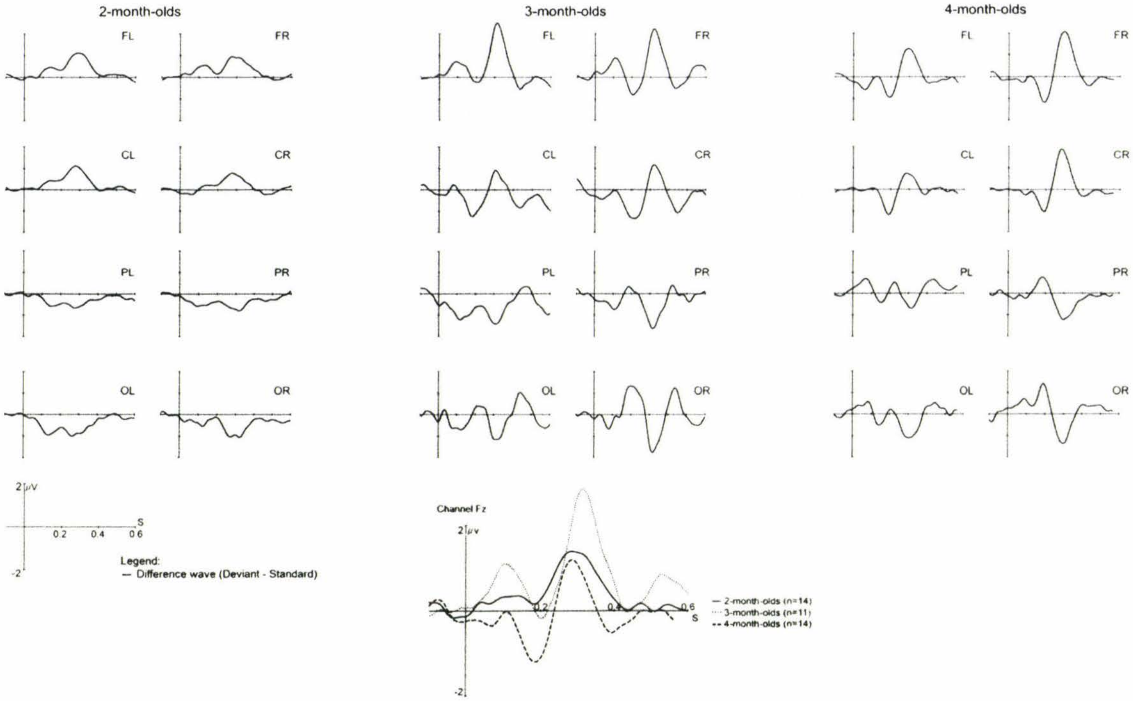
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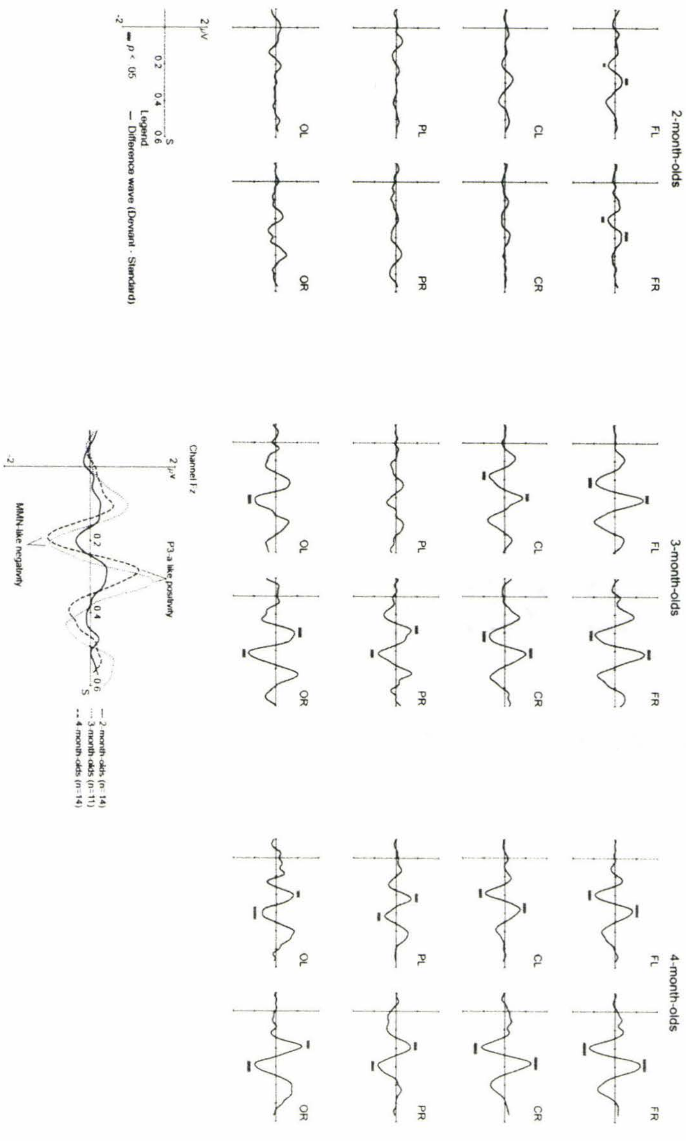
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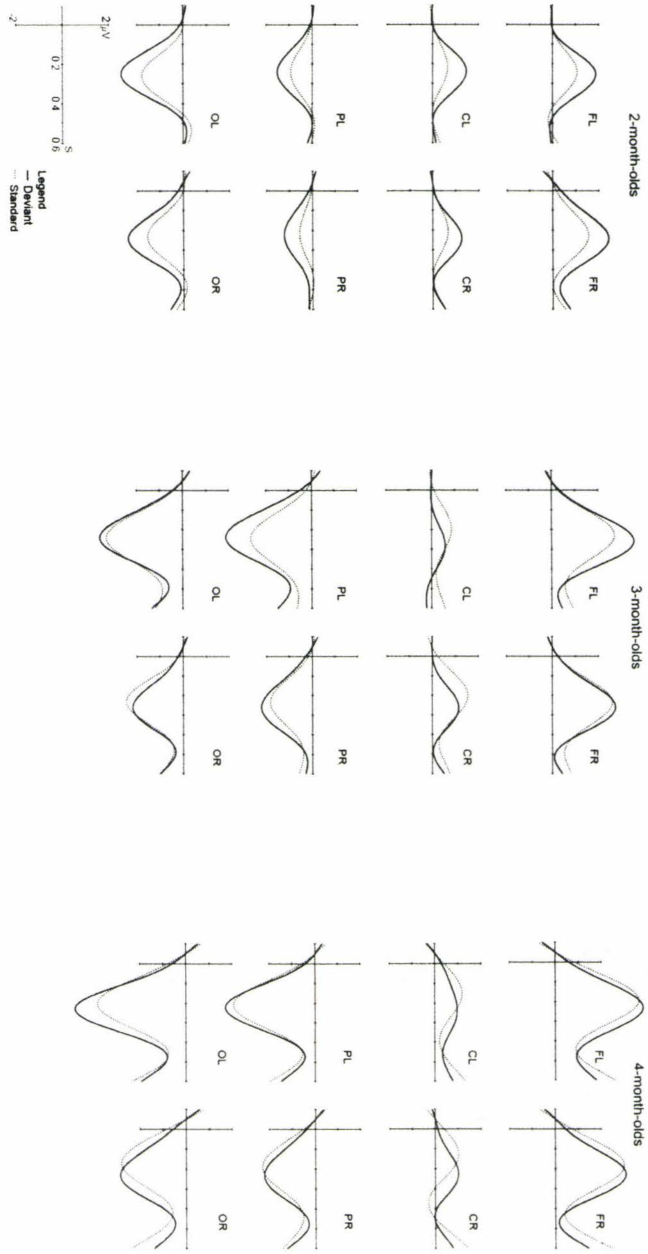
P3-a like positivity
MMN-like negativity
— 2-month-olds (n=14)
··· 3-month-olds (n=11)
- - 4-month-olds (n=14)
4-month-olds
FL
FR
CL
CR
PL
PR
OL
OR


2-month-olds
FL
FR
CL
CR
PL
PR
OL
OR
2μV
-2
0.2
0.4
0.6
s
Legend
— Deviant
··· Standard
3-month-olds
FL
FR
CL
CR
PL
PR
OL
OR
4-month-olds
FL
FR
CL
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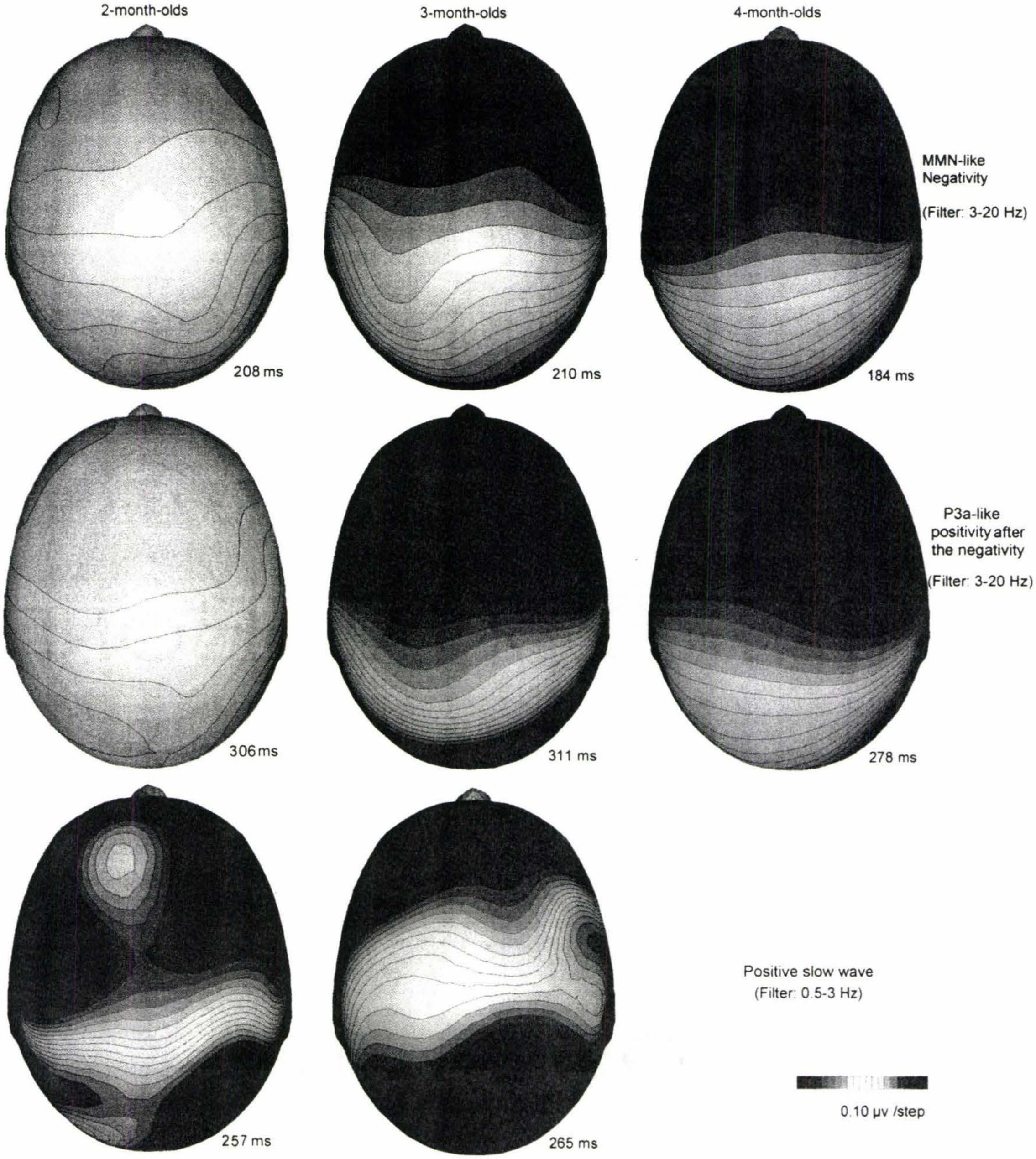
PL
PR
OL
OR


2-month-olds
3-month-olds
4-month-olds
MMN-like Negativity
(Filter: 3-20 Hz)
208 ms
210 ms
184 ms
P3a-like positivity after the negativity
(Filter: 3-20 Hz)
306ms
311 ms
278 ms
Positive slow wave
(Filter: 0.5-3 Hz)
257 ms
265 ms
0.10 µv /step

Chapter 3:

MATTURATION OF CORTICAL MISMATCH RESPONSES TO OCCASIONAL PITCH CHANGE IN EARLY INFANCY: EFFECTS OF PRESENTATION RATE AND MAGNITUDE OF CHANGE

This chapter is manuscript in publishing. Journal name: Neuropsychologia. Authors: He, Hotson & Trainor. Title: Maturation of cortical mismatch responses to occasional pitch change in early infancy: Effects of presentation rate and magnitude of change

Introduction to the Chapter 3

We suggested in the previous chapter that the two MMRs might represent the fact that different neural mechanisms are prominent at different stages of maturation in early infancy. However, in the literature, it is still under debate as to whether the two types of MMR are simply different expressions of the same neural mechanism or whether they represent different underlying processes.

In this chapter, we examined whether the MMRs we observed in Chapter 2 are functionally distinct by varying two parameters: the stimulus presentation rate and the magnitude of pitch change. Both 2 and 4-month-olds were tested to enable cross comparisons with the results from Chapter 2.

The results showed that the two types of MMRs were again present. The magnitude of pitch change only slightly affected the two types of MMRs. The stimulus presentation rate, on the other hand, influenced the two types of MMRs differently. There was only a small influence on the negative MMR but a large increase in the amplitude of the positive MMR. These results suggest that the two types of MNR reflect different underlying processes: the positive MMR, which predominates at 2 months of age, appears to reflect some immature format of automatic change detection neural processes, while the negative MMR, which predominates at 4 months of age, appears to reflect more mature, possibly adult like change detection processes.

Maturation of cortical mismatch responses to occasional pitch change in early infancy:

Effects of presentation rate and magnitude of change

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Running Head: Pitch change responses in infancy

Keywords: Mismatch negativity (MMN), infant, pitch, development, tempo, presentation rate, magnitude of stimulus change.

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Abstract

Previous studies have reported two types of event-related potential (ERP) mismatch responses in infants to infrequent auditory changes: a broad discriminative positivity in younger infants and a negativity resembling adult mismatch negativity (MMN) in older infants. In the present study, we investigated whether the positive discriminative slow wave and the adult-like MMN are functionally distinct by examining how they are affected by presentation rate and magnitude of change. We measured ERPs from adults, 2-month-olds, and 4-month-olds to a repeating piano tone (standard) that occasionally changed in pitch (deviant). The pitch changes between standards and deviants were either small (1/12 octave) or large (1/2 octave) in magnitude, and the stimulus presentation rate was either slow (800 ms SOA) or fast (400 ms SOA). As the presentation rate increased, both adults and 4-month-olds showed an MMN response that decreased in latency, but was unaffected in amplitude. As the magnitude of the pitch change increased, MMN increased in amplitude. On the other hand, only a broad positive mismatch response was seen in 2-month-olds. As the presentation rate increased, 2-month-olds' responses to standard tones decreased in amplitude while their responses to deviant tones were unaffected. The magnitude of the pitch change did not affect 2-month-olds' responses. These results suggest that pitch is processed differently in auditory cortex by 2-month-olds and 4-month-olds, and that a cortical change-detection mechanism for pitch discrimination similar to that of adults emerges between 2 and 4 months of age.

Introduction

Thirty years of extensive research in adults indicates that the mismatch negativity (MMN) component of the event-related potential (ERP) is a reliable physiological representation of cortical auditory discrimination processes in adults (Näätänen & Winkler, 1999). MMN is a frontocentrally negative component (with polarity reversal below the Sylvian fissure) elicited by occasional changes (deviants) in a sequence of identical sounds or sounds from the same category (standards). MMN occurs in response to occasional deviations in pitch, duration, loudness, phonemic category, rhythmic pattern, and other abstract features, with the peak latency (between 120 and 230 ms from the onset of deviant stimulus) depending on the stimulus rate, magnitude of change, and type of change (for a review, see Picton et al., 2000). MMN is often followed by a frontal-positive P3a component around 280 ms that reflects involuntary capture of attention by perceptually novel stimuli (Sams et al., 1985; Czigler et al., 1992; Polich, 1988; Gaeta et al., 2001). However, MMN itself can be elicited automatically without attention or an overt response, suggesting that it is related to the detection of deviant events at a pre-attentive level (e.g., Sussman et al., 1998; Oades & Dittmann-Balcar, 1995). Thus, it is of interest to use MMN in developmental research with prelinguistic infants who have limited repertoires of behavioural responses.

Eighteen years have passed since the first study on the infant mismatch response was conducted (Alho et al., 1990). Although ERPs potentially provide an objective measure of the relation between brain and behaviour in the early years of life, ERP responses in infants and young children differ substantially from those of adults (for a review, see Trainor, 2007). For example, the N1b component generated in auditory cortex is not seen robustly in children until about five years of age, and does not reach adult levels of maturity until the late teenage years (Ponton et al., 2000; Shahin et al., 2004). Mismatch responses are also different in young infants compared to adults. In fact, two different responses to stimulus change have been reported in infants: (1) a negative response similar in morphology to adult MMN (e.g., Alho et al., 1990; Čeponiené et al., 2000, 2002; Hirasawa et al., 2003; Trainor et al., 2001, 2003; He et al., 2007) and (2) an increase in the slow positive wave that dominates young infants' ERP responses (e.g., Cheour et al., 1999; Leppänen et al., 1997, 2004; Morr et al., 2002; Trainor et al., 2001, 2003; He et al., 2007). He et al. (2007) summarized these studies in a table, and discussed the merits of various hypotheses concerning the conditions required for their elicitation. As explanations for when negative and when positive mismatch responses will be observed in infants, they ruled out infant state, physiological conditions such as risk for dyslexia, use of different stimuli, and methodological differences such as choice of reference electrode(s) and rate of stimulus presentation. On the other hand, Trainor et al. (2001, 2003), examining responses to the occasional insertion of a 16 ms silent gap in a repeated sequence of tone pips, found that younger infants showed only an increase in the slow positive wave whereas by 6 months, infants showed a negative response resembling the adult MMN. They proposed that the two responses represent different processes, and that the adult-like MMN response develops with cortical maturation (Moore & Guan, 2001). He et al. (2007) further demonstrated that a similar shift from the discriminative positive slow wave to the adult-like MMN occurs for pitch changes of half an octave, although the shift occurred slightly earlier, between 2 and 4 months of age. The presence of both components at 3 months of age suggested further that they represent different processes. In the present study, we investigated whether the positive discriminative slow wave and the adult-like MMN are functionally distinct by examining how they are affected by presentation rate and magnitude of change.

There is debate in the adult literature as to the nature of the MMN response. For example, it has been proposed that MMN is simply an augmentation of the N1 response (Jääskeläinen et al., 2004). N1 is a vertex-negative component that can be evoked in adults by virtually any transient sound, with typical latency around 100 ms. N1 is thought to be generated by the afferent transient detecting neurons in the auditory cortex (for a review, see Hyde, 1997). Like MMN, N1 increases in amplitude when occasional deviant stimuli are inserted in a repeating pattern. This is thought to occur because the neural circuits representing the standard stimuli become somewhat refractory/adapted whereas those encoding the occasional deviant stimuli do not, resulting in larger responses to the deviant than standard stimuli. However, a number of lines of evidence suggest that MMN and N1 are distinct (for a review, see Näätänen et al., 2005). One line involves manipulation of stimulus presentation rate. The N1 response diminishes in amplitude with increases in presentation rate, indicative of a refractory process (Mäntysalo & Näätänen, 1987; Czigler et al., 1992), whereas the MMN amplitude remains the same or increases in amplitude with increases in presentation rate (Friedman et al., 2001; Sabri & Campbell, 2001; Roeber et al., 2003), indicative of a change detection mechanism. A second line involves manipulation of the magnitude of stimulus change. With smaller differences between standards and deviants, the difference in N1 elicited by standards and deviants becomes very small, again suggesting a refractory process because the representations of standards and deviants increasingly overlap as they become more similar (Näätänen et al., 2005). With decreasing magnitude of stimulus change, the amplitude of the MMN also decreases (Näätänen & Alho, 1997). However, it remains relatively robust with very small differences between standard and deviant stimuli, again suggesting a change detection mechanism at work (Sams et al., 1985; Scherg et al., 1989)

In the present study, we examined whether the adult-like MMN seen in older infants and the discriminative slow positive wave seen in younger infants behave like the MMN seen in adults. We used the piano tone stimuli of He et al. (2007), but manipulated the stimulus presentation rate and the magnitude of the pitch change between standard and deviant stimuli. Regarding the stimulus presentation rate, if changes in the presentation rate have little effect on the amplitude of the infant mismatch response, this would be consistent with a change detection mechanism. If, on the other hand, the infant mismatch response diminishes with faster presentation rates, this would be consistent with an N1-like refractory response. A few previous studies found no effect of presentation rate on the adult-like MMN in infants (Pihko et al., 1999; Kushnerenko et al., 2002; Hirasawa et al., 2003), suggesting that this component behaves as if reflecting a change detection mechanism rather than a refractory N1 mechanism, but there are no studies examining the effect of presentation rate on the infant discriminative slow positive mismatch response. As far as the magnitude of the pitch change, one study (Morr et al., 2002) suggested that the discriminative positive slow wave might only occur in response to large stimulus changes. Here we test whether the infant MMN and discriminative slow positive wave responses are different for pitch changes near threshold compared to those well above threshold.

Methods

Participants

Three different age groups (2-month-olds, 4-month-olds, adults) were tested in two conditions involving a small pitch change (semitone), one at a fast presentation rate and one at a slow presentation rate. Ten (7 female) healthy university students (aged 18 to 20 years, mean age 18.7 years) with no hearing deficits participated (2 were tested in the slow SOA condition only, 2 in the fast presentation rate condition only, and 6 in both). Informed written consent was obtained from all the participants prior to the experiment and course credits were assigned to compensate their participation. A totally of 67 healthy, full term infants with no known hearing deficits were included in the final sample. The slow presentation rate condition included 15 2-month-olds (10 female) and 15 4-month-olds (9 female). The fast presentation rate condition included 22 2-month-olds (14 female) and 15 4-month-olds (10 female). All the infants were awake during testing. An additional 23 infants (15 2-month-olds and 8 4-month-olds) were excluded from the final sample either because they fell sleep during testing (8 2-month-olds and 4 4-month-olds) or because they became fussy during testing and failed to produce the minimum of 100 artifact-free deviant trials for averaging (7 2-month-olds and 4 4-month-olds). Informed written consent was obtained from all the parents prior to the experiment. After the experiment, a certificate and a bath toy were provided as thanks for their participation.

In order to examine the effect of the magnitude of the pitch change, the data from the 14 4-month-olds (9 female) and 14 2-month-olds (11 female) in the large (tritone) pitch change (slow presentation rate) condition of He et al. (2007) were compared to the present data in the small (semitone) pitch change (slow presentation rate). In addition, 8 (5 female) university students (18 to 23 years, mean age 20.2 years) were tested in the large (tritone) condition (slow presentation rate), as the previous study did not include data from adult participants.

Stimuli

In both the slow and fast presentation rate conditions, piano tones C_5 and $C\#_5$, with fundamental frequencies of 523.25 and 554.37 Hz were used as standard and deviant stimuli, respectively, representing a pitch change of 1/12 octave (semitone). In the large pitch change (slow presentation rate) condition, the standard was again C_5 but the deviant was $F\#_5$ ($f_0 = 698.46$), representing a pitch change of half an octave (tritone). For the slow presentation rate, the duration of the stimuli was 600 ms and the stimulus onset asynchrony (SOA) was 800 ms to enable direct comparison with the previous dataset of He et al. (2007). For the fast presentation rate, the duration of the stimuli was 300 ms and the SOA was 400 ms. Stimuli were shorter in this condition to accomodate the short SOA. For such piano tones, with abrupt onsets and where the amplitude subsequently fades gradually to zero, the ERP response to the tone offset is negledgeable.

Apparatus

All of the piano tones were synthesized with Reason 2.0 software (Propellerhead Software) and recorded with Adobe audition 1.0 software (Adobe Software). Stimuli were played using E-prime 1.1 software (Psychology Software Tools. Inc) on a Dell OptiPlex280 computer with an Audigy 2 platinum sound card (Creative Labs) through a WestSun loudspeaker (WestSun Jason Sound, JSIP63) located one meter directly in front of the participant. The stimuli were presented at a level of 70 dB (A) at the location of the head of the participant, over a background noise level of 29 dB (A).

Procedure

Participants sat on a comfortable chair (infants sat on their parents' laps) in a sound-treated room containing floor-to-ceiling double velvet curtains and acoustic ceiling panels. Participants watched a silent movie (adult participants) or an animated video (infants) in a passive protocol while the piano tone stimuli were played. An oddball paradigm was used with 80% standard trials and 20% deviant trials. Stimulus order was randomized with the constraint that at least two standards occurred between successive deviants. The complete experiment consisted of 1600 trials (320 deviant trials) but testing was stopped early if infants became fussy. For adult participants who completed both the slow semitone and fast semitone conditions, the order of conditions was randomized. All study procedures were approved by the McMaster University Research Ethics Board.

Recording and Analysis

EEG was recoded from 124 locations on the scalp for infants and 128 locations for adults with a Geodesic Sensor net (Electrical Geodesics, Inc). All electrode impedances were maintained below 50 kΩ. The electrical potential was digitized at 1000 Hz. The online recording was referenced to the vertex with a band-pass filter of 0.1-400 Hz.

EEG responses were filtered between 0.5 and 20 Hz for adults. In order to isolate the infant slow discriminative mismatch response and the adult MMN-like fast negative mismatch response, band pass filters of 0.5- 3 Hz and 3 -20 Hz were used, respectively. In all cases, filters had a roll-off of 24 dB/oct. (For more detail of this method, see He et al., 2007.) The filtered continuous data were then segmented into 700-msec epochs, including a 100-msec prestimulus-onset baseline (50-msec baseline for the fast presentation rate condition, as stimuli were separated only by a 100-msec inter-stimulus interval in this condition). EEG epochs from adult participants were then subject to fixed threshold (± 120 μV) epoch rejection to omit the artifact due to eye blinks. The number of accepted deviant epochs across all 9 adult participants ranged from 233 to 308 (*M* =282). For infants, channel independent epoch rejection with a threshold of ±120 μV was conducted to remove the epochs contaminated by blinks, eye, head, or body movement. The number of accepted deviant epochs across the 67 infants ranged between 114 and 271 (*M* = 206). The accepted standard and deviant epochs were averaged separately, excluding the standard epochs immediately following deviant epochs, baseline corrected, and referenced to an average reference. Difference waves were obtained by subtracting the standard from the deviant waveforms.

76 of 124 selected channels were divided into four groups for each hemisphere to represent the average response from frontal (20 channels), central (20 channels), parietal (20 channels), and occipital (16 channels) scalp regions. (See He et al 2007, for details of the grouping scheme). Two-tailed paired *t*-tests were calculated at each time point between standard and deviant waveforms to reveal the time periods of significant difference separately for adults and infants at all eight scalp regions (see Figures).

For the MMN in adults and the MMN-like negativity in 4-month-olds, the peak latency and absolute amplitude of the MMN-like negativity and the following P3a-like positivity were measured in the difference waveforms of each participant. The MMN-like negativity was defined as the largest frontally-negative peak between 100 and 300 ms, and the P3a-like positivity as the largest frontally-positivity between 200 and 400 ms. When a peak could not be measured, it was treated as missing data. Separate ANOVAs were calculated on peak latencies and amplitudes for the MMN-like negativity and the P3a-like positivity in order to examine whether they varied significantly across hemisphere and scalp region. For the broad discriminative slow wave mismatch responses in 2- and 4-month-olds, slow wave deflections rendered peak picking difficult, so the absolute average amplitudes of the difference wave (deviant – standard) in successive 50-msec time bins between 0 and 400 ms after stimulus onset were measured for each scalp region. Repeated-measures ANOVAs were performed to test whether the slow discriminative positivity varied significantly across presentation rate, magnitude of pitch change, time bin, hemisphere, and scalp region.

In all of the above ANOVAs, the Greenhouse-Geisser correction was applied to all within-subjects measures with more than two levels. The Tukey HSD test was used for post hoc comparisons. The Bonferroni correction was used for multiple within-subject comparisons.

Results

Effect of presentation rate

Infant mismatch responses and adult MMN in slow (800 ms SOA) and fast (400 ms) stimulus conditions with the small magnitude of pitch change were compared in order investigate the influence of presentation rate on infant mismatch responses at different stages of maturation. Figures 1-3 shows the difference waves of 2-month-olds, 4-month-olds, and adults in the slow and fast conditions. Adult showed MMN to the pitch changes in both fast and slow presentation rate conditions (Figure 1), with earlier responses to the slow rate. For infants, clear differences in amplitude between fast and slow presentation rates can be observed in the slow discriminative positive mismatch responses of both 2- and 4-month-olds (Figure 2) under the 0.5 -3 Hz bandpass filter. As for the MMN-like negative mismatch responses in infants (Figure 3), under 3-20 Hz bandpass filter 2-month-olds showed only hints of a negative response at both presentation rate. However, 4-month-olds displayed a response pattern that parallels the adult MMN, with earlier peaks for the slower presentation rate. Statistical analyses were conducted to compare fast and slow presentations rates at each age.

Insert Figure 1 to 3 here

The slow discriminative positive slow wave (0.5 -3 Hz bandpass filtered)

Adults showed no evidence of slow wave activity, but standard and deviant waves in both 2- and 4-month-olds showed a prominent slow wave with similar topography (anterior positivity and posterior negativity; Figure 4). However, the positivity was larger for deviants than standards. The differences between the two resulted in a broad discriminative positivity. To compare the broad discriminative positivity between the fast and slow conditions the absolute averaged amplitude of the difference waves in each successive 50 ms time bin from 0 to 400 ms was calculated and then subjected to a repeated measures ANOVA, with presentation rate and age as a between-subjects factor and time bin (8 bins in total), brain region (frontal, central, parietal, occipital), and hemisphere (left, right) as within-subject factors. The main effect of presentation rate was significant ($F_{(1, 63)} = 6.78$, p=0.01, η^2=0.097), with larger amplitude in the fast (1.12 +/- 0.049μV; Std.Errors are reported with all means) than in the slow (0.93 +/- 0..053μV) condition. The presentation rate by time bin interaction was significant, $F_{(7, 441)} = 2.82$, p=0.03, η^2=0.043, indicating that the amplitudes in the fast condition were particularly stronger than in the slow condition at certain time periods. Post Hoc comparisons found significant differences between 150-200 ms (p=0.01), 250- 300 ms (p=0.02),300-350 ms (p=0.02), and 350-400 ms (p=0.001). Not surprisingly, the main effect of time bin was also significant, $F_{(7, 441)} = 39.40$, p<0.001, η^2=0.385, reflecting a stronger amplitude between 150 and 400 ms than between 0 and 150 ms (all *ps* < .05), indicating the presence of the broad discriminative positivity between 150 and 400 ms. Although the main effect of age was not significant, the time bin by age interaction was, $F_{(7, 441)} =$ 3.77, p=0.008, η^2=0.056, with larger absolute amplitude in 2-month-olds than in 4-month-olds only between 150 to 200 ms (p=0.05). This result can be seen in Figure 2 in the delayed slow positive wave in 4-month-olds in comparison to 2-month-olds, which was possibly due to left over unfiltered fast MMN-llike activity. The main effect of region achieved significance ($F_{3, 189} = 4.90$, p=0.004, η^2=0.072) with larger amplitudes (p =.02) at occipital (1.14 +/- 0.054μV) region than at parietal region (0.943 +/- 0.051μV), consistent with previous studies (He et al., 2007).

Insert Figure 4 here

A larger discriminative positivity for fast compared to slow presentation rates was not expected. To examine this effect further, the standard and deviant waves in infants (as shown in Figure 4) were analyzed by conducting an five-way ANOVA analysis on the absolute mean peak amplitude between standard and deviant waves among the time bins where the slow wave was present (150 - 400 msec). The between subject factors were presentation rate and age and the within subject factors were stimulus type (deviant, standard), scalp region, and hemisphere. The result of ANOVA found a significant main effect of stimulus type ($F_{(1, 63)} = 51.60$, $p<0.001$, η^2=0.45), with a larger absolute mean amplitude in the deviant (1.48 +/- 0.063 μV) than in the standard (0.84 +/- 0.062 μV) waves, which again confirmed that the broad positive mismatch response in the difference waves was significant. The main effect of presentation rate was also significant, $F_{(1, 63)} = 41.80$, $p<0.001$, η^2=0.399, indicating a larger amplitude in the slow (1.45 +/- 0.064μV) than in the fast (0.89 +/- 0. 059μV) condition. A stimulus type by presentation rate interaction was significant as well ($F_{(1, 63)} = 7.48$, p=0.008, η^2=0.106), further indicating that, although both deviant and standard waves have smaller ampltitude in fast presentation rate condition than in slow presentation condition, the amplitude difference of two conditions in the standard waves (0.81 μV, $p<0.001$) is much larger than the difference between the two conditions in the deviant waves (0.32 μV, p=0.01).

The comparison of the mean amplitude between the slow and fast presentation rate condition is shown in Figure 5. Because the larger responses in the slow compared to the fast condition were much larger for standards than for deviants, the standard rather than deviant waves contribute most to the difference waves, resulting in the larger discriminative positivity for the fast compared the slow presentation rates Other significant effects were age ($F_{(1, 63)} = 38.50, p<0.001, \eta^2=0.237$), with a larger mean amplitude in 4-month-olds (1.36 +/- 0.065 μV) than in 2-month-olds (0.97 +/- 0.058 μV), and a main effect of region ($F_{(3, 189)} = 16.7, p<0.001, \eta^2=0.209$). The effect of region was similar as in the analyses of the difference waves, above.

Insert Figure 5 here

In sum, the slow wave response in standards decreased with increased presentation rate, consistent with a refractory or inhibitory process. There was less decrement with deviants, which were more spread out in time at both the fast and slow presentation rate because they occur relatively rarely.

The adult MMN-like negativity

2-month-olds

Although there were hints of the MMN-like negitivy in the difference wave for 2-month-olds, no significant response peaks were found between deviant and standard waves by paired wise t-test (indicated by significant bars in Figure 3.) at either the slow or fast presentation rates. This result is consistant with a previous study by He et al.

(2007) using a similar paradigm and stimulus, which indicates that the adult MMN-like negativity is only beginning to emerge at this age. A P3a-like component was also marginally present, with short regions of significance at a couple of regions.

4-month-olds

Because both an MMN-like negativity and a P3a-like positivity were prominent in the difference waves of 4-month-olds, separate analyses were conducted to compare the latency and amplitude differences between the fast and the slow conditions for each peak.

For the MMN-like negativity, the peak latencies were measured from each infant and subjected to an ANOVA with presentation rate as a between-subjects factor and hemisphere and scalp brain region as within-subject factors. The main effect of presentation rate was significant, $F_{(1, 28)} = 7.60$, $p=0.01$, $\eta^2=0.213$, reflecting earlier peak latency for the slow (221+/- .003 ms) than for the fast (232 +/- .003ms) presentation rates. The peak amplitude of the MMN-like negativity was subjected to an ANOVA with the identical factors as for the latency analysis, above. No significant main effect or interactions involving presentation rate were found. The only significant effect was region, $F_{(3, 84)} = 10.05$, $p<0.001$, $\eta^2=0.264$, with amplitudes at frontal sites (1.08 +/- 0.11μV) greater than at occipital sites (1.05 +/- 0.099μV), which were greater than at central sites (0.89 +/- 0.074 μV), which were greater than at parietal sites (0.74 +/-0.064 μV).

The results for the P3a-like positivity echoed those of the MMN-like negativity. For latency, there was a significant main effect of presentation rate, $F_{(1, 28)} = 6.00$,

p=0.02, η^2=0.176, with earlier peaks in the slow (320 +/- .003ms) than in the fast (329+/- .003 ms) condition. For amplitude, only the region effect was significant, $F_{(3, 84)} = 9.45$, p<0.001, η^2=0.252, with amplitudes at occipital sites (1.10 +/- 0.12μV) greater than at frontal sites (0.96 +/- 0.11 μV), which were greater than at central sites (0.81 +/- 0.081μV), which were greater than at parietal sites (0.73 +/- 0.074μV).

In sum, the presentation rate did not affect the peak amplitude of either the MMN-like negativity or the P3a-like positivity, but latencies were earlier for the slow compared to the fast presentation rate for both peaks.

Adults

MMN and P3a components in adults were analyzed in the same way as in 4-month-olds. For the MMN, the ANOVA on latency found a significant effect of presentation rate, $F_{(1, 14)} = 5.14$, p=0.04, with earlier peaks in the slow (111+/- .006 ms) than in the fast (130 +/- .006 ms) condition. The ANOVA on amplitude found only a significant effect of region, $F_{(3, 42)} = 9.45$, p<0.001, with amplitudes at occipital sites (0.76 +/- 0.051 μV) greater than at frontal sites (0.70 + /-0.049μV), which were greater than at central sites (0.68 +/- 0.045 μV), which were greater than at parietal sites (0.49 +/- 0.032μV).

The ANOVA on peak P3a latency showed no significant main effects or interactions. For P3a amplitude the only significant main effect was region F (3, 42)=64.50, p<0.001, with the amplitudes at occipital sites (0.95 +/- 0.037μV) greater that at central sites (0.85 +/- 0.041μV), which were greater than at frontal sites (0.74 + /- 0.032μV), which were greater than at parietal sites (0.46 +/- 0.031μV).

In sum, for adults, the presentation rate had no effect on MMN or P3a amplitude. However, MMN (although not P3a) was significantly later for the fast compared to the slow presentation rate. The latencies of MMN in adults were about 100 ms earlier than latencies of MMN-like negativity in 4-month-olds.

Effect of Magnitude of Pitch Change

Difference waves for small (6% of f_0) and large (33% of f_0) pitch change conditions from 2-month-olds, 4-month-olds, and adults are shown in Figures 6-8. Adults showed an increased MMN for large compared to small pitch changes (Figure 6). Under the 0.5-3 Hz band pass filters (Figure 7) a discriminative slow wave for both magnitudes of pitch change can be seen for 2- and 4-month-olds, but discriminative slow waves were similar in amplitude for both small and large pitch changes. Under the 3-20 Hz band pass filter (Figure 8), 4-month-olds showed clear MMN and P3a responses, again parallel with adult MMN, while 2-month-olds showed hints of a MMN-like response . ANOVAs were conducted with the same factors as those in the analyses of presentation rate, above.

Insert Figure 6-8 here

The slow discriminative positive slow wave (0.5 -3 Hz bandpass filtered)

Adults showed no evidence of slow wave activity. For 2- and 4-month-olds, the ANOVA on the amplitude of the discriminative positivity between small and large pitch change conditions revealed no significant main effect of age, no significant main effect of the magnitude of pitch change and no signficiant interaction between magnitude of pitch change and time bin. The only significant factors were time bin ($F_{(7, 378)} = 32.5, p<0.001, \eta^2=0.375$), with larger amplitudes between 150 and 400 ms than between 0 and 150 ms (all ps < .05), indicating that the slow wave occurred between 150 and 400 ms, time bin by age interaction ($F_{(7, 378)} = 3.924, p=0.01, \eta^2=0.069$), indicating that the slow wave started later for 4-month-olds as with the analyses of presentation rate above, and region ($F_{3, 162} = 4.205, p=0.01, \eta^2=0.075$), again with similar details as for the analyses of presentation rate. Thus, both age groups showed a discriminative positive slow wave, but it was not affected by the magnitude of the pitch change.

These results indicate that there was no evidence that the magnitude of pitch change affected this discrimination process.

The adult MMN-like negativity

2-month-olds

The 2-month-olds showed hints of an MMN-like response pattern with the 3-20 Hz filter, with two of eight regions showing short periods of significance (Figure 8). There were also hints of a P3a-like response, with short periods of signficance at two of eight regions.

4-month-olds

The ANOVA on the latency of the MMN-like negativity revealed a significant main effect of magnitude of pitch change, $F_{(1, 27)} = 25.82, p<0.001, \eta^2=0.489$, with an earlier latency for the large (199 +/- .003 ms) than for the small (221 +/- .003ms) pitch difference. The main effect of region was also significant, $F_{(3, 81)} = 5.83, p=0.002, \eta^2=0.178$, with a later latency in parietal (216 +/- .002ms) than in frontal (206 +/- .002ms, $p=0.02$) and central (205 +/- .003 ms, $p=0.008$) regions. The ANOVA on MMN-like amplitude only found a significant main effect of region, $F_{(3, 81)} = 7.67, p<0.001, \eta^2=0.221$, with amplitudes at frontal sites (1.22 +/- 0.099 μV) greater than at occipital sites (1.16 +/- 0.12 μV), which were greater than at central sites (1.073 +/- 0.088 μV), which were greater than at parietal sites (0.87 +/- 0.083 μV). The main effect of magnitude of pitch change was not significant, but there was a trend for larger peak amplitude with the larger (1.22 +/- 0.120 μV) than with the smaller (0.95 +/- 0.116μV) pitch change, $F_{(1, 27)} = 2.63, p=0.12, \eta^2=0.089$.

Analyses of the P3a-like positivity echoed the above results of the MMN-like negativity. The ANOVA on latency showed a significant main effect of presentation rate, $F_{(1, 27)} = 25.30, p<0.001, \eta^2=0.49$, with much earlier peak latency for the large (294 +/- .004ms) than for the small (321 +/- .004 ms) pitch differences. The main effect of region was also significant, $F_{(3, 81)} = 4.51, p=0.01, \eta^2=0.133$, with a trend for later latency in parietal (313 +/- .003 ms) than in frontal (304 +/- .003ms, $p=0.02$) and central (303 +/- .003 ms) regions. The ANOVA on amplitude found a significant main effect of magnitude of pitch change, $F_{(1, 27)} = 5.35, p=0.03, \eta^2=0.165$, reflecting larger peak amplitude for the large (1.29 +/- 0.13μV) than for the small (0.87 +/- 0.13μV) pitch changes. The main effect of region was also significant ($F_{(3, 81)} = 4.48$, p=0.02), with amplitudes at occipital sites (1.24 +/- 0.11 μV) greater than at frontal sites (1.09 +/- 0.12 μV), which were greater than at central sites (1.06 +/- 0.10μV), which were greater than at parietal (0.94 +/- 0.071μV) sites.

In sum, the above analyses showed that, for 4-month-olds, the larger pitch change led to larger peak amplitudes and earlier peak latencies for both the MMN-like negativity and the P3a-like positivity.

Adults

The ANOVA on MMN latency found no significant main effects or interactions. The ANOVA on MMN amplitude found a significant effect of magnitude of pitch change, $F_{(1, 13)} = 36.58$, $p<0.001$, $\eta^2=0.738$, with larger peaks for the large (0.86 +/- 0.019 μV) than for the small (0.70 +/- 0.018μV) pitch changes. The main effect of region was also significant ($F_{(3, 39)} = 17.13$, $p<0.001$, $\eta^2=0.569$), with larger amplitudes at occipital sites (0.87 +/- 0.031 μV) than at frontal sites (0.83 +/- 0.022 μV), which were larger than at central sites (0.76 +/- 0.019 μV), which were larger than at parietal sites (0.66 +/- 0.021 μV).

The ANOVA on peak P3a latency showed no significant main effects or interactions. For P3a amplitude, the main effect of magnitude of pitch change was significant, $F_{(1, 13)} = 5.34$, p=0.04, $\eta^2=0.291$, with smaller amplitude for the large (0.62 +/- 0.035μV) than for the small (0.73 +/- 0.032 μV) pitch changes. The main effect was effect of region was also significant, ($F_{(3,39)}=60.99$, $p<0.001$, , $\eta^2=0.824$), with amplitudes at occipital sites (0.87 +/- 0.035 μV) greater than at central sites (0.75 +/- 0.035μV), which were greater than at frontal sites (0.64 +/- 0.019μV), which were greater than at parietal sites (0.45 +/- 0.031 μV). P3a amplitude was actually smaller for the large pitch changes. However, the literature suggests that the P3a following the MMN is normally parallel to the MMN, with peak amplitudes correlating to the magnitude of stimulus change (Gaeta et al., 2001). One possibility is that the P3a result in the above analysis occurred because the strong MMN we observed partially overlapped the P3a component, decreasing its apparent amplitude. Indeed, a reanalysis with either Cz or the average of the mastoids as the reference showed no significant difference in P3a amplitude between the small and large pitch changes. To get around this, instead of measuring the absolute peak voltage from baseline, we measured the amplitude of the MMN-P3a complex from the peak of the MMN to the peak of the P3a, and then carried out the same ANOVA as above. In this case, the MMN-P3a complex amplitude was significantly larger in the large (mean = 1.22 +/- 0.036 μV) than in the small (mean = 0.97 +/- 0.026μV, $p = 0.04$) pitch change condition. Thus, we conclude that the magnitude of the MMN-P3a complex actually changed similarly to that of the MMN, and in the same manner as with 4-month-olds.

In sum, the amplitudes of MMN and the P3a (as measured in the MMN-P3a complex analysis) in adults were sensitive to the magnitude of pitch change, with larger amplitude for the large than for small pitch change. These results for amplitude parallel those of 4-month-olds. Unlike 4-month-olds, however, the magnitude of pitch change did not affect the latency of these peaks in adults.

Discussion

The present study investigated how stimulus presentation rate and magnitude of pitch change influence the two types of infant mismatch responses. We found that the MMN/P3a components in adults and the MMN/P3a-like mismatch responses in 4-month-olds showed very similar patterns of change across conditions, suggesting that the mismatch responses in 4-month-olds have similar functional characteristics as the adult MMN responses. The broad discriminative positivity in the infants at 2 and 4 months of age, on the other hand, showed a different response pattern across conditions, suggesting that the slow positivity reflects different underlying neuromechanisms than the mismatch responses in older infants and adults.

In adults, the effects of presentation rate and magnitude of stimulus change on the MMN and P3a responses were consistent with the literature. MMN and P3a remained robust in amplitude with fast presentation rates, and MMN latency was later for the faster than for the slower presentation rate (consistent with, e.g., Friedman et al., 2001; Gonsalvez at al., 1999; Sabri & Campbell, 2001; Schröger et al., 1995; Roeber et al., 2003; Trainor, et al., 2002). The magnitude of stimulus change affected the amplitude of the MMN and P3a such that both were correlated positively with the magnitude of stimulus change (consistent with Katayama & Polich, 1998; Lang et al., 1990; Näätänen & Alho, 1997; Sams et al., 1985).

In 4-month-olds, the presentation rate had no effect on the amplitude of MMN or P3a, but MMN and P3a were later at faster presentation rate. This response pattern is very similar to that of adults, and suggests that the MMN-like component seen in 4-

month-olds likely represents change detection processes, as in adults, rather than refractory or habituation processes, because a decrease in amplitude would be expected with increased presentation rate in the latter case. As far as the magnitude of pitch change, MMN and P3a were larger and earlier for the larger pitch change, as in adults. However, adults did not show earlier peaks for larger pitch change. This may be because the smaller pitch change is approaching behavioural thresholds of infants at 4 months of age (Olsho et al., 1982), but this pitch change is well above adults' thresholds. That the MMN and P3a responses in infants remain robust for a pitch change near threshold is once again consistent with the MMN representing an adult-like change-detection process.

The broad discriminative positivity seen in 2- and 4-month-olds behaved differently than the MMN/P3a components seen in 4-month-olds and adults. Although the slow wave appeared to begin slightly later in 4-month-olds than in 2-month-olds, likely due to the presence of overlapping MMN-like activity in older infants, the effects of presentation rate and magnitude of pitch change were similar at both ages. The amplitude of the broad discriminative positivity was not affected by the magnitude of pitch change. For presentation rate, the amplitudes of the deviant waves were similar across fast and slow presentation rates, but the standard waves decreased substantially in amplitude with the faster compared to slower presentation rate. This is consistent with refractory processes, as suggested by Čeponienė et al. (2002) and Trainor et al. (2003; 2007), according to the following argument. At the fast presentation rate, the standard stimuli are sufficiently close in time that the neural circuit encoding the pitch in 2- and 4-month-olds is unable to fully recover between presentations of the standard stimulus, leading to reduced amplitude of the slow wave response. The deviant stimuli, on the other hand, occur more rarely, and are thus relatively far apart in time, even at the fast presentation rate, so less refractory reduction in amplitude is seen. This suggests that the standards and deviants had somewhat different generators as a result of their different spectral makeup, although we did not have sufficient resolution to see significant differences between them in our analyses of region.

Despite the functional and morphological similarities between the mismatch responses of 4-month-olds and adults, it is still possible that the underlying neuromechanisms might be different. In adults, the MMN appears to be generated in the deeper layers of auditory cortex (for a review, see Näätänen & Alho, 1997; Picton et al., 2000). However, the deeper layers of auditory cortex are still largely immature in terms of functional neural connections at the age of 4 months. (Moore & Guan, 2001). In fact, it has been suggested that the frontal and temporal components of the MMN have different maturational time-courses, with the temporal component still being immature in 5-year-olds (Gomot et al., 2000). As for the broad discriminative positivity in 2-month-olds, it remains for future research to determine the neural circuits that give rise to the slow positive responses. What is clear from the present results is that a cortical change detection mechanism for pitch discrimination emerges around 3 to 4 months of age.

Conclusion

The present study investigated how the two types of infant mismatch response are affected by the presentation rate and the magnitude of pitch change. The MMN-like and P3a-like responses in 4-month-olds behaved similarly to the adult MMN and P3a, suggesting that the mismatch responses at 4 months reflect a change-detection mechanism, as in adults. The broad discriminative positivity in 2-month-olds, on the other hand, showed a different pattern. We conclude that cortical maturation between 2 and 4 months allows for the emergence of an adult-like change detection mechanism for pitch.

Figure Captions

Figure 1. The effect of presentation rate on adult mismatch responses. Difference waves (deviant–standard) show an MMN around 130 ms followed by an early P3a around 250 ms, with earlier MMN peaks for the slow compared to fast rate, but similar peak amplitudes. Portions of the waveforms where MMN and P3a are significant are shown in the bars above and below these components, respectively.

Figure. 2. The effect of presentation rate on the infant broad discrmininative positive mismatch responses. Difference waves (deviant–standard) illustrate that both 2- and 4-month-olds showed a broad discriminative positivity centered around 300 ms, with larger peak amplitude for the fast than slow presentation rate. Portions of the waveforms where the discriminative positivity is significant are shown in the bars above this components.

Figure. 3 The effect of presentation rate on infant MMN-like mismatch responses. For 4-month-olds, difference waves (deviant–standard) show an adult-like MMN centered around 200 ms followed by a P3a-like positivity around 300 ms, with earlier peaks for the slow compared to fast presentation rate, but no clear difference in peak amplitude. For 2-month-olds, there were trends for a similar MMN-like response pattern as in 4-month-olds, but only the P3a-like component achieved significance, and in only a few regions.

Portions of the waveforms where MMN and P3a are significant are shown in the bars above and below these components, respectively.

Figure. 4 Standard and deviant waves at fast and slow presentation rates for 2- and 4-month-olds.

There is a trend for the slow wave to be larger in amplitude for slow compared to fast presentations rates for both standard and deviant waves, but this trend is larger and only reaches significance for standard waves.

Figure 5. The mean amplitude of the slow positive wave in deviants and standards for fast and slow presentation rates in 2 and 4-month-olds infants. With increases in presentation rate, standards decrease in amplitude much more than do deviants. As standards are more frequent, and therefore closer in time on average compared to deviants, these results are consistent with the interpretation that the slow positive wave is subject to refractory processes.

Figure. 6. The effect of magnitude of pitch change on adult mismatch responses.

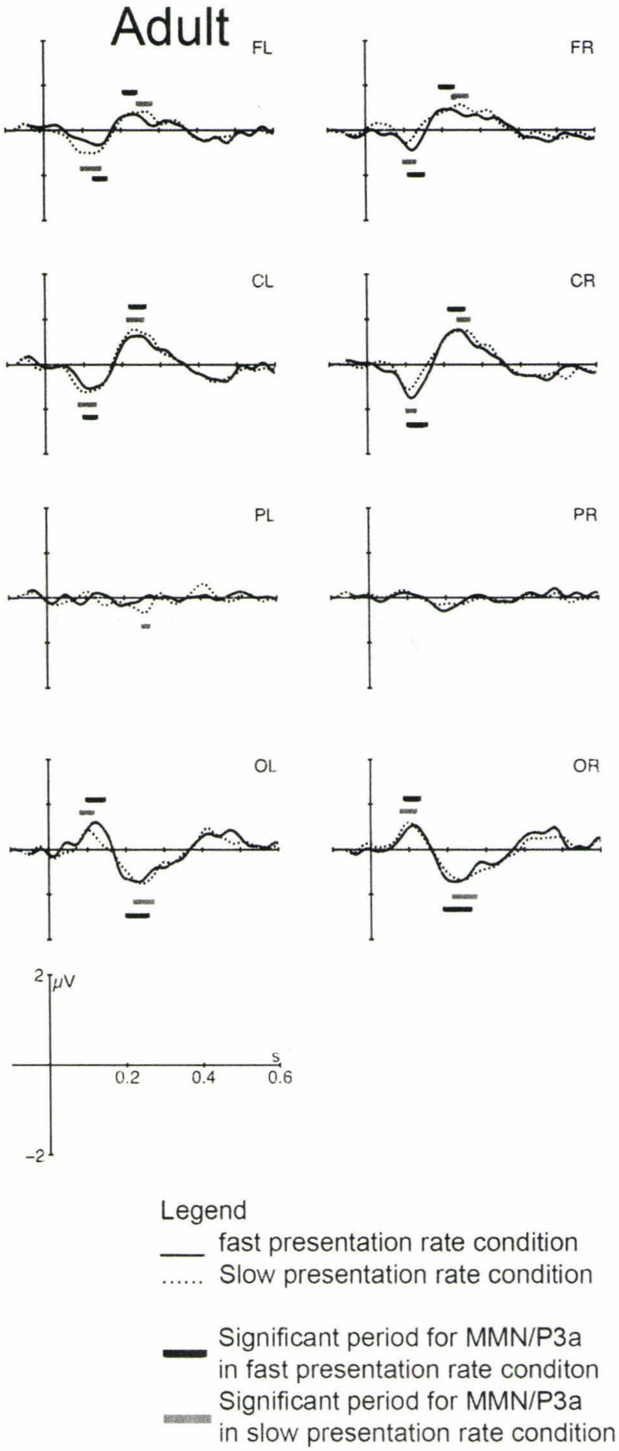
Difference waves (deviant–standard) show clear MMN and P3a components. The MMN was larger for the large pitch change compared to the small pitch change, with no significant difference in latency. Portions of the waveforms where MMN and P3a are significant are shown in the bars above and below these components, respectively.

Figure. 7 The effect of magnitude of pitch change on the infant broad discrmininative positive mismatch responses. Difference waves (deviant–standard) illustrate that both 2- and 4-month-olds show a broad discriminative positivity centered around 300 ms for both large and small pitch changes. There was no significant difference in the broad discriminative positivity between large and small pitch changes in either 2- or 4-month-olds. Portions of the waveforms where the discriminative positivity is significant are shown in the bars above this components.

Figure. 8 The effect of magnitude of pitch change on infant MMN-like mismatch responses

Only a few regions in 2-month-olds showed a significant MMN-like response . For 4-month-olds, difference waves (deviant–standard) illustrate that the MMN-like negativity shows a larger amplitude for larger than for smaller pitch changes . Portions of the waveforms where MMN and P3a are significant are shown in the bars above and below these components, respectively.

Figures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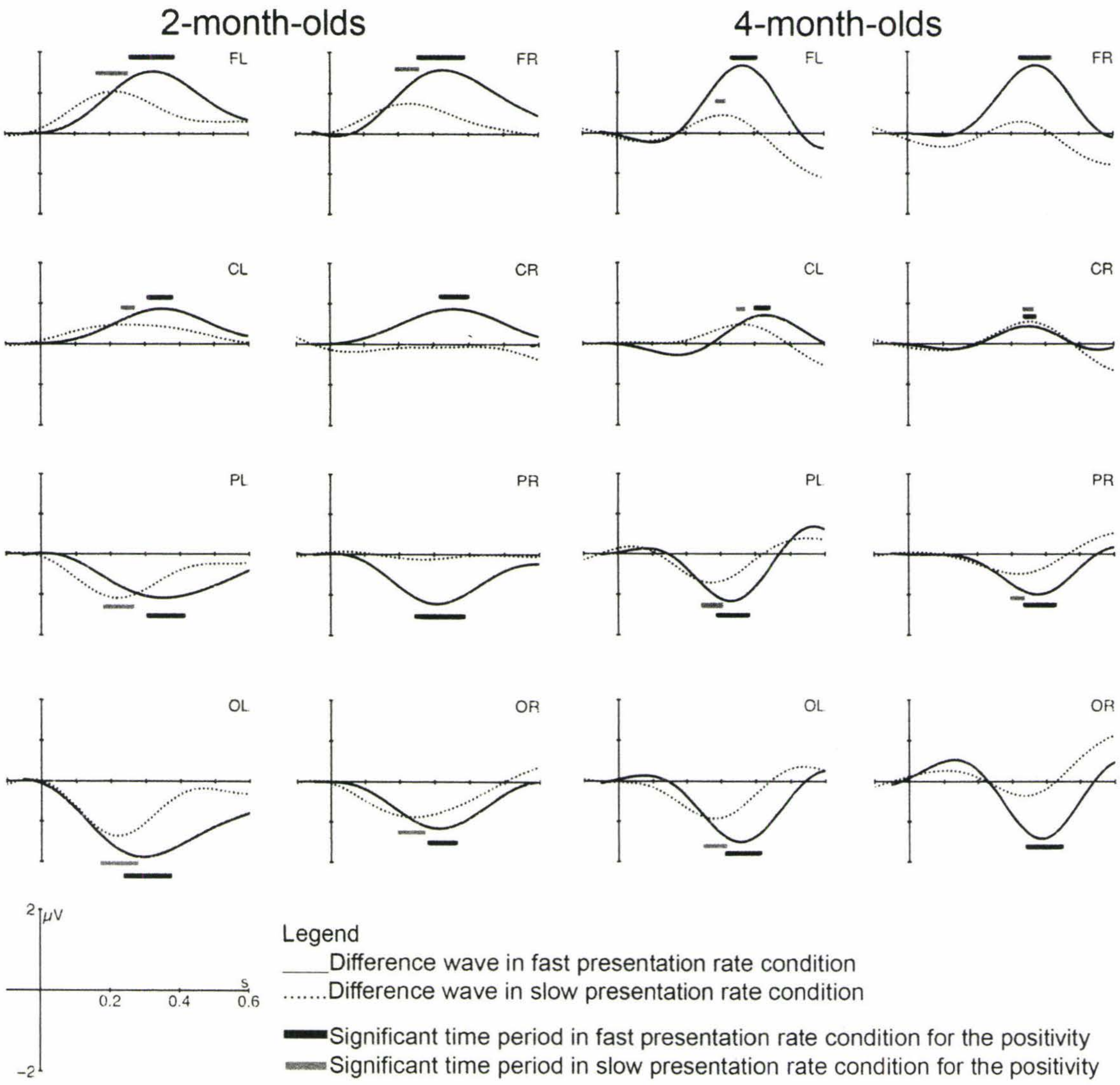
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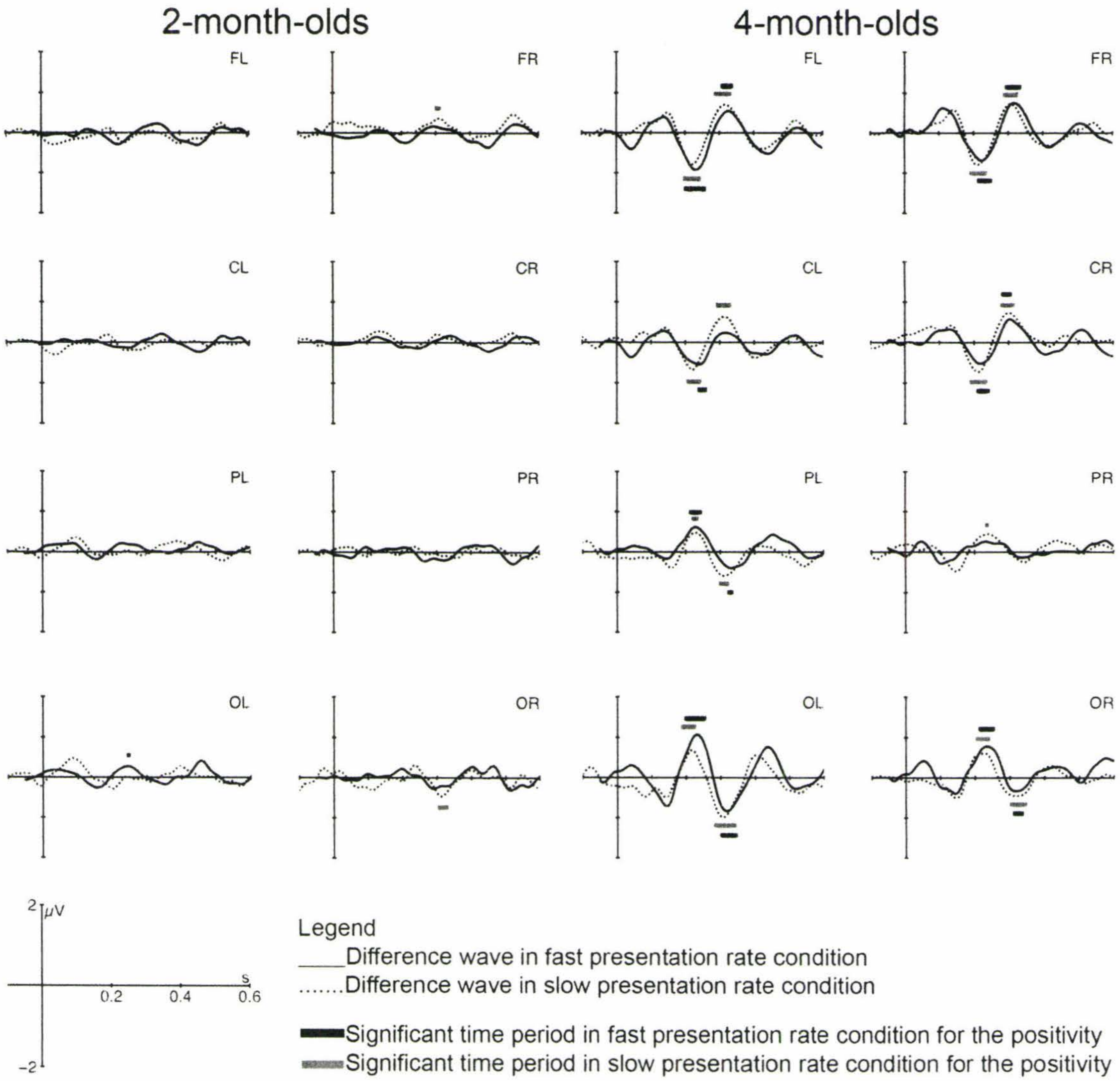
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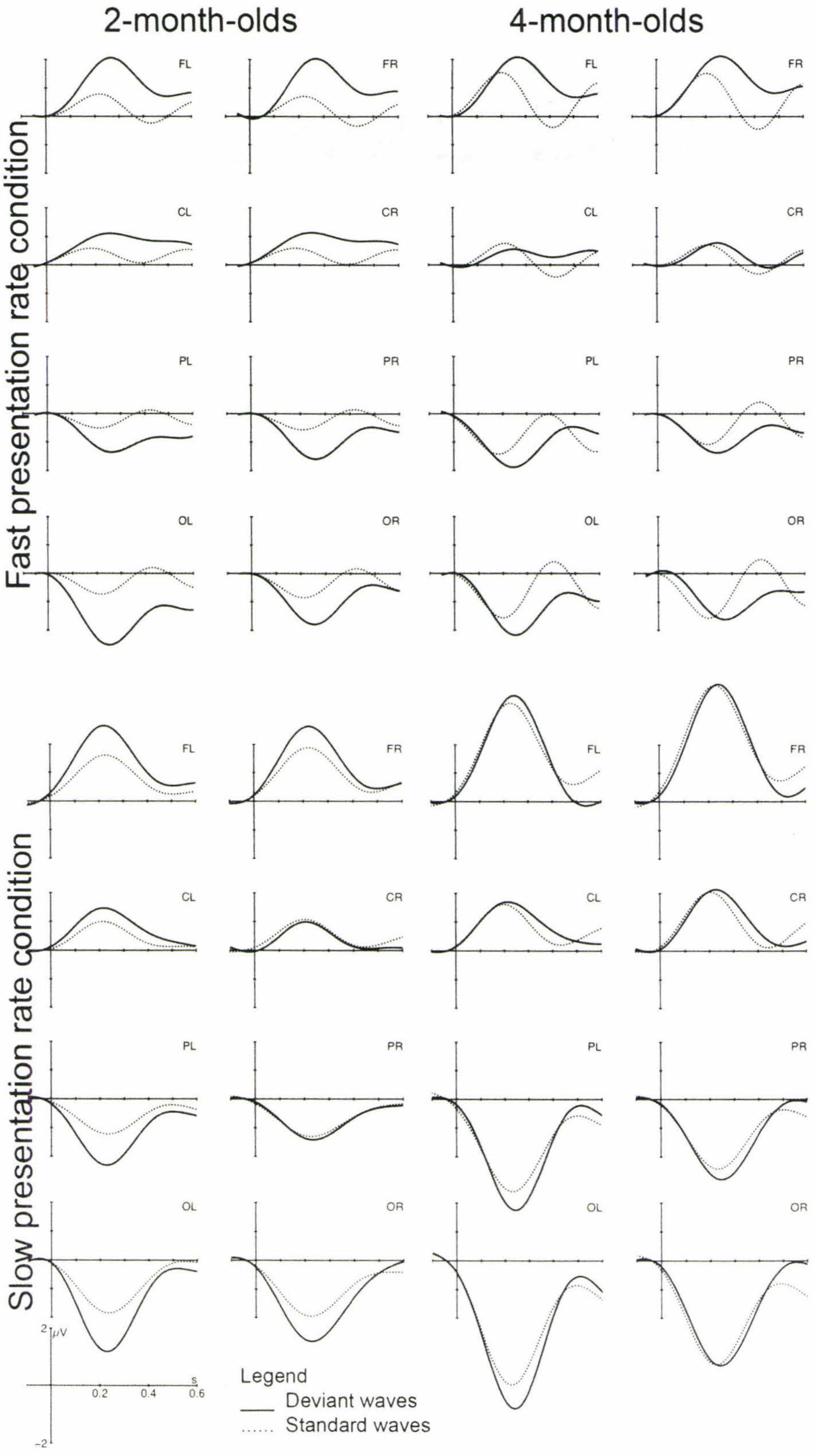
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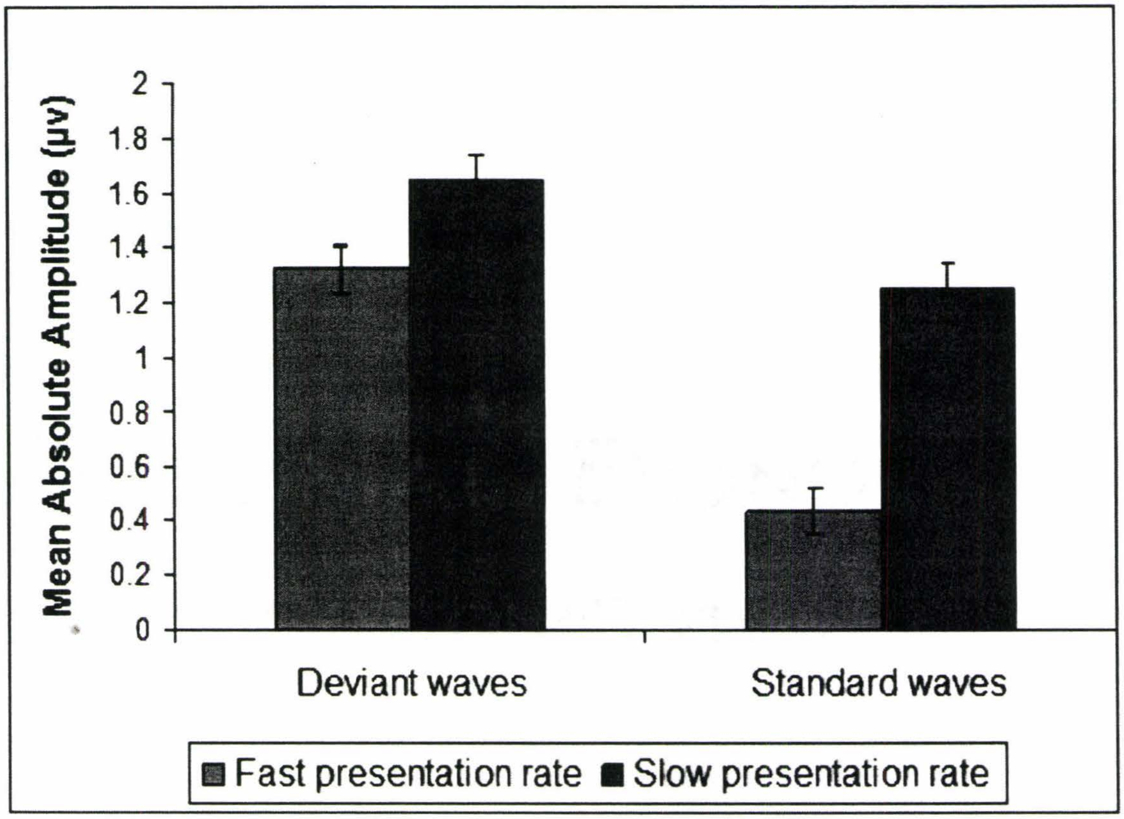
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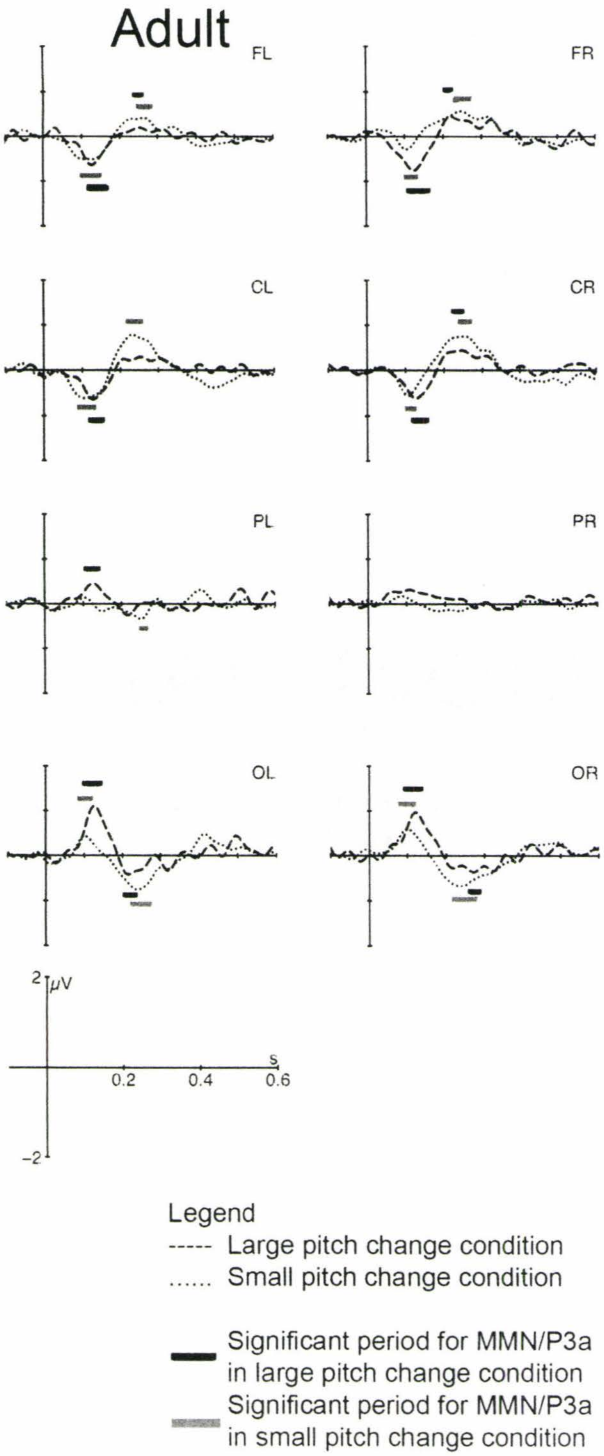
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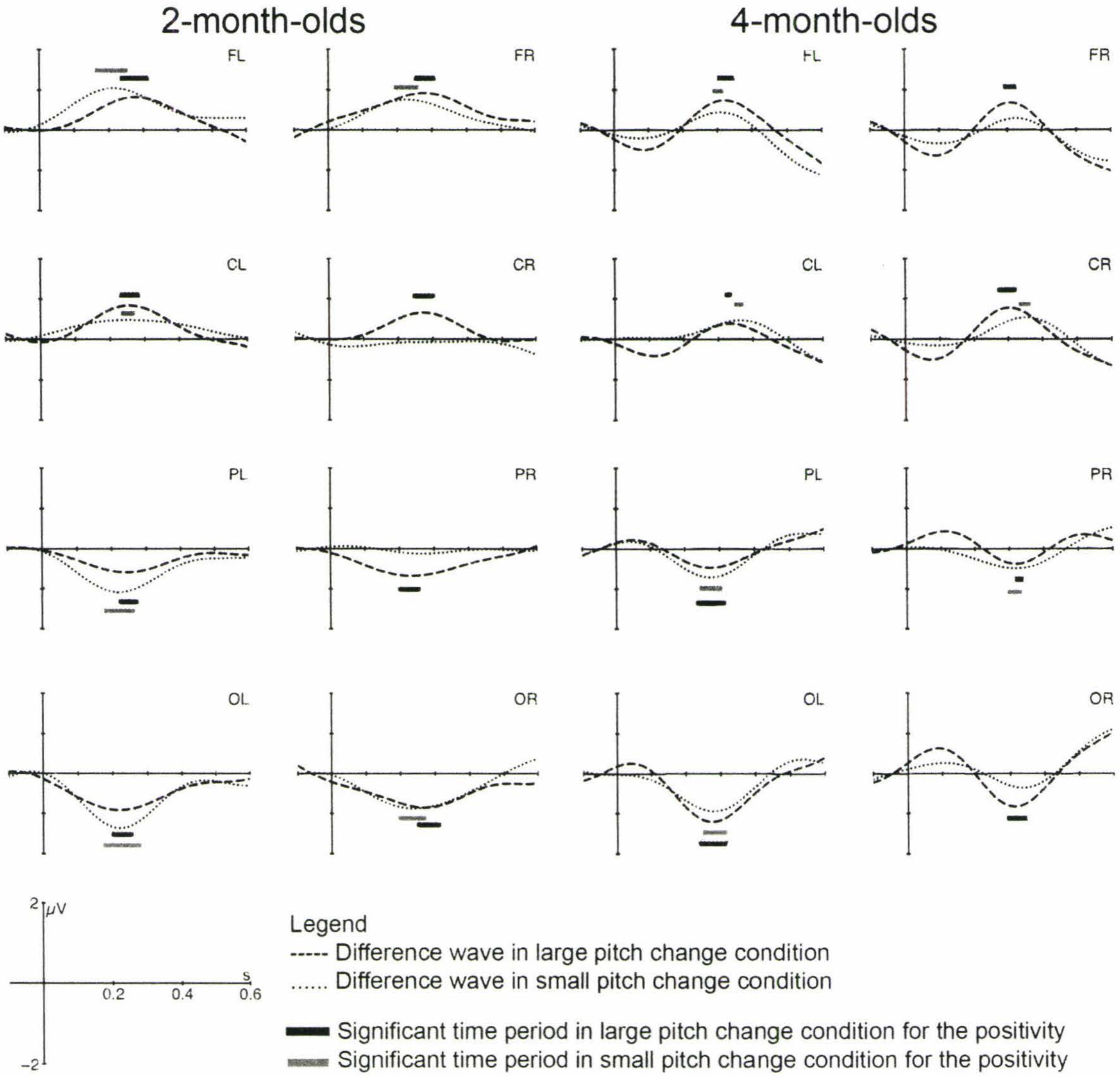
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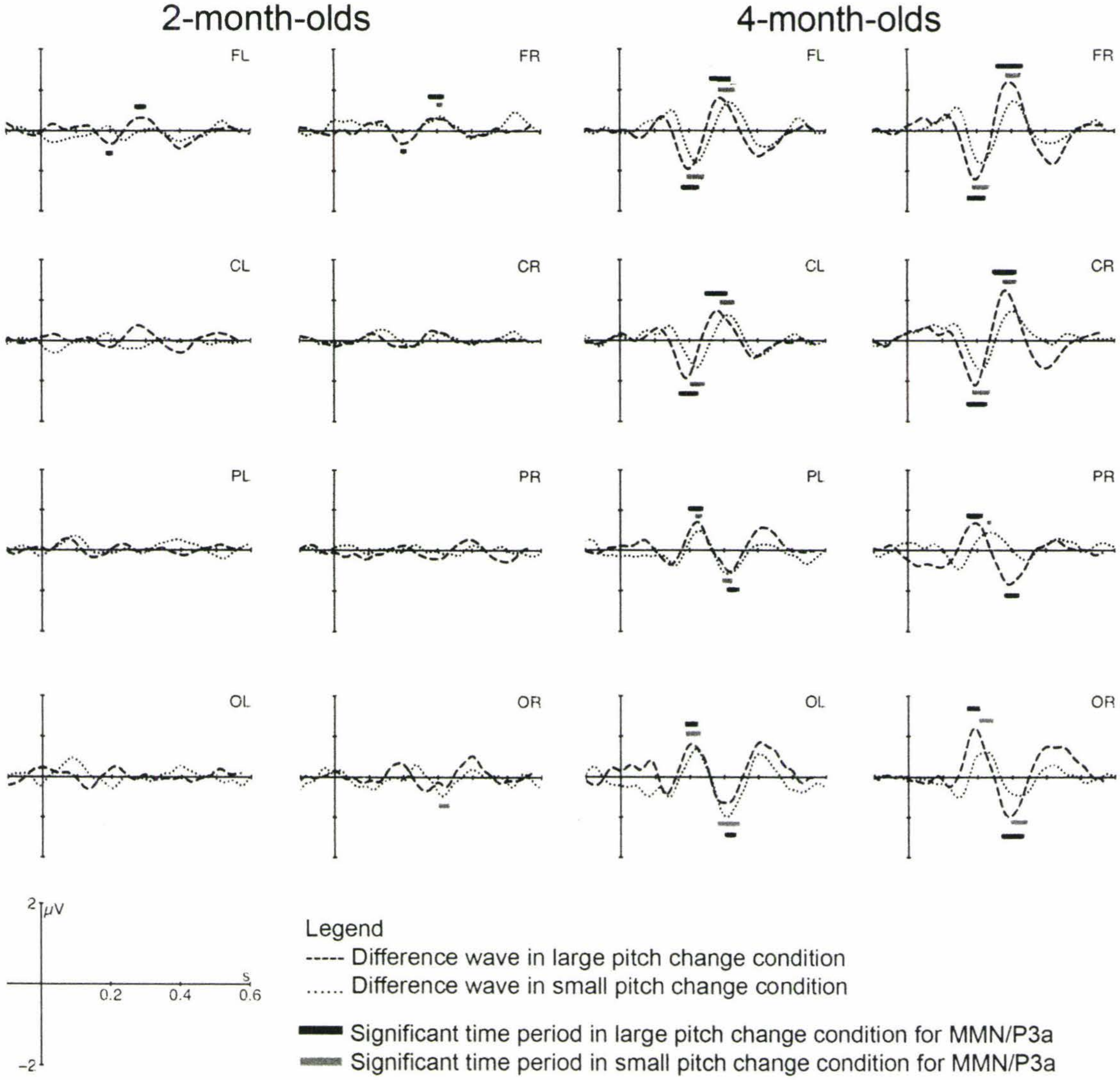
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Significant time period in large pitch change condition for MMN/P3a
Significant time period in small pitch change condition for MMN/P3a

Acknowledgements

This research was funded by a grant to LJT from the Canadian Institutes for Health Research. We thank Andrea Unrau, for help in testing the infants.

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Chapter 4:

DEVELOPMENT OF INFANT MISMATCH RESPONSES TO AUDITORY PATTERN CHANGES BETWEEN 2 AND 4 MONTHS OF AGE

This chapter is a manuscript submitted to Journal of European Neuroscience, authors: He, Hotson & Trainor. Title: Development of infant mismatch responses to auditory pattern changes between 2 and 4 months of age

Introduction to the Chapter 4

Several hypotheses have been proposed to explain the mechanisms underlying the two types of MMR reported in previous studies. One hypothesis is that the mechanisms of positive and/or negative MMR may be similar to adult MMN, reflecting cortical change detection mechanism. A different hypothesis is that one or both is similar to the adult N1 that represents the release of certain neural circuits from refractory states.

The experiment in the present chapter was designed to investigate whether MMRs can be elicited by abstract pitch pattern changes in 2 and 4-month-olds. Specifically, we introduced an occasional change in the order of tones in a pattern. This change does not introduce any new tones, so responses to the change cannot reflect refractory processes. In adults, such changes elicit MMN.

We found that the positive MMR, that had been present in 2-month-olds in previous studies in response to a pitch change, was no longer present, suggesting that a refractory response plays a role in its elicitation. The MMN-like negative MMR in 4-month-olds, on the other hand, was robustly present, suggesting it may be functionally similar to adult MMN and reflect a change detection mechanism rather than a refractory process.

Development of infant mismatch responses to auditory pattern changes between 2 and 4 months of age

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Running Head: Infant discrimination of auditory patterns

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Abstract

In order to process speech and music, auditory cortex must learn to process patterns of sounds. Our previous studies showed that with a stream consisting of a repeating (standard) sound, younger infants show an increase in the amplitude of a positive slow wave in response to occasional changes (deviants) in pitch or duration, whereas older infants show a faster negative response that resembles mismatch negativity (MMN) in adults (Trainor et al., 2001, 2003; He et al., 2007). MMN reflects an automatic change detection process that does not require attention, conscious awareness or behavioural response for its elicitation (Picton et al., 2000; Näätänen et al., 2007). It is an important tool for understanding auditory perception because MMN reflects a change-detection mechanism, and not simply that repetition of a stimulus results in a refractory state of sensory neural circuits while occasional changes to a new sound activate new non-refractory neural circuits (Näätänen et al., 2005). For example, MMN is elicited by a change in the pattern of a repeating note sequence, even when no new notes are introduced that could activate new sensory circuits (Alain 1994, 1999; Schröger et al., 1996). In the present study, we show that in response to a change in the pattern of two repeating tones, MMN in 4-month-olds remains robust whereas the 2-month-old response does not. This indicates that the MMN response to a change in pattern at 4 months reflects the activation of a change-detection mechanism similarly as in adults.

Introduction

Extracting patterns among successive auditory stimuli is an essential part of identifying auditory objects, and a vital basis for processing the complex communication signals comprising speech and music. Animal studies indicate that single neurons in primary and secondary auditory cortex can be activated by changes in auditory patterns (e.g., cats: McKenna et al., 1989; Robin et al., 1990; marmosets: Wang et al., 1994). In humans, Event Related Potential (ERP) studies have shown that the brain automatically tracks patterns in incoming auditory stimuli and, on the basis of this information, makes predictions about future events (Näätänen et al., 2007; Trainor & Zatorre, in press). If such predictions fail to match the incoming stimuli, a frontally negative ERP deflection called mismatch negativity (MMN) is seen, with the main generators located in secondary auditory cortex (for reviews, see Picton et al., 2000; Näätänen et al., 2007; Näätänen & Winkler, 1999). A few behavioral studies suggest that infants as young as 2 months process sound patterns in that they discriminate languages on the basis of prosodic features (Nazzi et al., 1998). In the present study, we investigated cortical responses to changes in pattern in infants at 2 and 4 months of age.

Previous ERP studies of sound discrimination in young infants have involved the occasional presentation of a deviant sound that differs from the repeating standard sound in pitch (e.g., Alho et al.,1990; Leppänen et al., 1997, 2004; Čeponiené et al., 2000; Fellman et al., 2004), duration (e.g., Trainor et al., 2001, 2003; Friederici et al., 2002;

Hirasawa et al., 2003), speech sound category (e.g., Cheour-Luhtanen et al.,1996; Cheour et al., 1998; Pang et al., 1998), or conjunctions of more than one feature (Pihko et al., 1999; Čeponiené et al., 2002; Dehaene-Lambertz & Pena, 2001; Ruusuvirta et al., 2003, 2004; Winkler et al., 2003). In response to such changes, younger infants typically show a slow frontally-positive response (e.g., Friederici et al., 2002; Friedrich et al., 2004; Leppänen et al., 2004; Morr et al., 2002; Novitski et al., 2007; Ruusuvirta et al., 2004; Trainor et al., 2001; Winkler et al., 2003;) and older infants an MMN-like frontally-negative response (e.g., Alho et al., 1990; Cheour et al., 1998; Čeponiené et al., 2000, 2002; Kushnerenko et al., 2002; Hirasawa et al., 2003; He et al., 2007; in press; Trainor et al., 2001, 2003;). In previous work (He et al., in press), we found that the slow positive difference to a simple pitch change in young infants decreases with increases in rate of presentation whereas the MMN-like negativity to pitch change seen in 4-month-olds remains robust with increases in tempo, suggesting that the two responses might be functionally distinct.

In these previous studies, the deviant and standard sounds activate different neurons in auditory cortex. However, in adults, such sensory-based responses to sound change have been distinguished from higher-order change detection mechanisms. Notably, sensory responses such as N1 decrease in amplitude as sounds are presented at faster rates, whereas MMN remains robust at fast tempi (Mäntysalo & Näätänen, 1987; Czigler et al., 1992). Alain et al. (1994) presented adults with a repeating two-tone sequence composed of one high and one low tone. They found that MMN responses were reliably elicited by a change in the order of the tones, even though no new tones were introduced, indicating that MMN can be elicited when incoming sounds violate only the pattern of the previous input. Furthermore, MMN can be observed when standard trials are randomly drawn from a set of tone sequences whose members contain no pitches in common, but have a common pattern, such as a rising pitch contour or a particular sequence of melodic intervals (e.g., Fujioka, et al., 2004, 2005; Paavilainen et al., 1995; Saarinen et al., 1992; Trainor, McDonald, & Alain, 2002). Such automatic extraction of sound pattern properties has been termed "primitive intelligence" (Näätänen et al., 2001).

Few studies have examined the development of mismatch responses in infants to changes in the pattern of auditory input. However, Carral et al. (2005) presented newborns with standard trials consisting of pairs of sine wave tones where the second note was higher in frequency than the first. They found a slow positive response to occasional deviants in which the second tone was lower than the first. Here we use stimuli similar to those of Alain et al. (1994) to examine responses to a pattern change in older infants, with a particular interest in the emergence of the adult-like MMN. Specifically, we presented in 2 and 4-month-old infants with two tones of different pitch in an alternating sequence, and examined slow wave and MMN responses to a change in the alternating pattern.

Materials and Methods

Participants

Eleven (7 female) healthy university students (aged 18 to 25 years, mean age 19.2 years) with no hearing deficits participated in the present study. All were between 38 and 42 weeks at birth and weighed at least 2500 grams. Informed written consent was obtained from all participants prior to the experiment and course credits were assigned to compensate their participation.

A total of 29 healthy, full term infants, either 2 months (16, 9 female) or 4 months of age (13, 6 female), with no known hearing deficits were included in the final sample. All the infants were between 38 and 42 weeks gestation and were over 2500 grams at birth. All infants were awake during testing. An additional 25 infants (14 2-month-olds and 11 4-month-olds) were excluded from the final sample either because they fell sleep during testing (6 2-month-olds and 4 4-month-olds) or because they became fussy during testing and failed to produced the minimum of 100 artifact-free deviant trials for averaging (8 2-month-olds and 7 4-month-olds). Informed written consent was obtained from all parents prior to the experiment. After the experiment, a certificate and a bath toy were provided as thanks for their participation.

Stimuli

Standard trials consisted of piano notes C_5 and $F\#_5$, with fundamental frequencies of 523 and 740 Hz, respectively, played in ascending pitch (C_5 followed by $F\#_5$). Deviant trials consisted of the same two notes, but played in descending pitch ($F\#_5$ followed by C_5). All notes were 400 ms in duration, and the onset asynchrony between adjacent notes, whether within or between trials was 450 ms so that a continuous alternating sequence was formed (Figure 1).

Insert Figure 1 here

Apparatus

All of the piano tones were monaural and synthesized with Reason 2.0 software (Propellerhead Software) and recorded with Adobe Audition 1.0 software (Adobe Software). Stimuli were played using E-prime 1.1 software (Psychology Software Tools Inc.) on a Dell OptiPlex280 computer with an Audigy 2 platinum sound card (Creative Labs) through a WestSun loudspeaker (WestSun Jason Sound, JSIP63) located one meter directly in front of the participant. The stimuli were presented at 70 dB SPL (A) in a room with a background noise level of 29 dB SPL (A).

Procedure

Participants sat on a comfortable chair (infants sat on their parents' laps) in a sound-treated room containing surround floor-to-ceiling double velour curtains and acoustic ceiling panels. Participants watched either a silent movie (adult participants) or an animated video (infants) in a passive protocol while the piano tone stimuli were played. An oddball paradigm was used with 85% standard trials and 15% deviant trials. Stimulus order was randomized with the constraint that at least two standards trials occurred between successive deviants. The complete experiment consisted of 1500 trials (225 deviant trials) but testing was stopped early if infants became fussy. All study procedures were approved by the McMaster University Research Ethics Board.

Recording and Analysis

EEG was recoded from 124 locations on the scalp for infants, and 128 locations for adults, with a Geodesic Sensor net (Electrical Geodesics, Inc). All electrode impedances were maintained below 50 kΩ. The electrical potential was digitized at 1000 Hz. The online recording was referenced to the vertex and a band-pass filter of 0.1-400 Hz was used.

Continuous EEG responses were off-line filtered between 0.5 and 20 Hz with filter roll-off of 24 dB/oct. The filtered continuous data were then segmented into 950-msec epochs, which covered the duration of both tones within one trial and included a 50-msec baseline before the onset of the first note. EEG epochs from adult participants were then subject to fixed threshold (+ 120 μv) epoch rejection to omit the artifact due to eye blinks. The averaged number of accepted deviant epochs across all 11 adult participants ranged from 127 to 219 (M=166). For infants, channel independent epoch rejection with a threshold of ±120 μv was conducted to remove the epochs contaminated by blinks, eye, head, or body movement (see He et al., 2007). The number of accepted deviant epochs across the 29 infants ranged between 103 and 183 (M = 136). Standard epochs immediately following deviant epochs were excluded. The accepted standard and deviant epochs were averaged separately, baseline corrected, and referenced to an average reference. Difference waves were obtained by subtracting the standard from the deviant waveforms.

For statistical analysis, 76 channels were selected and divided into five groups for each hemisphere to represent the average response from frontal (20 channels), central (20 channels), parietal (20 channels), and occipital (16 channels) scalp regions. Midline electrodes were excluded in order to examine hemispheric differences; extreme frontal and peripheral electrodes were eliminated in order to reduce contamination from eye movement and other muscle movement (see He et al., 2007, for details of the grouping scheme). Two-tailed paired t-tests were calculated at each time point between standard and deviant waveforms to reveal the time window of significant difference separately at each of the eight scalp regions for adults, 4-month-olds and 2-month-olds.

In 4-month-olds and adults, the peak latency and absolute amplitude of the MMN or MMN-like negativity after the first and after the second note of each trial were measured in the difference waveforms of each participant. The MMN was defined as the largest negative peak between 100 and 300 ms in the frontal regions. Separate ANOVAs were calculated on peak latencies and amplitudes for the MMN-like negativity to examine whether it varied significantly between adults and 4-month-olds, between first and second notes in deviant tone pairs, and across hemispheres and scalp regions. Because 2-month-olds exhibited only broad discriminative slow wave deflections that rendered peak picking difficult (consistent with He et al., 2007, He et al., under review), the average standard and deviant amplitudes in successive 50-msec time bins between 100 – 450 ms and 550 ms - 900 ms after stimulus onset were measured for each scalp region and subjected to repeated-measures ANOVAs to test whether the waveforms varied significantly between standard and deviant conditions and/or across time bin, hemisphere, and scalp region.

In all of the above ANOVAs, the Greenhouse-Geisser correction was applied to all within-subjects measures with more than two levels. The Tukey HSD test was used for post hoc comparisons. The Bonferroni correction was applied to multiple within-subject comparisons.

Results

MMN in adults and MMN-like negativity in 4-month-olds

Group difference waves (deviant – standard) for adults and 4-month-olds are shown in Figures 2 and 3, respectively. Adults showed typical MMN responses peaking around 150-msec after both tones of deviant trials (Figure 2). The polarity of the MMN peak reversed at the back of head, consistent with generators in auditory cortex. For 4-month-olds, a MMN-like negative response was clear in response to both deviant tones, but the latency of this negativity was much later (around 250-msec) than for adults. This negativity is similar to that found for a change in a single pitch in infants of a similar age (e.g., Kushnerenko et al.,2002; Morr et al., 2002; Fellman et al., 2004; He et al., 2007; He et al., under review) as well as for changes in duration (Trainor et al., 2001, 2003). In order to compare the MMN response in adults and the MMN-like negativity in 4-month-olds, peak latencies and absolute amplitudes were subject to separate ANOVAs with age as a between-subject factors, and note (first or second note within tone pairs), hemisphere, and scalp brain region as within-subject factors.

Insert Figure 2 and 3 here

For amplitude, the main effect of age was significant, $F_{(1,\ 22)} = 17.0$, $p<0.001$, reflecting larger peak amplitudes in 4-month-olds (mean amplitude = 1.28 μv, SE =.066 μv) than in adults (0.88 μv, SE =.071 μv). The main effect of note was also significant, $F_{(1,\ 22)} = 8.55$, $p=0.008$, with a larger peak amplitude in response to the first note within the tone pair (1.193 μv, SE = .068 μv) than to the second note (0.966 μv, SE =.055 μv). Region was also significant, $F_{(3,\ 66)} = 3.01$, $p=0.04$, reflecting different peak amplitudes in different regions. The largest peak amplitude was in the occipital region (1.259μv, SE = .091 μv) and the smallest in the central region (0.944 μv, SE = .944 μv), but no two regions differed significantly by post hoc tests. The age by hemisphere interaction approached significance, $F_{(1,\ 22)} = 3.48$, $p=0.08$, reflecting a trend for a larger peak amplitude in the right hemisphere (1.37 μv, SE = .077 μv) than in the left hemisphere (1.19 μv, SE = .075 μv) among 4-month-olds but not adults. The whole head topographic voltage map of 4-month-olds and adults at the peak latency of the mismatch responses are shown in Figure 4.

Insert Figure 4 here

The ANOVA on the latencies of the MMN/MMN-like negativity revealed an extremely robust main effect of age, $F_{(1, 22)} = 5394$, $p<0.001$ due to much longer latencies in 4-month-olds (mean = 252 ms, SE =1 ms) than in adults (mean = 149 ms, SE = 1 ms) . The main effect of note was also significant, $F_{(1, 22)} = 53.1$, $p<0.001$, with shorter peak latencies for the second (206 ms, SE=1 ms) than the first MMN peak (195 ms, SE=1 ms) . The main effect of hemisphere was also significant, $F_{(1, 22)} = 8.18$, $p=0.009$, with later peak latencies in the left hemisphere (202 ms, SE= 1 ms) than in the right hemisphere (199 ms,. SE = 1 ms). The interaction between hemisphere and age, $F_{(1, 22)} = 5.38$, $p=0.03$, further showed that the hemisphere difference was only significant in 4-month-olds, with significantly shorter ($p=0.001$) latencies (250 ms, SE = 1 ms) in the right hemisphere than in the left hemisphere (255 ms, SE = 1 ms).

To summarize, both adults and 4-month-olds showed mismatch in response to changes in the pitch pattern. However, the MMN in adults and MMN-like negativity in 4-month-olds differed substantially in both latency range and peak amplitude. For 4-month-olds, a right hemisphere dominance of MMN-like negativity was also found, which is similar to the results of He at al. (2007) for simple pitch changes in infants of the same age. Interestingly, both MMN and MMN-like negativity were smaller in amplitude and shorter in latency in response to the second note in the pair compared to the first note.

Responses in 2-month-olds

Unlike 4-month-olds and adults, the standard and deviant waves (see Figure 5) of the 2-month-olds were significantly different in amplitude at only a few regions in the paired t-test result (see significance bars in Figure 5). Neither a negative mismatch response, like that of 4-month-olds and adults, nor a positive mismatch response, like that found in He et al (2007) for 2-month-olds for simple pitch changes, is clear. However, both notes in both standard and deviant tone pairs elicited a slow positive wave, which is similar to the positivity that has been reported in previous studies (e.g., Leppänen et al., 1997, 2004; Friederici et al., 2002; Friedrich et al., 2004, He at al., 2007; Trainor et al., 2003).

Insert Figure 5 here

Since peak picking is difficult for slow wave activity, we calculated the absolute average amplitude of standard and deviant waveforms in each successive 50 ms time bin from 100 to 450 ms and 550 ms to 900 ms, then conducted a 4-way repeated measures ANOVA to further investigate the difference between the standard and deviant waves in 2-month-olds, with stimulus type (deviant, standard), time bin (14 bins in total), brain region (frontal, central, parietal, occipital), and hemisphere (left, right) as within-subject factors. The results indicated significant main effects of time bin, $F_{(13, 195)} = 7.88$, $p<0.001$, and region, $F_{(3, 45)} = 14.80$, $p<0.001$, the former reflecting the presence of the slow wave (largest between 150-250 ms and smallest between 600- 650 ms, all *ps* <.05) and the latter the frontal-occipital focus (largest at occipital regions and smallest at parietal regions, all *ps* <.05). Neither the main effect of stimulus type nor the stimulus type by time bin interaction was significant, which indicates that, by this analysis, the deviant and standard waves were not significantly different.

Discussion

The present study demonstrates that infrequent changes in the order of a sequence of alternating piano tones elicits an MMN-like response in 4-month-old infants that is similar to that of adults, although with a longer latency and a trend for right-hemisphere dominance. The MMN response to the change in pattern in 4-month-olds appears to be similar to that previously reported for simple changes in pitch, duration, and speech sounds (e.g., Alho et al., 1990; Cheour et al., 1998; Čeponiené et al., 2000, 2002; Kushnerenko et al., 2002; He et al., 2007; Hirasawa et al., 2003; Trainor et al., 2001, 2003), suggesting that all of these MMN responses at 4 months may represent the operation of a true change detection mechanism.

The 2-month-olds in our previous study (He et al., 2007) showed no adult-like MMN response to a simple change in pitch, but they did show a positive slow wave response. In the present study, the 2-month-olds showed neither a slow positive response nor an adult-like MMN response to a change in pitch pattern. This is particularly surprising given that Carral et al. (2005) reported a slow positive response to a change in pitch pattern in newborn infants. We should note, first, that although the ANOVA of our 2-month-old data did not reveal any significant differences between standard and deviant responses, multiple t-tests comparing the two responses at each time point did reveal a few regions of significance (see Figure 5). Post-hoc pairwise comparisons subsequent to the ANOVA also showed trends suggesting the possible presence of small increases on deviant trials in frontal slow positive responses during the time windows of 200-250 ms ($p = .015$) and

800-850 ms (p < .001). Examination of individual infants revealed that two of the sixteen 2-month-old infants demonstrated clear positive mismatch responses in their waveforms (see Figure 6 for the average waveforms for these two infants).

Insert Figure 6 here

The question becomes, then, why the positive response to change was larger in the newborn infants in the Carral et al. (2005) study than in the 2-month-olds of the present study. The most intriguing possibility is that the slow wave response diminishes with increasing age, as has been found for the response to simple changes in pitch (He et al., 2007) and duration (Trainor et al., 2003).

However, there are at least three other possibilities. First, the infants in the Carral et al. (2005) study were asleep whereas our 2-month-olds were awake. The slow wave activity might well decrease when infants are more alert. The other two possibilities have to do with differences in the stimuli used. A recent study by Kushnernko et al. (2007) found that the newborn, but not adult, response to an occasional change in an auditory stimulus was driven largely by the spectral bandwidth of the deviant stimulus. In particular, when presented with a stream of tones, occasional white noises, whose sensory representations would span large areas of auditory cortex, elicited large responses in newborns. We used harmonically rich piano tones whereas Carral et al. used pure tones, so it is possible that this may have lead to the difference across studies, although the exact mechanism remains unclear. The third possibility has to do with the nature of the pattern used in the two studies. Carral et al. presented tone pairs at a different pitch level on each presentation of a standard stimulus whereas we used only two alternating pitches and occasionally changed their order. In our case, when the order was changed, the same note was repeated (see Figure 1). Thus when the deviant note was presented, the neural circuits encoding that note had very recently been activated and therefore might have been in a somewhat refractory neural state, making them less able to respond. This suggests one of two possibilities. The slow positive response to change might be sensitive to refractory processes as suggested by He et al. (2007) and unlike adult MMN, or a sensory refractory process is occurring at the same time as the response to change, and masking it. In sum, more research is needed in order to know whether the very small positive response to the pattern change seen at 2 months reflects refractory processes or a developmental decrease in the amplitude of this component with increasing age.

There are still questions remaining as to the nature of the response to pattern changes in 2-month-old infants, but there is clearly no evidence for an adult-like MMN response at this age. On the other hand, a clear adult-like MMN response is seen at 4 months, likely reflecting the operation of a change detection mechanism similar to that of adults.

Figure Captions

Figure 1. The illustration of stimuli

Figure 2. Adult mismatch negativity response to a change in pitch pattern. Difference waves (deviant–standard) show an MMN around 150 ms after onset of both tones in the pair. The amplitude of the MMN is larger for the first than for the second tone. Portions of the waveforms where MMN is significantly different from zero are shown in the bars above and below the waveforms. (F= frontal, C=central, P=parietal, and O=occipital sites. L=left hemisphere and R=right hemisphere.)

Figure 3. Four-month-old infants' response to a change in pitch pattern. Difference waves (deviant–standard) show an MMN-like negativity around 200 ms after onset of both tones in the pair. The amplitude of the MMN-like negativity is larger for the first than for the second tone. Portions of the waveforms where MMN is significantly different from zero are shown in the bars above and below the waveforms. (F= frontal, C=central, P=parietal, and O=occipital sites. L=left hemisphere and R=right hemisphere.)

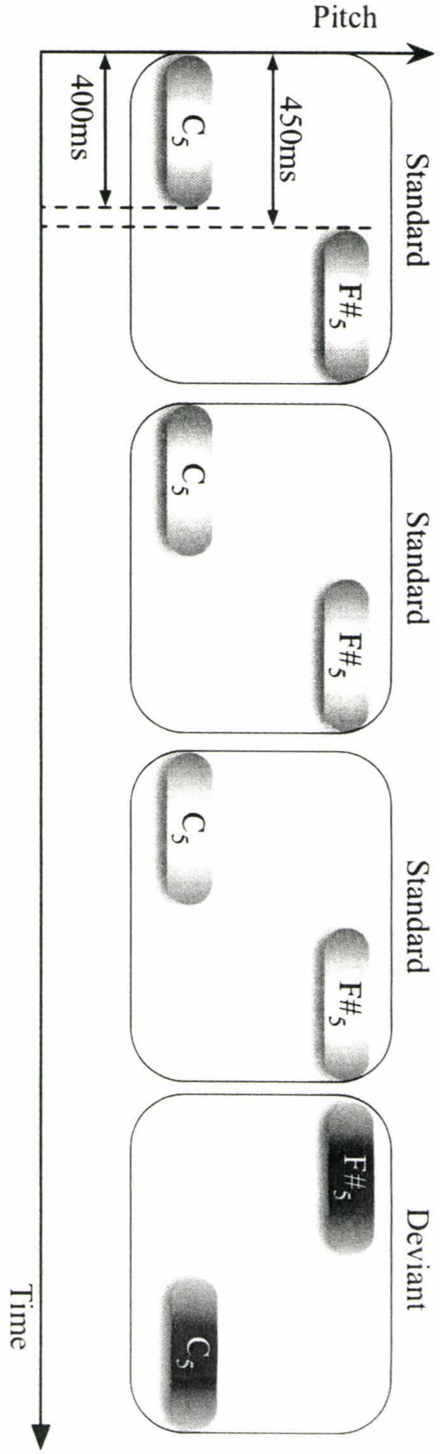
Figure 4. Whole head voltage map of MMN in adults and 4-month-olds. The MMN was maximal at frontal-central locations in adults. As seen in left panel of current figure, the negativity of 4-month-olds was frontal and bilaterally distributed, while having a more

frontal focus in the right than in the left hemisphere, which is consistent with the statistical test results (see Results section).

Figure 5. Standard and deviant waves of 2-month-olds to a change in pitch pattern. Portions of the waveforms where standards and deviants were significantly different are shown in the bars above and below the waveforms. The standard and deviant waves were largely similar. Both tones elicited a positive response around 250 ms after tone onset. A few sites showed a trend for larger amplitude in deviant than in standard waveforms around 200-300 ms after the onset of each tone. (F= frontal, C=central, P=partietal, and O=occipital sites. L=left hemisphere and R=right hemisphere.)

Figure 6. Standard and deviant waves of the two 2-month-olds showing a positive mismatch response to a change in pitch pattern. Only two of the 16 infants showed a clear positive mismatch response. The deviant waves were larger in amplitude than the standard waves around 250 ms after the onset of each tone in the pair. However, the frontal positivity in response to the standard waves in these two infants was rather small. (F= frontal, C=central, P=parietal, and O=occipital sites. L=left hemisphere and R=right hemisphere.)

Figures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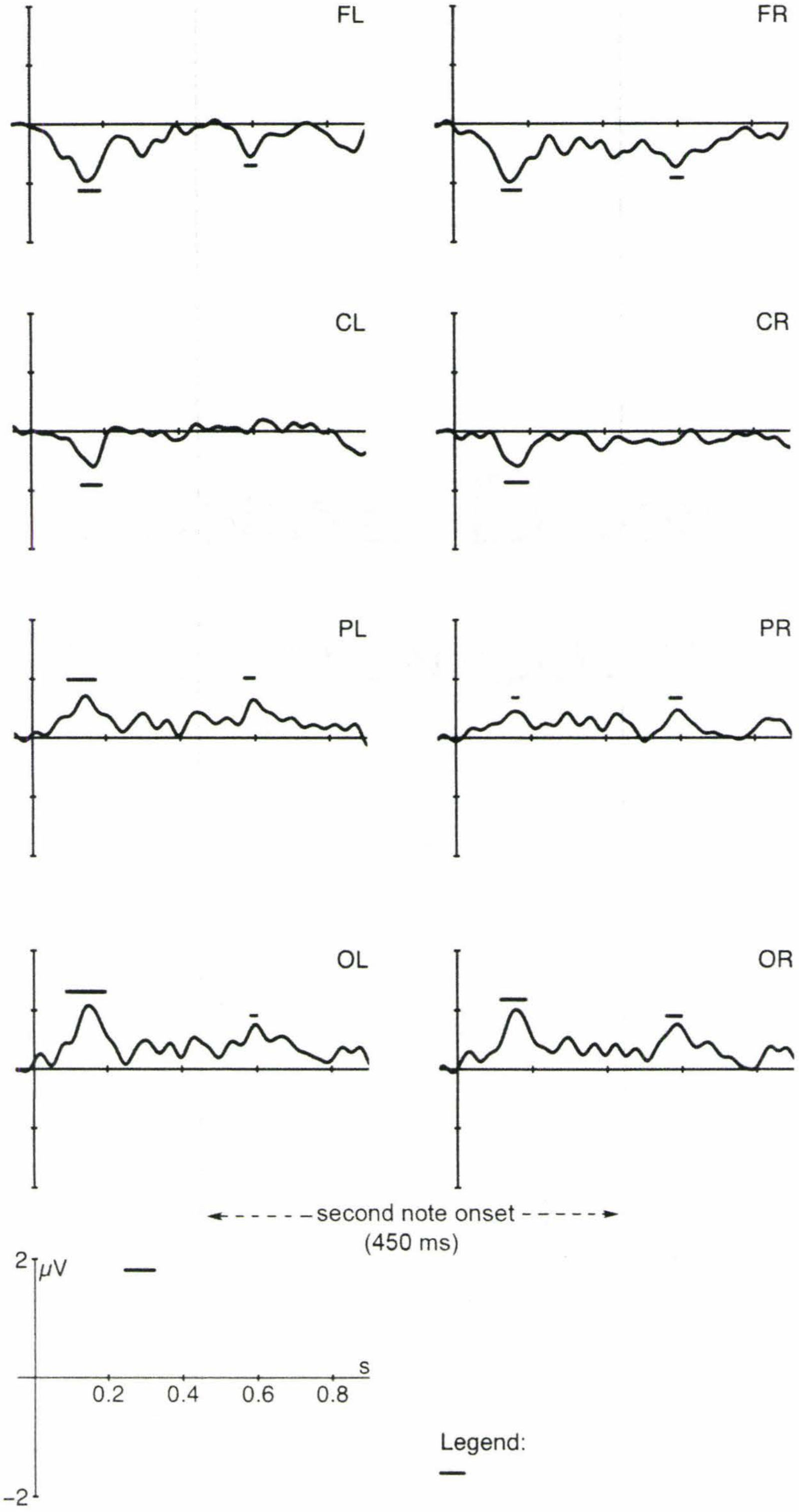
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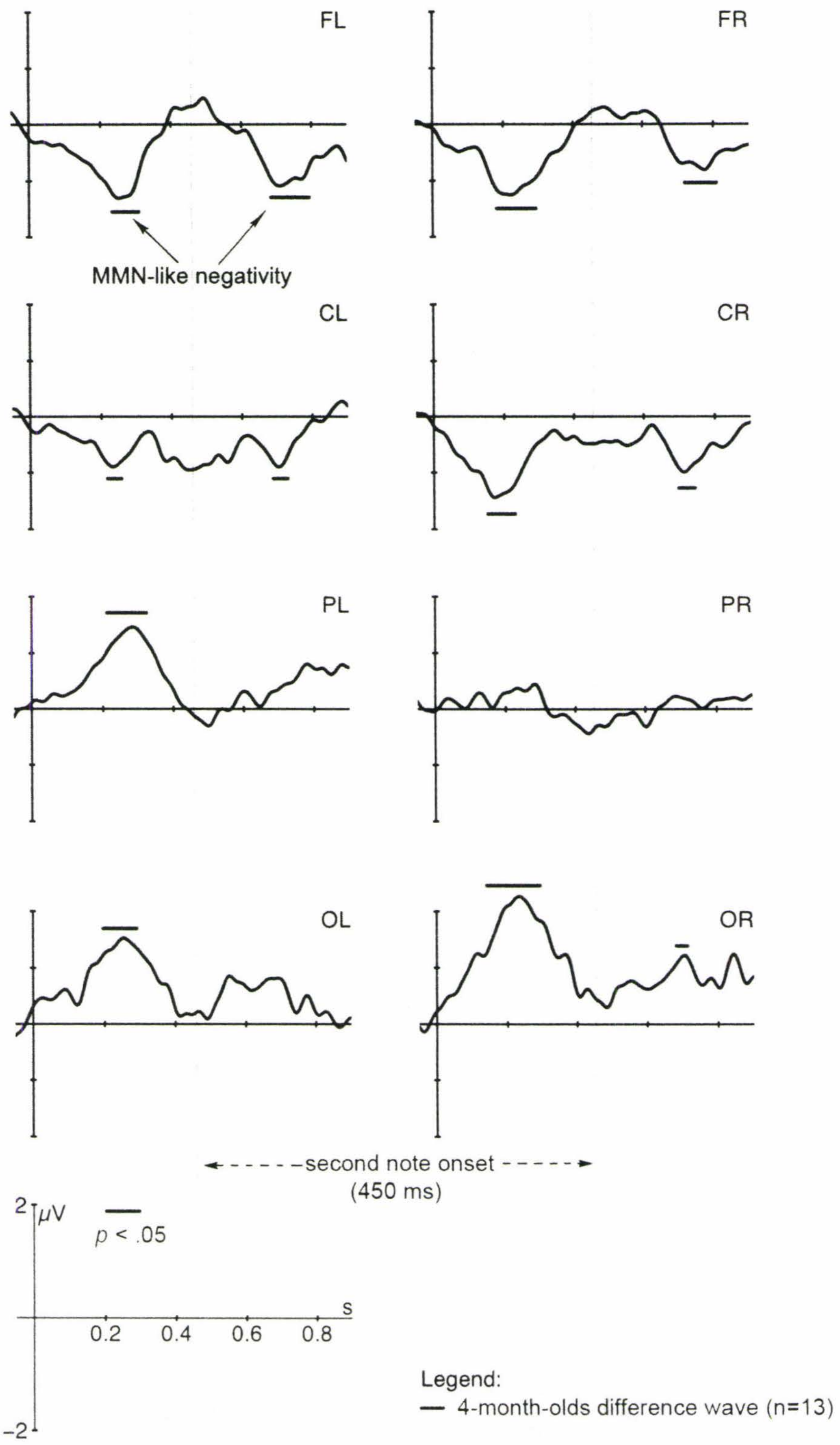
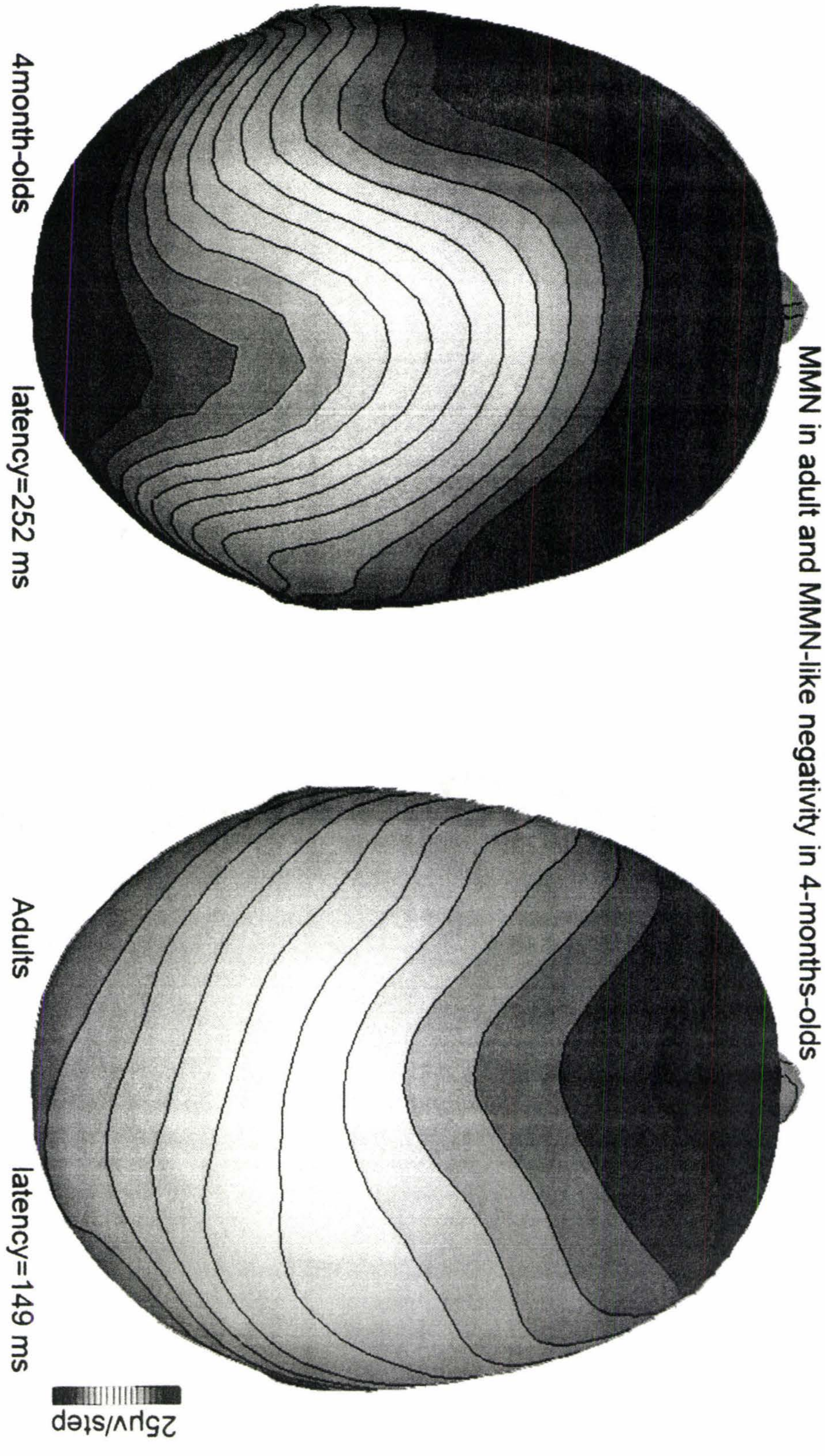
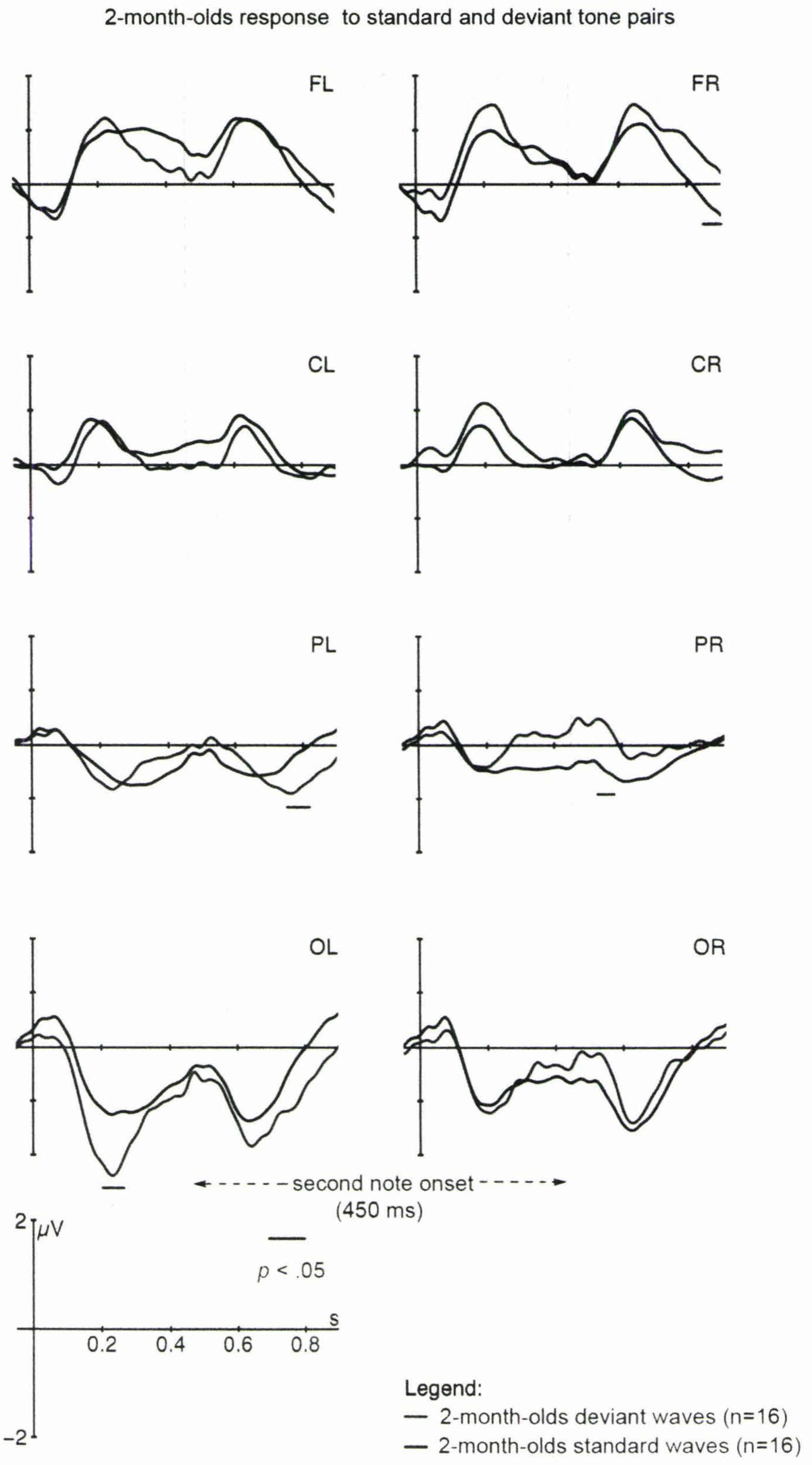
4-month-olds MMN-like negativity to pitch pattern change





Whole head voltage map of
MMN in adult and MMN-like negativity in 4-months-olds


2-month-olds response to standard and deviant tone pairs
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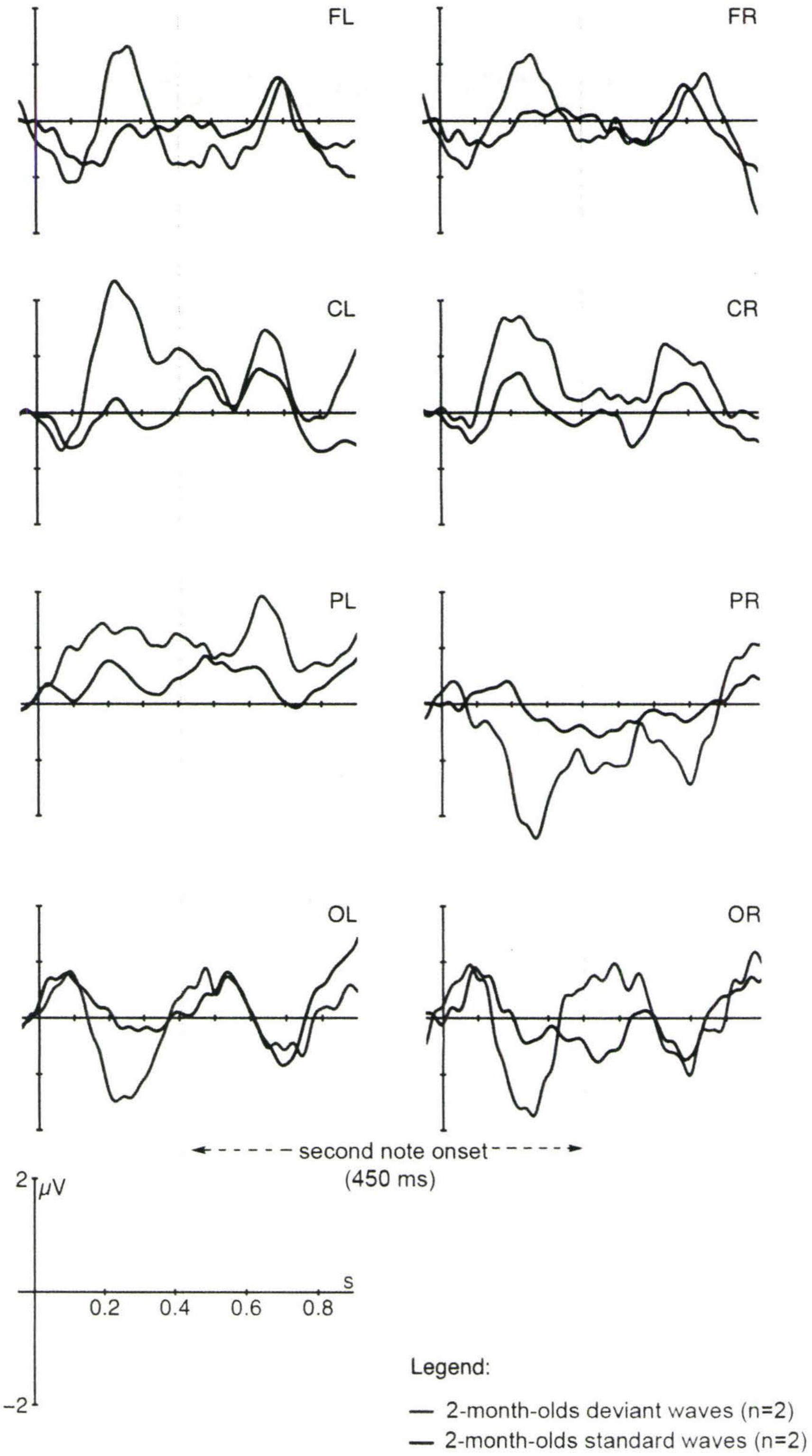
— 2-month-olds deviant waves (n=16)
— 2-month-olds standard waves (n=16)

Standard and deviant waves for 2 2-month-olds that showed positive mismatch response



Acknowledgements

This research was funded by a grant to LJT from the Canadian Institutes for Health Research. We thank Andrea Unrau for help in testing the infants.

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Chapter 5:

FINDING THE PITCH OF THE MISSING FUNDAMENTAL IN INFANTS

This chapter is manuscript submitted to Nature, authors: He & Trainor. Title: Finding the pitch of the missing fundamental in infants

Introduction to the Chapter 5

The MMN in adults can be elicited in response to various auditory changes. It has thus been widely used to study auditory perception. Having confirmed that negative MMR in infants may be functionally similar to adult MMN, it is possible to utilize it to study the development of pitch perception in early infancy.

How the pitch of harmonically complex tones is perceived in infancy is an important topic for understanding the development of pitch perception. Traditional behavioural methods have found that infants as young as 7 months can integrate the harmonics of complex tones, even when the fundamental frequency is removed, but younger infants have not been tested because the complexity of the behavioural procedure. The experiments of this chapter set out to examine this topic by designing stimuli in such a way that the MMR response would only be elicited if infants can hear the pitch of the missing fundamental tone. Infants of 3, 4, and 7 months of age were tested.

Both the 7-month-olds and 4-month-olds showed a negative MMR, similar to that of adults, in response to a pitch change that could only be perceived if infants process the pitch of the missing fundamental, but 3-month-olds showed no clear response pattern. This finding suggests that infants as young as 4-month-olds are able to perceive the pitch of the missing fundamental.

Finding the Pitch of the Missing Fundamental in Infants

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Sounds that give rise to a pitch sensation, such as musical tones and spoken vowels, typically have energy at a fundamental frequency, f_0, corresponding to the perceived pitch. These sounds are actually made up of complex combinations of frequencies, the majority of which are at integer multiples of f_0. Pitch is not directly present in the physical sound, but is derived in the nervous system, which integrates these components into a coherent representation of pitch[1,2]. One of the best demonstrations of this spectrotemporal integration is that removal of energy at f_0 does not change the perceived pitch but merely its timbre, a phenomenon known as hearing the pitch of the missing fundamental. Recent studies in adults indicate that although sound frequency information is processed subcortically, the integration of the frequency components into a pitch sensation corresponding to f_0 is not accomplished until beyond primary auditory cortex, in a region near its anterolateral edge[1,3]. Auditory cortex is immature at birth in terms of the number[4] and efficiency[5] of connections between neurons, and undergoes rapid development during the next few months. Here we analyze the development of electrophysiological responses to the pitch of the missing fundamental and show that the representation of pitch in auditory cortex emerges between 3 and 4 months of

age. Species as diverse as birds, fish, nonhuman primates and other mammals perceive the pitch of the missing fundamental, attesting to the importance of pitch for perceiving the auditory world[6]. Our results indicate that there is a profound change in auditory perception in early infancy with the emergence of true pitch perception between 3 and 4 months of age.

Pitch perception is essential for learning language and processing music. Pitch perception is also critical for auditory scene analysis, the process whereby the auditory system decomposes the complex wave reaching the ear into separate representations for each sounding object in the environment that contributed to the incoming wave[7]. Pitch provides information about object identity, such as body size[8], characteristics of people, such as age[9], gender[10], and even race[11], and pitch contours carry emotional information in speech and music[12].

Physical sounds that give rise to the sensation of pitch typically have energy at integer multiples of a fundamental frequency, f_0, such that the repetition rate of the complex waveform is unchanged when the fundamental frequency is missing. Regardless of whether the fundamental frequency is present or not, the auditory system extracts the pitch through complex spectrotemporal analysis, allowing people to identify the pitch of objects in environments where low frequencies are attenuated or missing. It also enables us, for example, to converse over the telephone, which does not transmit all frequencies in the f_0 range of the human voice, to perceive the lowest notes of organs whose pipes are too short to physically produce these fundamentals, to hear the bass notes in music through loudspeakers that cannot transmit their fundamentals, and to enjoy the unique timbre and pitch of the kettle drums, which arises in part from the fact that the vent hole largely dampens the fundamental frequency[13].

Although frequency is encoded at the level of the basilar membrane in the inner ear and in temporal firing patterns in the auditory nerve, and although there are tonotopic frequency maps in many subcortical nuclei and in primary auditory cortex, a number of lines of evidence indicate that in humans, pitch is not represented until beyond primary auditory cortex, in a region in lateral Heschl's gyrus. These include fMRI studies[14-16], lesion studies[17], and a case study using depth electrodes[3]. Single cell recordings in marmoset monkeys also confirm a pitch-sensitive region which is localized to an area adjacent to primary auditory cortex[1], and studies of primary auditory cortex in macaque monkeys have failed to find even a population representation of the missing fundamental in primary auditory cortex[18].

In humans, the auditory brainstem, which supports frequency representation, is quite mature at birth. However, in auditory cortex, synaptic density increases dramatically over the first months after birth[4]. Neurofilament expression, which reflects the ability of neurons to communicate efficiently, can only be seen in cortical layer I prior to 4 months, at which time expression begins in deeper cortical layers IV, V and VI[5]. If auditory cortex is necessary for the integration of frequency components into a representation of a single auditory object with a particular pitch, then very young infants would not be expected to be able to do this. Behavioural studies indicate that 7-month-olds can integrate harmonics and perceive the pitch of the missing fundamental[19-21]. However, these behavioural techniques are difficult to apply to younger infants.

We tested whether infants of 3, 4, and 7 months are sensitive to the pitch of the missing fundamental using event-related potentials (ERPs) derived from electroencephalogram (EEG) recordings, and compared the infant results to those of adults. Specifically, we made use of the mismatch negativity (MMN) component of the

ERP, as previous studies have used MMN to demonstrate processing of the pitch of the missing fundamental in adults[22,23]. When a sound is presented repeatedly, or exemplars from a sound category are presented repeatedly, occasional changes in the sound or sound category elicit an MMN response in adults between 120 and 220 ms after the onset of the unexpected deviant sound[24,25]. At the surface of the head, MMN appears as an electrical field with negativity at the front and positivity at the back, which is consistent with generators of MMN in left and right auditory cortices. Because MMN occurs in response to deviance in an ongoing stream of sound events, it is thought to reflect auditory memory trace formation. In previous studies, we have shown that for a change in pitch, an MMN-like response is readily elicited from 3- and 4-month-olds infants around 210 ms after stimulus onset[26]. At 2 months, infants show an increase in a slow frontal positive wave, rather than a frontal negativity as in the case of older infants and adults[26].

To test how the pitch of the missing fundamental is perceived across age, we presented standard trials consisting of two tones, each with 10 harmonics including the fundamental frequency, such that the pitch always increased from the first to the second tone and each harmonic increased in frequency from the first to the second tone (see Supplementary Figure 1). However, from trial to trial the pitch of the first tone varied and the amount of pitch increase from the first to second the second tone varied. Pitch increases were chosen to be clearly perceptible to infants but not to consist of Western musical intervals. Occasionally we presented deviant trials, consisting of a first tone with the fundamental as in standard trials, and a second tone where all 10 harmonic components increased in frequency from the first to second tone, but where the components of the second tone were all integer multiples of a low-pitched missing fundamental. If the missing fundamental was perceived, the pitch heard decreased from the first to the second tone on deviant trials. However, if the pitch of the missing fundamental was not perceived, the pitch of each component increased from the first to the second tone, as in standard trials.

Waveforms from 124 (128 in adults) electrode sites distributed across the scalp were averaged into regions representing activity at left and right frontal, central, parietal, and occipital regions (see Supplementary Figure 2). In adults, a typical MMN was seen in response to missing fundamental deviants (Figure 1), indicating that adults represent the pitch of the missing fundamental in auditory cortex, as expected. In infants, MMN was also seen in 4- and 7-month-olds, but no significant response, positive or negative, was present in 3-month-olds (Figure 2). This indicates that a cortical representation for the pitch of the missing fundamental appears to emerge between 3 and 4 months.

Analyses of 4-month, 7-month and adult waveforms indicated that the latency of the MMN peak decreased with age, $F(2, 34.5) = 6.09$, $p < .001$, with the peak in 4-month-olds [192 ± 3 ms (s.e.m.) after second tone onset] significantly later ($p < .001$) than in 7-month-olds [166 ± 3 ms (s.e.m.)], and the peak in 7-month-olds significantly later ($p < .001$) than in adults [135 ± 4 ms (s.e.m.)]. The electrical field distribution over the scalp at the time of the MMN peak showed a bipolar pattern in 4-month-olds, 7-month-olds and adults, with an anterior negativity accompanied by a posterior positivity (Figure 3), consistent with primary generators of the activity in the left and right auditory cortices. At the same time, the scalp distribution also varied somewhat across age as shown by a significant interaction between age and region, $F(6, 110) = 3.45$, $p = .004$. In particular, in adults the auditory cortical neurons involved in generating the response appear to be oriented in a more central direction compared to those of the younger infants. Finally, across all age groups, MMN was slightly but significantly earlier in the left [162 ± 2 ms (s.e.m.)] than right [167 ± 2 ms (s.e.m.)] hemisphere, $F(1, 237) = 4.71$, $p = .03$.

These results show that infants begin to respond to the pitch of the missing fundamental between 3 and 4 months of age, indicating integration of the harmonic frequency components into a pitch percept by 4 months. Infants younger than 3 months do respond to changes in the pitch of complex tones if the fundamental frequency is present[26]. It is difficult to measure phenomenologically what infants experience at this age when presented with complex sounds such as phonating voices or musical instruments, but the present results suggest that these early responses are based on representations of frequency rather than pitch. For example, if young infants processed only the fundamental frequency of complex sounds containing fundamentals that give rise to pitch sensations in adults, they would appear to be able to process pitch. What is clear is that between 3 and 4 months of age there is a major shift in how pitch is represented in the cortex, such that by 4 months components that stand in harmonic relations fuse into a single percept whose pitch corresponds to the fundamental, whether or not it is actually present in the stimulus.

Methods.

Participants.

We tested 29 3-month-old infants (mean age = 110 days; range = 97-118; 16 female), 15 4-month-olds (mean age = 142 days; range = 131-149 days; 9 female), 15 7-month-olds (mean age = 228 days; range = 219-236; 8 female), and 10 adults (mean age = 20 years;

range = 18-26 years; 6 female) with normal hearing. Data from an additional 34 infants was excluded because they fell asleep (6, 7, 7 infants at 3, 4, and 7 months, respectively), or became fussy and failed to produce the minimum of 100 artifact-free deviant trials (2, 4, 8).

Stimulus presentation.

Tones were synthesized using Adobe audition 1.0 (Adobe Software) and played using E-prime 1.1 (Psychology Software Tools, Inc.) on a Dell OptiPlex280 computer with an Audigy 2 platinum sound card (Creative Labs) through a custom-built WestSun loudspeaker with flat spectrum response. Each tone in the standard stimulus tone pairs was synthesized by adding together 10 sine wave tones in random phase that were at integer multiples of the fundamental frequency (selected from the first 15 harmonics), such that intensity decreased by 4 dB/octave. Each resulting complex tone was micro-frequency (1% of the fundamental frequency) modulated at a rate of 5 Hz in order to increase the perceived synthesis of the sine wave components. The fundamental frequency was always present in both tones of each of the six standard pairs. The pitch always increased from the first to the second tone in each of the standard tone pairs (with no musical relation), and each sine wave component also increased from first to second tone. The pitch of the first tone varied between 209 Hz and 314 Hz, and the pitch increase from first to second tone varied between 82 and 142 Hz (See Supplementary Figure 1). Each tone of each standard tone-pair stimulus was 150 ms, including linear onset and offset ramps of 15 ms and the two tones were separated by 50 ms. Standard tone pairs were presented on 6/7th of trials, with each of the 6 standard tone pairs presented equally often (1/7th of the total trials). Tone pairs were separated by 400 ms. On deviant trials, the first tone was constructed as in the standard trials and contained the fundamental frequency. Each sine wave component of the first tone increased in frequency between the first and second tones of the pair, similarly as with the standard tone pairs. However, the components of the second tone in deviant stimuli were create so as to form a missing fundamental that decreased in pitch. The likelihood of a deviant trial was equal to that of each standard trial (1/7). Trials were presented in quasi-random order with the constraints that the same standard pair was never played twice in a row and that at least two standard trials preceded each deviant trial. Stimuli were presented in a sound-treated room at approximately 68 dB (A) at the position of the participant's head over a noise floor of 29 dB (A). The lower sine wave components of the presented sounds were measured at 58 dB in the sound field. Any difference tones created by non-linearities in the cochlea that might arise would be at least 25 dB below this (< 33 dB) [27,28]. Given that infant thresholds at 3-4 months of age are around 30 dB for these frequencies[29], it is not possible that infant ERP responses reflect non-linearities of the ear.

Data Analysis.

EEG was recorded from 124 locations on the scalp (128 for adults) though Geodesic Sensor nets (Electrical Geodesics, Inc.) and digitized at 1000 Hz with a vertex reference and bandpass filter of 0.1–400Hz, while impedance was maintained below 50 kΩ. Offline, the data were filtered between 0.5 and 20 Hz with a roll off of 24 dB/octave, segmented into 1050 ms epochs starting 200 ms before the onset of the first tone in each trial, and trials with eye artifact were removed. For each age group for each electrode site, standard and deviant trials were averaged separately relative to the 200 ms baseline before onset of the first tone. Subsequently, groups of electrodes were averaged together in left and right frontal, central, occipital and parietal regions (Figure 4). Difference waves were created for each participant by subtracting the deviant average from the standard average. Points where the waveforms were significantly different were determined by t-tests. For each infant, MMN was defined as the largest frontally negative peak between 100 and 250 ms (100 and 200 ms for adults) after the onset of the second tone. Peak amplitude and latency were analyzed with linear mixed effects model analyses of variance (ANOVAs), with age group (4 months, 7 months, adults), scalp region (frontal, central, parietal, occipital), and hemisphere (left, right) as variables. Bonferroni corrections were applied to multiple comparisons.

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Supplementary Information

Accompanies the paper on **www.nature.com/nature**.

Supplementary Figure 1.

Stimulus excerpt illustrating the pitch of the missing fundamental. Three standard tone pairs are shown followed by a deviant tone pair, followed by three additional standard tone pairs. Each tone in each standard tone pair was comprised of 10 sine-wave frequency components chosen from the first 15 components, and the spectral slope is -4dB/octave. Each resulting complex tone is micro-frequency (1% of the fundamental frequency) modulated at a rate of 5 Hz in order to increase the perceived synthesis of the sine wave components. For each tone, the lowest component is the fundamental frequency, f_0. Each of the components increased in frequency from the first to the second tone, as did the perceived pitch, which corresponds to the lowest frequency component, f_0, shown in the figure. Occasionally deviant tone pairs were randomly interspersed with the standards, occurring 1/7th of the time. Deviant tone pairs were similar to standards in that both tones contained 10 components, each of which increased in frequency from the first to the second tone of the pair. However, in deviant stimuli, all components of the second tone were integer multiples of a missing fundamental that was lower in pitch than the f_0 of the first tone of the pair. Thus, if the pitch of the missing fundamental was processed, the perceived pitch decreased between the two tones on deviant trials, whereas it always increased on standard trials.

Supplementary Sound example. Listen to the excerpt shown in Supplementary Figure 2. Notice that the fourth tone pair is a deviant stimulus. Whereas the pitch is perceived to rise for each of the other tone pairs, it is perceived to fall for the deviant pair, even though there is no physical energy at the low pitch (the missing fundamental).

Supplementary Figure 2.

EEG electrode grouping scheme for data analyses. EEG was measured from 128 channels on the head using Geodesic nets. The locations of the electrodes are shown in a flattened representation with the forehead at the top of the representation and the back of the head at the bottom. 76 of the electrodes were grouped into left and right frontal (FL, FR), central (CL, CR), parietal (PL, PR), and occipital (OL, OR) regions, optimal for examining MMN. In this scheme, peripheral electrodes are not included as they tend to be noisy, midline electrodes are not included in order to examine hemispheric differences, and far frontal electrodes are not included as they primarily monitor artifact from eye movements. Waveforms from electrodes within each of the 10 regions were averaged prior to data analysis.

Acknowledgements. This research was supported by a grant to L.J.T. from the Canadian Institutes of Health Research. We thank Lisa Hotson and Dorcas Yung for help in testing the infants and Steven Brown and Daphne Maurer for comments on an earlier draft.

Author Contributions. The study was designed by C.H. and L.J.T., the data analysis performed by C.H. in consultation with L.J.T., and the paper written by L.J.T. and C.H.

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Figure Captions

Figure 1.

Averaged ERP responses from adults. a. The averaged response from the right frontal region to standard tone pairs (with rising pitch) and to deviant tone pairs (with falling pitch if the missing fundamental is perceived), filtered between 1.5 and 20 Hz. Because the auditory cortex is located around the Sylvian fissure, the orientation of axons in this region gives rise to electrical fields at the surface of the head that have a frontal positive or negative pole concurrent with a posterior polarity reversal. The y-axis marks the onset of the first tone and the grey line the onset of the second tone in each pair. Both standard and deviant waveforms show similar P1, N1, and P2 responses to both tones. Deviant waveforms show an additional mismatch negativity (MMN) in response to the deviants, indicating clear processing of the pitch of the missing fundamental in adults. **b.** The averaged difference waveform (deviant–standard) at the right frontal region. The bar under the waveform marks the time periods during which the waveform is significantly different from zero. It can be seen that at the right frontal site, the standard and deviant waves differ only between 108 ms and 167 ms, at the time of the MMN. **c.** The waveforms from left and right frontal (FL, FR), central (CL, CR), parietal (PL, PR), and occipital (OL, OR) scalp regions. The MMN response reverses polarity at the back of the head, consistent with primary generators along the Sylvian fissure in left and right auditory cortices.

Figure 2.

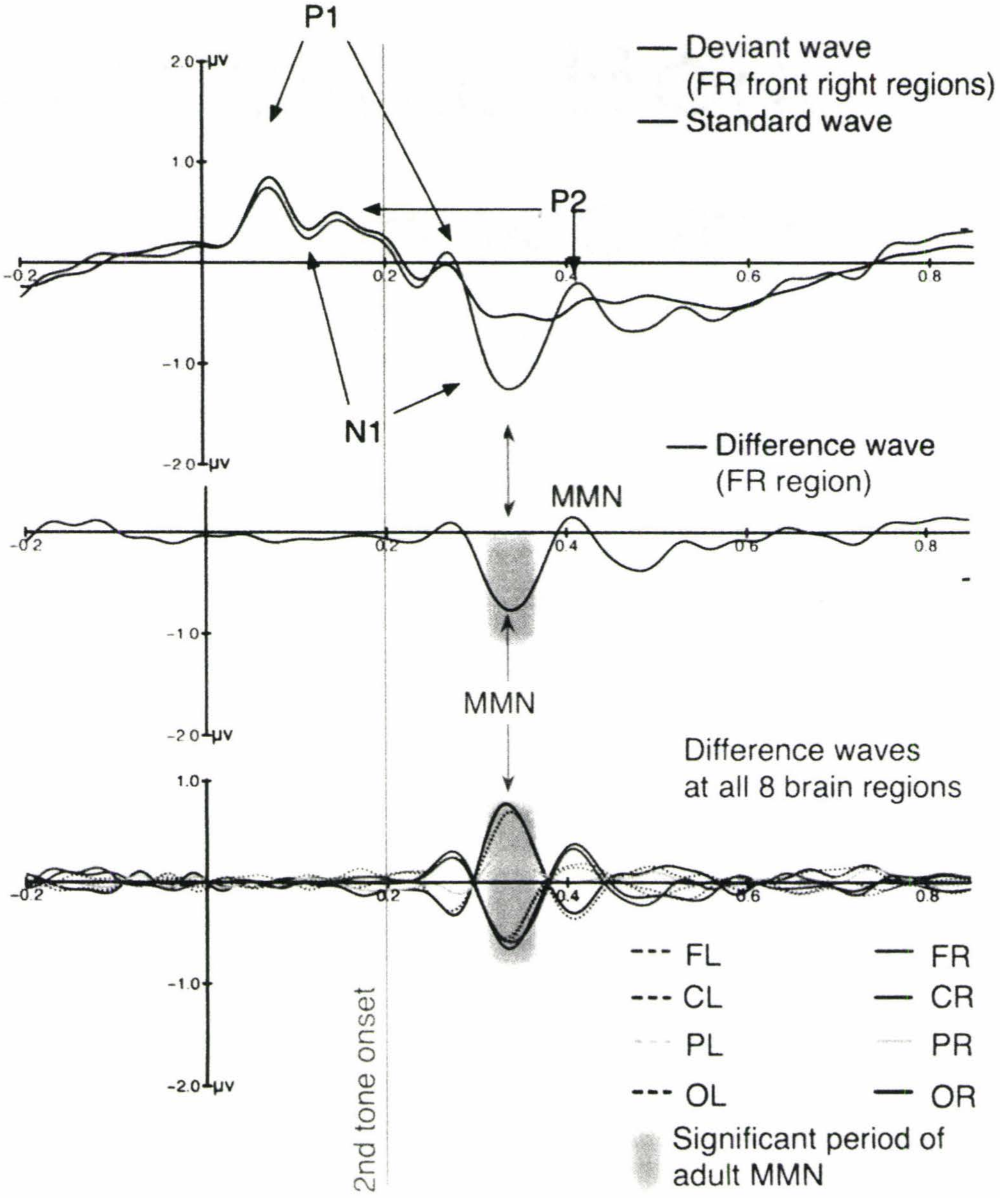
Averaged difference waves (deviant–standard) from infants. Waveforms from left and right frontal (FL, FR), central (CL, CR), parietal (PL, PR), and occipital (OL, OR) scalp regions are shown filtered between 1.5 and 20 Hz. The y-axis marks the onset of the first tone and the grey line the onset of the second tone in each pair. The dipolar pattern of MMN, with anterior negativity and posterior positivity, can be seen peaking at 166 ms after the onset of the second tone in 7-month-olds and at 192 ms in 4-month-olds, but not in 3-month-olds. The shaded area over the waveforms marks the time periods during which the difference wave at the right frontal (FR) region is significantly different from zero (338ms to 393 ms for 7-month-olds and 365ms to 423 ms for 4-month-olds). In 7-month-olds, 7 of the 8 regions showed significant MMN; in 4-month-olds, 6 of the 8 regions showed significant MMN; in 3-month-olds, none of the regions showed significant MMN. In the 4- and 7-month-olds, there appears to be a frontally-positive component following the MMN. This component has been observed in other studies of

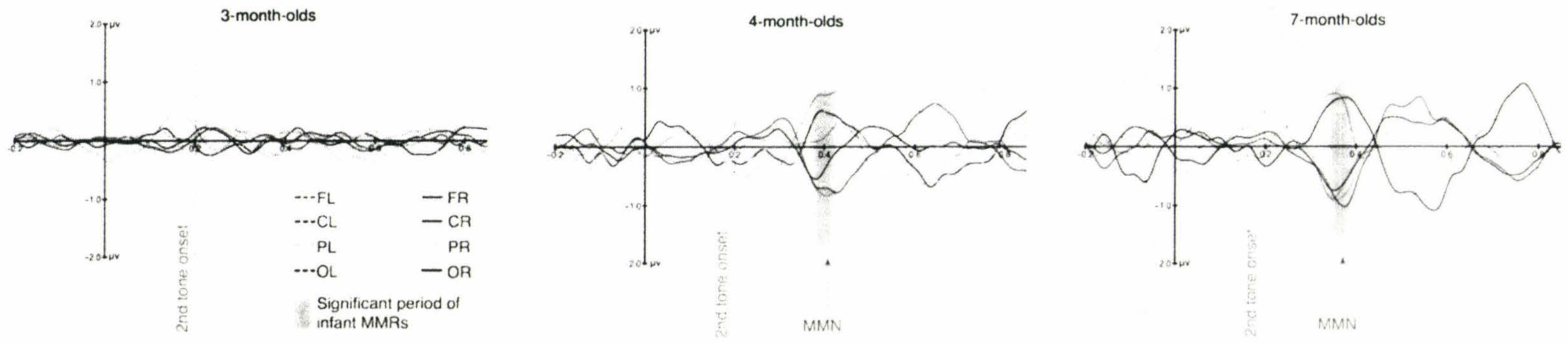
MMN[30] and may correspond to the adult P3a component, reflecting capture of attention. Note that we doubled the number of infants in the 3-month group in order to obtain greater power to examine small effects, but no suggestion of an MMN response emerged. The results indicate that cortical responses to pitch of the missing fundamental emerge between 3 and 4 months of age.

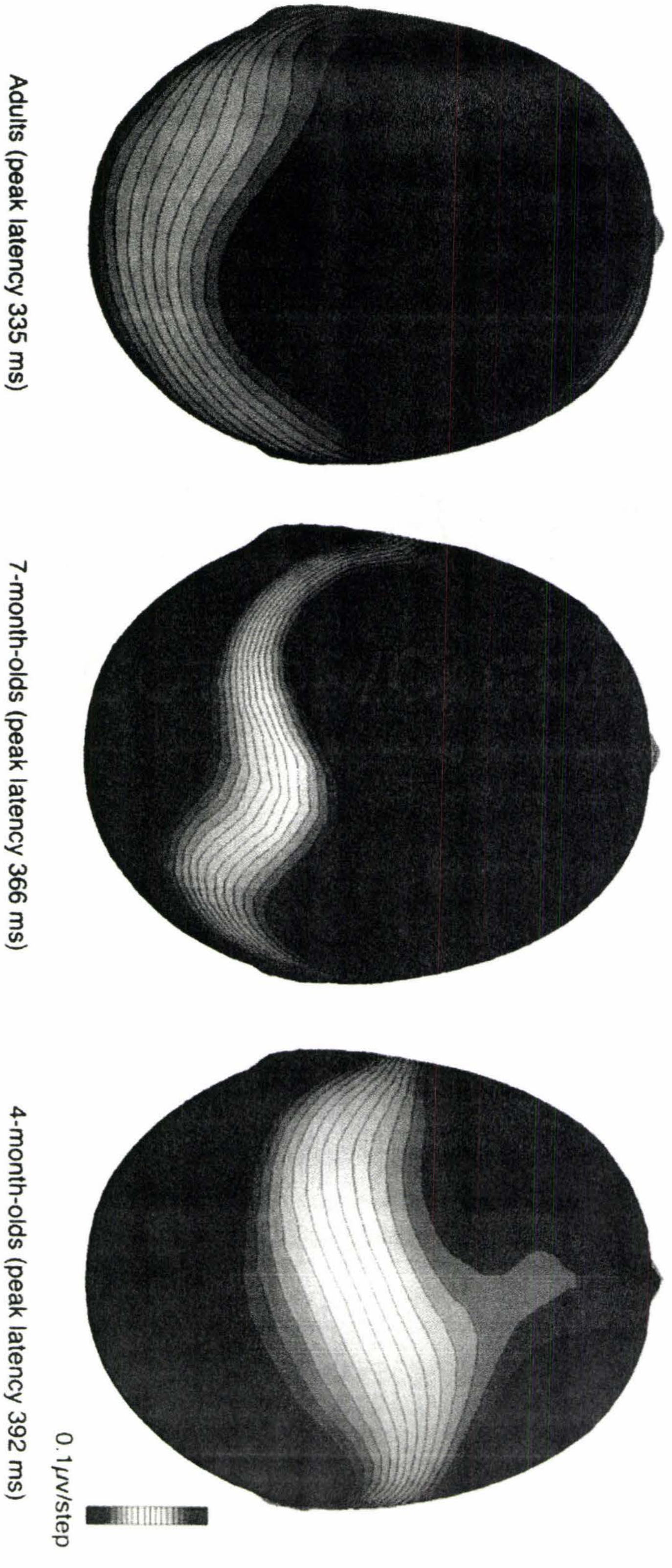
Figure 3.

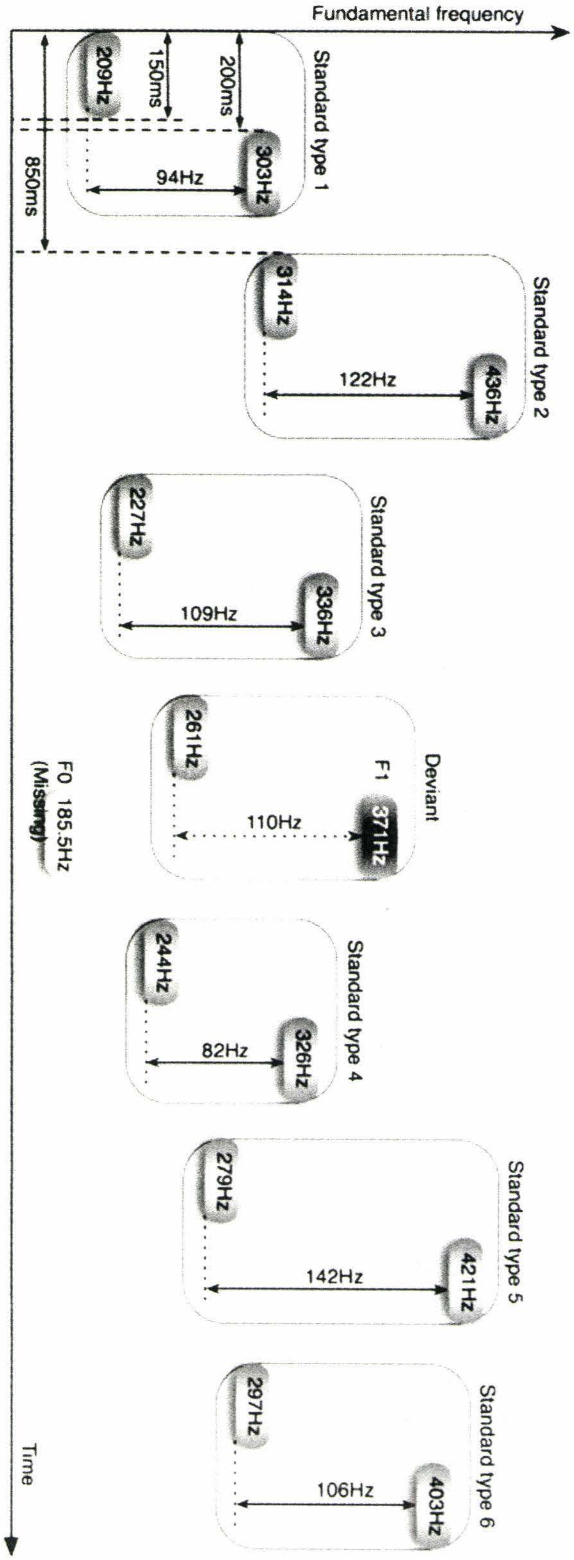
Scalp distribution of MMN in adults, 7-month-olds and 4-month-olds. Isovoltage contour maps at the peak of the MMN response show a frontal negativity and posterior positivity in all three age groups consistent with generators around the Sylvian fissure in left and right auditory cortices. However, with increasing age the negativity becomes more central in focus, and the clear bi-hemisphere pattern less distinct. This suggests that the orientation of the neurons contributing to the response changes somewhat with development.

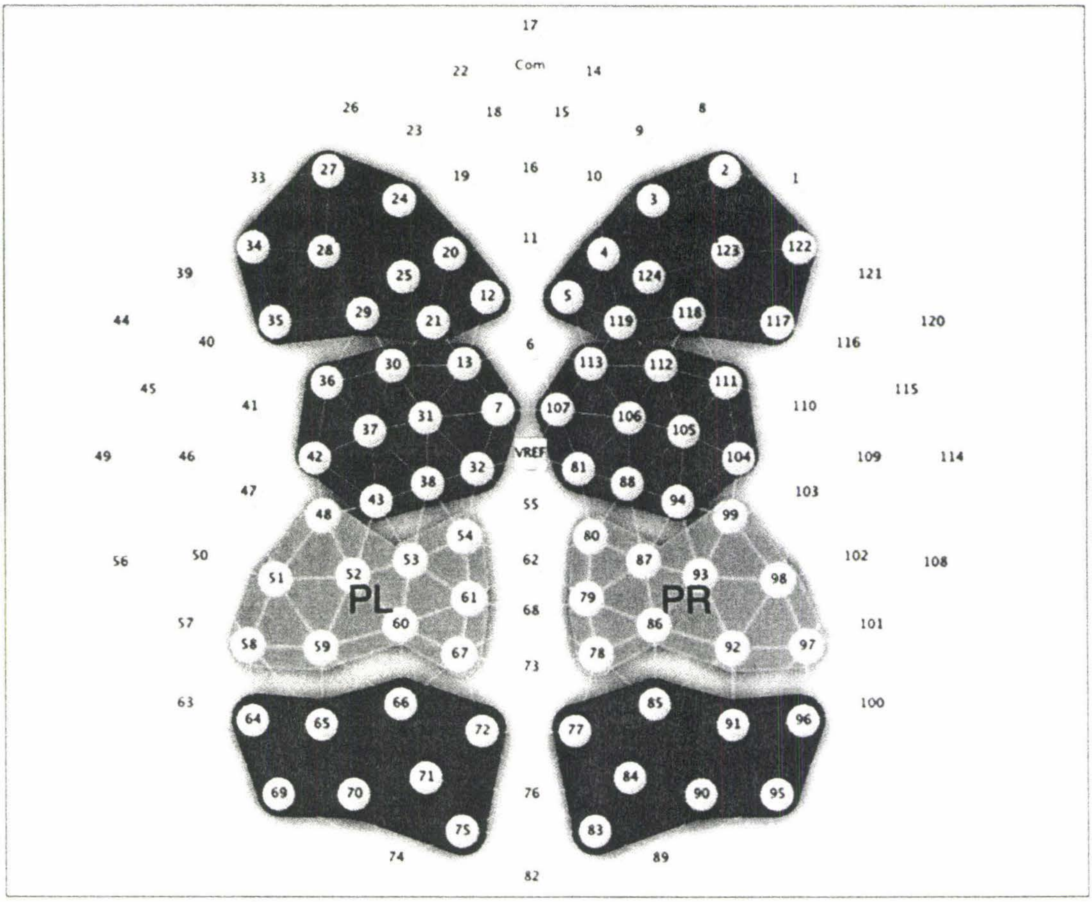
Figures


P1
2.0 μv
1.0
-1.0
-2.0 μv
-0.2
0.2
0.4
0.6
0.8
P2
N1
— Deviant wave
(FR front right regions)
— Standard wave
— Difference wave
(FR region)
MMN
MMN
Difference waves
at all 8 brain regions
1.0
-1.0
-2.0 μv
2nd tone onset
--- FL
— FR
--- CL
— CR
PL
PR
--- OL
— OR
Significant period of
adult MMN


3-month-olds
4-month-olds
7-month-olds
2.0 µv
1.0
-1.0
-2.0 µv
-0.2
0.2
0.4
0.6
0.8
2nd tone onset
MMN
---FL
---CL
PL
---OL
— FR
— CR
PR
— OR
Significant period of infant MMRs


Adults (peak latency 335 ms)
7-month-olds (peak latency 366 ms)
4-month-olds (peak latency 392 ms)
0.1μv/step


Fundamental frequency
Time
Standard type 1
209Hz
303Hz
94Hz
150ms
200ms
850ms
Standard type 2
314Hz
436Hz
122Hz
Standard type 3
227Hz
336Hz
109Hz
Deviant
F1
261Hz
371Hz
110Hz
F0 185.5Hz
(Missing)
Standard type 4
244Hz
326Hz
82Hz
Standard type 5
279Hz
421Hz
142Hz
Standard type 6
297Hz
403Hz
106Hz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Chapter 6:

GENERAL CONCLUSION

Summary and Conclusions of Current Dissertation

The ability to identify and discriminate pitch in sound is fundamental to extracting information from auditory stimuli. Understanding how this ability develops during infancy is an important topic for auditory development research. Over the past few decades, neural imaging techniques, such as event related potentials (ERPs), have provided an alternative approach to traditional psychophysical methods for studying the development of pitch perception in infancy. More particularly, an ERP component called mismatch negativity (MMN) is well suited for the study of pitch perception in young infants because it reflects cortical discrimination processes and does not require attention or a behavioural response for its elicitation. However, research on infant mismatch responses (MMR) prior to this dissertation had reported inconsistent results; thus Picton & Taylor (2007) concluded that the mismatch paradigm should not be used for evaluating auditory discrimination in infants until reliable normative data are available. This thesis begins to rectify this situation.

In order to understand infant MMRs and to evaluate the possibility of utilizing infant MMR in studying infant pitch perception, we first systematically investigated the infant MMR. In the studies of Chapter 2, we recorded ERPs from infants between 2 and 4 months of age in response to infrequent pitch changes in an ongoing stream of repeating tones. In the averaged ERP waveforms, we observed both a broad positive MMR and the adult MMN-like MMR. Both MMRs have been previously reported in the literature but this is among the first studies to demonstrate that the positive MMR decreases in amplitude from 2 to 4 months of age, while the negative MMN increases in amplitude and becomes prominent during the same time period. These results rule out the hypothesis that the polarity of the infant mismatch response is determined solely by the characteristics of the infant, as suggested by some previous studies (e.g., Cheour et al., 1999, suggested that the positive MMR is a type of characteristic brain response from infants with cleft palate). The study reported in Chapter 2 also found a developmental transition from prominently positive to prominently negative MMR between 2 and 4 months of age, consistent with the hypothesis that the different forms of MMR observed relate to developmental maturation (Trainor et al., 2003). The fact that infants in the 3-month-old group in this study demonstrated both positive and negative MMRs at the same time, suggests that two types of MMR are distinct processes.

The results from Chapter 2 suggest that the two types of infant MMR reflect different underlying neural processes because of their different characteristics (latency, polarity, morphological distribution) and different developmental trajectories, rather than just different morphological expressions of the same ERP component as brain regions mature as Leppenen et al (2004) suggested. In order to further investigate whether the two MMRs are functionally distinct, we conducted a second study in Chapter 3 with infants 2 and 4 months old to examine how the two MMRs are affected when the stimulus presentation rate and the magnitude of pitch change vary in infants. We discovered that the magnitude of pitch change has only a slight influence on both MMRs even as the magnitude of pitch change approaches frequency discrimination thresholds for infants of that age. However, changing the stimulus presentation rate produced a very large change in the positive MMR but only slightly affected the negative MMR. When the presentation rate increased, the slow positive waves elicited by deviant tones remained similar, but the slow positive waves elicited by standard tones decreased dramatically. This finding indicates that the slow positive wave may represent the obligatory response to incoming sounds and the positive MMR may reflect the difference between the neurons encoding the standard stimulus, which are in a somewhat refractory state for fast presentation rates, compared to the neurons encoding the occasional deviant stimuli. Hence, when the stimulus presentation rate increases, the neural circuit encoding the standard tones is unable to fully recover between two standard tones, resulting in a decrease of amplitude of the obligatory responses. Regardless of presentation rate, the deviant tones are always far apart in time, so the recovery time of neural circuits is not affected, and the obligatory responses to the deviant tones remain similar across different rates of presentation.

To further understand the underlying neural mechanisms of infant MMRs, in the experiments in Chapter 4 we studied infant MMRs to pitch pattern changes during the same period of early infancy (2 – 4 months of age). Specifically, a tone pair was presented repeatedly, and deviants consisted of inverting the order of two tones in the pair without introducing any novel tones. The results showed that while the negative MMR was similar to the MMR for simple pitch changes in the previous studies, the positive MMR was greatly reduced. These findings are consistent with the hypothesis that the positive MMR reflects the absence of refractory processes in deviants compared to standards. According to this explanation, the positive MMR is not strongly present for pattern changes because no novel tones are introduced so there is no release from a refractory state. The negative MMR, on the other hand, may be functionally similar to the adult MMN, because it can be elicited not only by a simple pitch change but also by abstract changes in pattern sequences. These results, combined with the results reported in Chapters 2 and 3, suggest that the two types of infant MMRs are functionally different and that the adult MMN-like MMR emerges in infants as early as 3 months of age.

Across all the studies in Chapters 2, 3 and 4, we consistently observed a dramatic change in infant MMRs between 2 and 4 months of age, indicating that infant evoked brain responses to pitch information mature tremendously during this age period. Neuroanatomical studies (Moore, 2002; Moore & Guan, 2001) have shown that prior to 4 months of age, mature synapses exist only in layer I of auditory cortex. Synapses begin to mature in deeper layers (IV, V, VI) around 4 months of age. Therefore, the change we observed in the studies of the present dissertation might be related to this aspect of physiological maturation. Prior to the maturity of synapses in auditory cortex, pitch discrimination might be processed by subcortical areas. The positive slow wave might reflect such processes, and might diminish in the case of pattern changes because these areas cannot support complex pitch processing. Perhaps, by the age of 4 months, as the deeper layer of secondary auditory cortex start to become functional, they begin to process pitch discrimination, as is the case in adults. According to this hypothesis, we are able to obtain the adult-like MMR in the brain response of 4-month-olds because of the maturation of auditory cortex. However, this scenario does not explain why the negative MMR develops at different ages for different sound features. However, to date there is only one study (Moore & Guan, 2001) examining synaptic maturation in human infants, so we must treat this interpretation with caution. We must wait for further data before we can fully understand how the results of the present thesis fit into the anatomical developmental literature.

Because we confirmed in Chapters 2, 3, and 4 that the negative MMR resembles adult MMN in infants 3 months and older, the negative MMR can be used as a tool to study pitch perception in infants. In Chapter 5, we examined infant pitch perception for harmonic tones with missing fundamental frequencies in infants between 3 and 7 months of age. Pitch perception is of fundamental importance for the processing of speech and music. For pitch perception, it is vital to develop the ability to integrate the harmonics of a complex tone into a single percept of that tone with a particular pitch. Perception of the pitch of the missing fundamental is one way to confirm that this integration has taken place. Our results are the first to show that 7-month-old infants show an MMR to the pitch in missing fundamental tones, consistent with the results from previous behavioural studies (Clarkson & Clifton, 1985; Montgomery & Clarkson, 1997). Moreover, we demonstrated that 4-month-olds show a similar MMR to that of 7-month-olds, a result that indicates that cortical processing of the pitch of the missing fundamental is present as young as 4 months of age. By contrast, 3-month-olds did not show any clear MMR to the same stimuli, a result that suggests that infants of this age may not be able to perceive the pitch when the fundamental is missing; at a minimum, 3-month-olds must be processing pitch in a very different way compared to older infants and adults. Overall, these findings show that infants as young as 4 months are able to, at cortical level, integrate the frequency components of a harmonic tone into a single percept with pitch.

To summarize, the studies comprising this dissertation systematically examined the infant mismatch response to pitch changes during early infancy and provide unique contributions to the understanding of infant MMRs and infant pitch perception in four main ways. The first contribution is a systematic study of the two types of MMRs over age (Chapter 2). Previous studies reported either the slow wave or the negative MMR, but not both. Our results demonstrated that both MMRs coexist in certain periods of early infancy, and that each response type has different morphological characteristics and developmental trajectories. The second contribution of this dissertation is the investigation of factors that influence the two types of MMRs, including stimulus presentation rate and magnitude of pitch change (Chapter 3). Previous studies have not tested both factors in the same group of infants or across age. Studies reported in Chapter 3 show that both presentation rate and magnitude of pitch change affect the negative adult-like infant MMR but that only the presentation rate affects the positive infant MMR. This is important because it shows that the two infant MMRs represent processes that function differently. The third contribution of the present dissertation is the investigation of the infant MMR response to abstract pitch pattern changes. Results of the studies reported in Chapter 4 provide evidence that the negative infant MMR is much more sensitive than the positive MMR to pitch pattern changes. The fourth contribution is in providing the first ERP investigation of infant pitch perception in stimuli with a missing fundamental. The results of Chapter 5 show that 4-month-olds have a MMR response to the pitch of the missing fundamental tone but that this response is not present at 3 months of age.

The present dissertation has important implications for our knowledge of infant auditory development in general. These experiments show that pitch perception is not fully mature in young infants, but takes many months, if not years, to reach adult levels of maturation. Furthermore, these experiments demonstrate that the cortical mechanisms for processing pitch change dramatically over the first months after birth, and that it is not until 4 months of age that complex pitch perception, whereby harmonics are integrated into single percepts, is established.

The present dissertation also establishes the infant MMR as a viable tool for measuring many aspects of auditory perception. Prior to this thesis, the state of the literature was such that Picton & Taylor (2007) concluded that we did not know enough yet about infant MMR responses to consider using MMN as a clinical tool. The experiments of the present thesis have shown that the two seemingly conflicting reports of positive and negative MMRs across previous studies can be reconciled. Specifically, both responses are present, but the former decreases in amplitude with increases age whereas the latter increases in amplitude with increases age. We have, therefore, established reliable objective procedures to study pitch perception and other aspects of auditory development in young infants, and these measures have the potential to be developed into clinical diagnostic tools.

Limitations and Future Directions

In the current dissertation, we thoroughly examined the infant MMRs to pitch changes and clarified the characteristics of infant MMRs and a number of the factors that influence them. We also successfully utilized MMR as a tool to study the perception of complex tones in infancy. However, there are some limitations in our studies. These are important to discuss in the context of future directions for studies of pitch and auditory perception in infancy.

In the studies of the present dissertation, we studied infant MMRs, but we did not test our infant participants with behavioural procedures. In adults, the MMN component is a very sensitive indication of the perception of changes in pitch and other characteristics of auditory stimuli, and MMN can be observed without attention, as long as these changes are above behavioural thresholds. However, there is no direct evidence to date showing that the same is true for infant MMRs. In Chapter 3 of the current dissertation, we were able to obtain MMRs from both 2- and 4-month-old infants using stimuli with a pitch change of only 5%, which is close to the 3% behavioural threshold reported for infants of this age (e.g Olsho et al., 1982, 1987). Thus, it is likely that MMRs in infants are as sensitive as MMNs in adults. Future studies comparing infant MMRs and behavioural thresholds in the same individual infants will be extremely helpful, although admittedly hard to carry out because, compared to adults, infants' data tend to have a lower signal-to-noise ratio and to be more variable due to movement, fussiness, and short attention spans.

As a result of these factors, we were only able to get reliable results by testing large numbers of infant participants in our studies. It would likely require several long recording sessions to achieve a similar signal-to-noise ratio in data from an individual infant, which can be challenging to arrange, and the results obtained from these multiple sessions at different times might be affected by the rapid brain development in early infancy as well. (For a review of the challenges of ERP studies in infants, see Picton et al., 2007). Nevertheless, it would still be beneficial to test participants in behavioural procedures with the same stimuli in order to provide convergent evidence, even at the group level instead of the individual level.

A second limitation of our studies is that we did not examine the role of the state of the infant on MMRs. All infant participants in all experiments of the present dissertation were fully awake. However, several other studies tested infants while they were asleep (e.g., Čeponiené et al., 2000, 2002; Cheour et al., 1998; Leppänene 1997, 1999). Friederic et al (2002) compared sleeping and awake infants and reported that the MMR was more negative when infants are awake. Although the asleep/awake state cannot explain which type of MMR is observed (see table 1 of Chapter 1), it would be interesting to compare the influence of state and sleep stage on infant MMRs, as it is known that adult MMN is greatly decreased when participants are asleep. If the negative MMR resembles adult MMN, it should be affected in a similar way, but if not, such a unique characteristic of infant MMR may help to further understand the underlying neural mechanisms of infant MMRs.

One further unresolved issue concerns the fact that the transition from the positive MMR to the negative MMR appears to occur at different ages for changes in different sound features, including speech sounds (e.g., Dehaene-Lambertz & Pena, 2001; Leppänen 1997, 1999), noise with brief gaps (Trainor et al., 2001, 2003), and tones presented from different spatial locations (Sonnadara et al., 2005). It has been shown in studies by Trainor et al. (2001, 2003) that the transition from positive MMR to negative MMR occurs between 4 to 6 months of age for gap stimuli. However, in studies by Sonnadara et al (2005), it was not until 8 to 10 months that a similar transition was seen for spatial location. Such inconsistent developmental timetables are not totally surprising, given that adult MMN varies in latency and scalp distribution depending on the feature of sound that is modified (e.g., Deouell & Bentin, 1998; Giard et al., 1995). It is also the case that for older children, auditory discrimination matures at different ages for different sound features (for a review, see Werner & Marean, 1996). What is interesting in the results of the MMR studies of infants, is that the maturational timetable for infant MMR for pitch, temporal, and spatial discrimination does not appear to fit neatly into the sequence of behavioural development. Hence, comparing the infant MMR to different sound features in the same infants, and tracking the development of these responses to different sound features in individual infants in a longitudinal design, is needed in order to better understand the mechanism underlying infant MMR.

Infant MMRs to pitch changes are the focus of the current dissertation, but in the literature of adult ERPs, the adult MMN is often followed by the P3a component that reflects involuntary attentional shifts (e.g., Sams et al., 1985; Gaeta et al., 2001). In the results of the present dissertation from Chapter 2 to Chapter 5, we also consistently found a positive component following the negative infant MMR, with a large peak amplitude. A similar component has also been reported by several previous studies (e.g., Leppänen et al., 1997; Pihko et al, 1999; Trainor et al., 2001, 2003). It is possible that this P3a-like positivity is an early phase of the adult P3a (Kunshnerneko et al, 2002), but it is also hard to rule out the possibility that this positivity is part of the positive infant MMR response. One way to approach this question is to test whether this positivity can be generated separately in a situation in which involuntary attention is shifted without the accompaniment of the negative infant MMR.

In Chapter 5, we successfully utilized the negative MMR to study infant pitch perception in harmonically complex tones with missing fundamentals. There are many further important questions regarding infant pitch perception that can be studied in a similar manner, some of which are not easily approachable with traditional behavioural tasks. For example, as reviewed in Chapter 1, pitch information is coded both spatially and temporally throughout the auditory system, but whether both pitch representations develop at the same time or not is currently unknown. With stimuli that can be encoded with only one of these representations, such as very high frequency tones for which pitch can only be encoded spatially or iterated ripple noise for which pitch can only be encoded temporally, such a topic can be investigated in young infants by examining the infant MMR to these stimuli.

Overall, this dissertation has clarified the differences between the different MMR responses and their developmental trajectories, and it has shown that infant MMR provides a powerful tool to look inside the world of pitch perception in early infancy. By examining infant MMRs, we found that brain responses to pitch information change dramatically between 2 and 4 months of age and that pitch perception of harmonic tones with a missing fundamental can be found in infants as young as 4 months of age.

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