3 Event-Related Potential (ERP) Measures in Auditory Development Research

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INTRODUCTION

Between birth and 2 years of age, the human cortex undergoes tremendous development, with region-specific and layer-specific patterns of synaptic maturation, overgrowth, and pruning that are undoubtedly influenced by environmental input and complex patterns of neurotransmitter expression (e.g., Huttenlocher & Dabholkar, 1997; Moore & Guan, 2001). During this period, the newborn, who is totally dependent on caregivers for survival, turns into a walking, talking, thinking, self-aware being. These anatomical and functional changes across development should be reflected *in vivo* in the electrical brain activity that can be measured at the scalp.

In practice, collecting data from infants can be rather difficult. While studies that condition a behavioral response, such as sucking or looking, are probably the most advanced of the techniques available, there remain considerable problems in the type and amount of data that can be collected from preverbal infants with short attention spans and immature motor response systems, especially in the first months after birth. Postmortem studies of brain development can also be problematic because death in infancy is usually associated with abnormalities that may invalidate generalizations to normal development. Many of the imaging techniques available for the study of adult brain responses are difficult to apply to human infants. For example, fMRI and MEG require that the subject remain very still throughout the testing period. It is thus possible to test sleeping infants, but rather difficult to test awake infants (Anderson et al., 2001; Hattori et al., 2001; Souweidane et al., 1999). Furthermore, the loud noise of the MRI machine can be very disturbing and distracting for infants. PET requires the use of radioactive materials, making its use with normally developing infants questionable. Because of

these problems, auditory event-related potentials (ERPs) derived from electroencephalogram (EEG) recordings have been the most popular choice by far for studying functional cortical development in infants (e.g., Segalowitz & Berge, 1995; Steinschneider & Dunn, 2002). However, ERP results are not always consistent from study to study, and there are still many methodological issues to work out.

One of the most surprising findings from the last decade of auditory developmental ERP research is that brain responses to sound are not fully mature until well into adolescence (Albrecht, Suchodoletz, & Uwer, 2000; Čeponiené, Rinne, & Näätänen, 2002; Johnstone, Barry, Anderson, & Coyle, 1996; Pang & Taylor, 2000; Ponton, Eggermont, Kwong, & Don, 2000; Shahin, Roberts, & Trainor, 2004; Trainor, Shahin, & Roberts, 2003). From a behavioral perspective, it has also become clear that sound processing continues to improve through this time period as well (e.g., Neijenhuis, Snik, Priester, van Kordenoordt, & van den Broek, 2002). Nonetheless, the most rapid behavioral strides occur during the first year (Werner & Marean, 1996). Hearing thresholds improve dramatically over the first months after birth, asymptoting at approximately 6 months of age (Tharpe & Ashmead, 2001). Speech processing changes qualitatively. Although infants are able to discriminate speech sounds in the first months after birth, by 10 months infants process speech according to the specific speech sound categories used in the language they are learning (e.g., Pisoni, Lively, & Logan, 1994; Werker & Tees, 1984). Sound localization abilities change from sluggish left-right discrimination in newborns to fast, accurate, within-hemifield discrimination after 4 months (Muir, Clifton, & Clarkson, 1989; Muir & Field, 1979). Nonetheless, the ability to attend to specific sounds, to understand degraded speech, and to understand speech in noise continues to improve into adolescence (Neijenhuis et al., 2002).

Recent work on the structural maturation of human auditory cortex also shows a protracted development. Although maximum synaptic density is reached at 3 months of age in auditory cortex, synaptic elimination continues until about 12 years of age (Huttenlocher & Dabholkar, 1997). Detailed work on the maturation of axonal conduction times reveals a layer-specific developmental timeline. Moore and Guan (2001) compared postmortem auditory cortical tissue from fetuses up to adults 27 years of age. They examined both the presence of cell bodies (using Nissl stain) and the maturation of neurofilaments (using an immuno stain). Immature neurofilaments are associated with small axonal diameter, a lack of myelin sheaths, and therefore slow conduction velocities, leading to sluggish communication between

neurons, and precluding highly synchronized neural activity. Moore and Guan (2001) found that at birth the cell bodies are largely in place, but that only layer I contains mature neurofilaments. Layer I is larger in early infancy than in adulthood, with banding into two sub-layers, compared to the single band in adults. After 4.5 months, mature neurofilaments begin to appear in deeper layers of auditory cortex (lower III, IV, V, and VI), and reach adult levels by about 3 to 5 years of age. Neurofilaments are very late to mature in superficial layers (II and upper III), with no evidence of their presence before 5 years of age; a mature level is not reached until about 12 years of age. Interestingly, primary areas do not mature earlier than secondary and tertiary areas, the same developmental sequence being apparent in areas 41/42 and 22.

The primary input to auditory cortex from thalamus is via pyramidal neurons in lower layer III and layer IV, which develop mature neural filaments between 4.5 months and 5 years of age. Layer II and upper layer III communicate extensively with other cortical areas (Moore & Guan, 2001). Upper layer III and layer II maintain immature synapses for a protracted period, a delay that is presumably important for the development of optimal communication with other cortical areas. Other animals also follow a similar developmental trajectory. For example, in neonatal kittens, the earliest responses from auditory cortex are generated in deeper cortical layers (Konig & Marty, 1974; Konig, Pujol, & Marty, 1972; Miyata, Kawaguchi, Samejima, & Yamamoto, 1982). It is also of interest that a lack of auditory input due to deafness during childhood appears to affect the development of superficial layers to a greater extent than the development of deeper layers in both cats (Kral et al., 2000) and humans (Ponton & Eggermont, 2001).

ERPs measured at the scalp reflect extra-cellular changes in electrical field potentials with cortical depth that are associated with depolarization, hyperpolarization, and firing of neurons (e.g., Mitzdorf, 1985; Vaughan Jr. & Arezzo, 1988). Therefore, the large layer-specific changes in synaptic density and functionality with development outlined above would be expected to result in large changes in measured ERPs across age. This chapter is not intended to be an exhaustive review of the auditory developmental ERP literature, but rather an illustration of how information from different levels of analysis needs to be combined to yield a deeper understanding of developmental processes. We begin with a review of adult auditory ERPs, then examine issues in recording ERPs in infants, and end with a review of ERP development in infants and children in relation to behavioral and anatomical changes.

DEVELOPMENT OF AUDITORY EVENT-RELATED POTENTIALS (ERPS)

What are ERPs?

The voltage difference between an electrode placed at a position of interest on the scalp and a reference electrode placed at a relatively neutral position with respect to the neural activity of interest yields an EEG, a time-varying voltage signal that reflects the activity of many neurons working in concert. Such recordings require the placement of electrodes on the scalp, either singly or embedded in a stretch cap or geodesic wire system, but are non-invasive in the sense that no large magnetic field or radioactive substance needs to be administered. If a stimulus event such as a sound is presented, some of the measured neural activity will reflect the processing of that sound event. This activity is termed the event-related potential (ERP). However, on a single trial, the neural activity not systematically related to the sound event, considered "noise," typically precludes observation of the ERP waveform of interest. Thus, multiple trials of the sound event must be given, the resulting waveforms lined up according to the onset of the sound events, each waveform baselined to a short period preceding the onset of the sound event (typically between 50 and 200 ms), and the waveforms averaged. If the "noise" from neural activity unassociated with the processing of the sound is stationary (i.e., its statistical properties do not change from trial to trial) and is not time locked to the onset of the sound, the noise will tend to average to zero. The number of trials needed to obtain a good representation of the ERP depends on the size of the signal and the size and characteristics of the noise.

An idealized auditory ERP response recorded at the vertex of the head is shown in Figure 3.1. The most common variables examined are the amplitude (in μV) and latency from stimulus onset (in ms) of each peak. During the first 10 ms, there is a series of seven small peaks, known as the auditory brain stem response (ABR). These peaks represent activity from successive subcortical areas, probably from the cochlear nucleus to the thalamus. The middle latency responses occurring during the next 50 ms represent neural activity in auditory cortex. Both the brainstem and middle latency responses require many trials averaged together because these responses are relatively small in amplitude compared to the background noise. The late ERP components follow the middle latency responses, beginning around 50 ms after stimulus onset. The same basic topography is seen whether an average or mastoid reference is used. For auditory stimuli, a P1 (first positive) component is typically seen around 50 ms, an N1b (first negative) component around

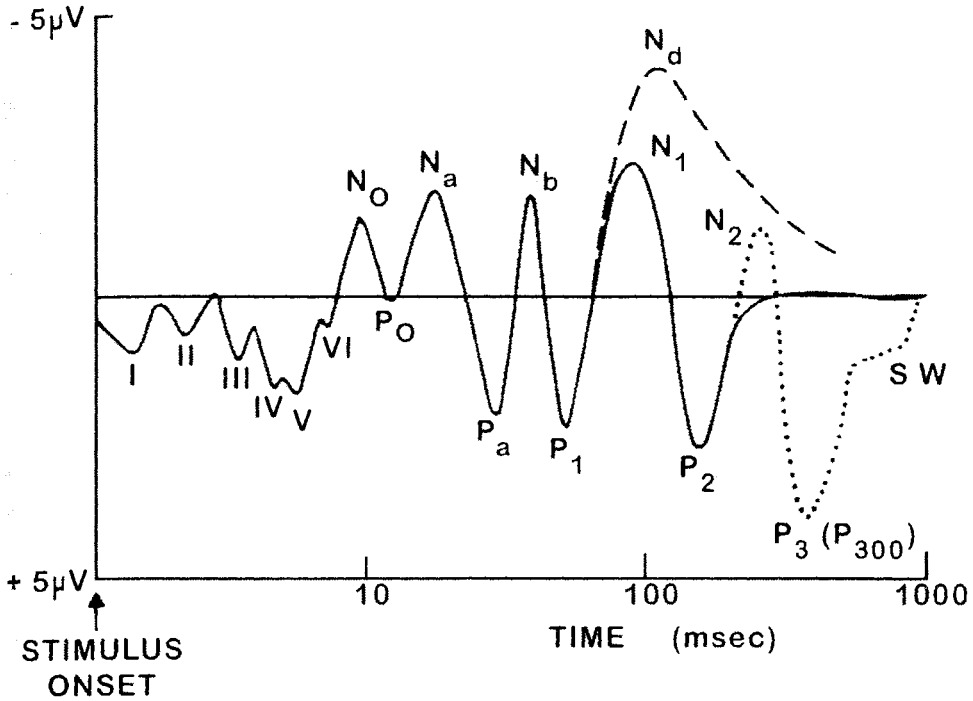

Figure 3.1. A stylized representation of the major ERP components measured at the Cz vertex of the scalp. Waves I to VI of the auditory brainstem response (ABR) occur within approximately the first 10 ms. The middle latency responses (No, Po, Na, Pa, Nb) reflect the first volley of activity into auditory cortex and occur between about 15 and 50 ms. The obligatory late auditory ERP components (P1, N1, P2) follow the middle latency responses. Task- and attention-related components may also be present (N2, P3, Nd, SW). Reprinted with permission from Hillyard and Kutus (1983).

100 ms, and a P2 component around 180 ms. If the listener is attending and performing a task related to the sound, the P2 will be followed by N2, P3, and slow wave (SW) components. A negative Nd component can overlap the N1 and P2 peaks (Figure 3.1).

The relation between ERPs measured at the scalp and their neural generators is complex (e.g., Mitzdorf, 1985; Steinschneider & Dunn, 2002; Vaughan Jr. & Arezzo, 1988). When a neuron fires, an extra-cellular sink is created by the flow of positive ions into the cell, flanked by more positive regions, termed sources. Electric fields are also created by the relatively stationary chemical depolarizations and hyperpolarizations that occur with excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP), respectively. With depolarization, an extra-cellular sink is created and the circuit will be completed with a source above or below the point of depolarization. Conversely, with hyperpolarization, a source is created, with a sink above or below. In order for these fields to be visible at the scalp, the sources and sinks must be oriented perpendicularly to the cortical surface. It is thus believed that cortical ERPs largely measure the activation of pyramidal cells, as these

cells, unlike the cortical stellate cells, are largely oriented in parallel in the optimal direction.

Extra-cellular electrical field patterns depend on a number of complex factors. For example, the locations of passive source returns – the opposite charge countering the effect of the synaptic activity – depend to some extent on how the surrounding networks of cells are connected and active. The strength, timing, and spread of components measured at the scalp depend on properties of electrical field propagation through the brain and other tissue. Indeed, animal studies with multiple electrodes at various depths reveal complex sequences of sinks and sources in various layers (e.g., Fishman, Reser, Arezzo, & Steinschneider, 1998, 2000). Nonetheless, in a simple pyramidal cell model, excitatory synaptic potentials (depolarization) in deeper layers (with the passive current returns in the apical dendrites in superficial layers) will appear as a surface positivity, whereas an excitation in upper layers will appear as a surface negativity (Creutzfeldt & Houchin, 1974; Eggermont & Ponton, 2003; Fishman et al., 2000). Given the orientation of auditory cortex around the sylvian fissure, activity generated in auditory cortex typically appears at the scalp in a dipolar pattern, with fronto-central positivity accompanied by posterior negativity or fronto-central negativity accompanied by posterior positivity.

The relation between ERP components and activation in the brain is further complicated by the fact that cortical components typically reflect the activation of several temporally overlapping generators. For example, P1 is thought to be generated by activity in both primary and secondary auditory cortices (e.g., Liégeois-Chauvel et al., 1994; Ponton et al., 2000; Steinschneider & Dunn, 2002). Importantly, P1 likely represents re-entrant activation either from thalamus or from other cortical areas. N1 has been studied extensively in adults and is known to consist of several subcomponents (Näätänen & Picton, 1987). The vertex-recorded N1, or N1b, is likely generated outside of primary auditory cortex and may represent intra-cortical excitatory input to layer II and upper layer III (Eggermont & Ponton, 2002; Vaughan Jr. & Ritter, 1970). N1 is thought to be associated with conscious detection of discrete sounds and is affected by attention (Hyde, 1997; Woldorff & Hillyard, 1991). The location of the P2 generator is distinct from that of the N1b (Shahin, Bosnyak, Trainor, & Roberts, 2003), and may involve generators closer to primary auditory cortex. In addition, a T-complex can be recorded, consisting of a positivity around 100 ms followed by a negativity, N1c, at around 150 ms. The T-complex is generated in association cortex with a radial orientation, and therefore appears on the scalp at temporal sites (Scherg & von Cramon, 1986). The P1, N1, and P2 components listed above are obligatory in the

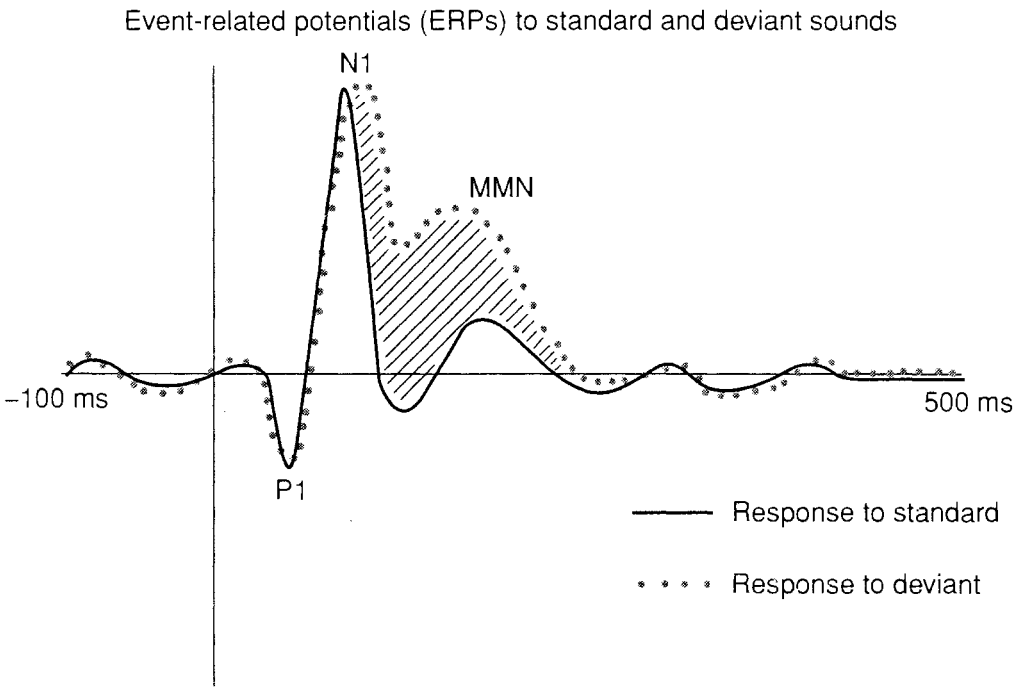

Figure 3.2. A stylized representation of the Mismatch Negativity (MMN). The ERP generated by the occasional deviant stimuli is more negative than that of the standard stimuli between about 140 and 240 ms after stimulus onset.

sense that they do not require the listener to perform a task, although they can be affected by attention.

Although the subcortically generated ABR can be readily recorded in newborns, and is widely used as a screening test for hearing impairment, it is very difficult, if not impossible, to measure cortically generated middle latency responses in young infants (e.g., Stapells, Galambos, Costello, & Makeig, 1988). The amplitudes of the middle latency responses in adults are small; the immaturity of primary auditory cortex in infancy may render the amplitude too small or inconsistent to measure with current technology. Similarly, the late auditory cortical ERP components, although much larger in adults, are also very immature or absent in infancy. In this chapter, we will concentrate on the maturation of these late obligatory ERP components.

Another obligatory auditory component needs to be discussed. In adults, the mismatch negativity (MMN) component peaks between approximately 150 and 250 ms after stimulus onset, depending on the particular stimuli (Näätänen, 1992; Näätänen et al., 2001; Näätänen & Winkler, 1999; Picton et al., 2000; Schröger, 1998). The MMN component is somewhat different from the components listed above because it is only seen in an oddball paradigm in which occasional change trials (deviants or oddballs) occur in a sequence of similar trials (standards) (see Figure 3.2). MMN occurs in

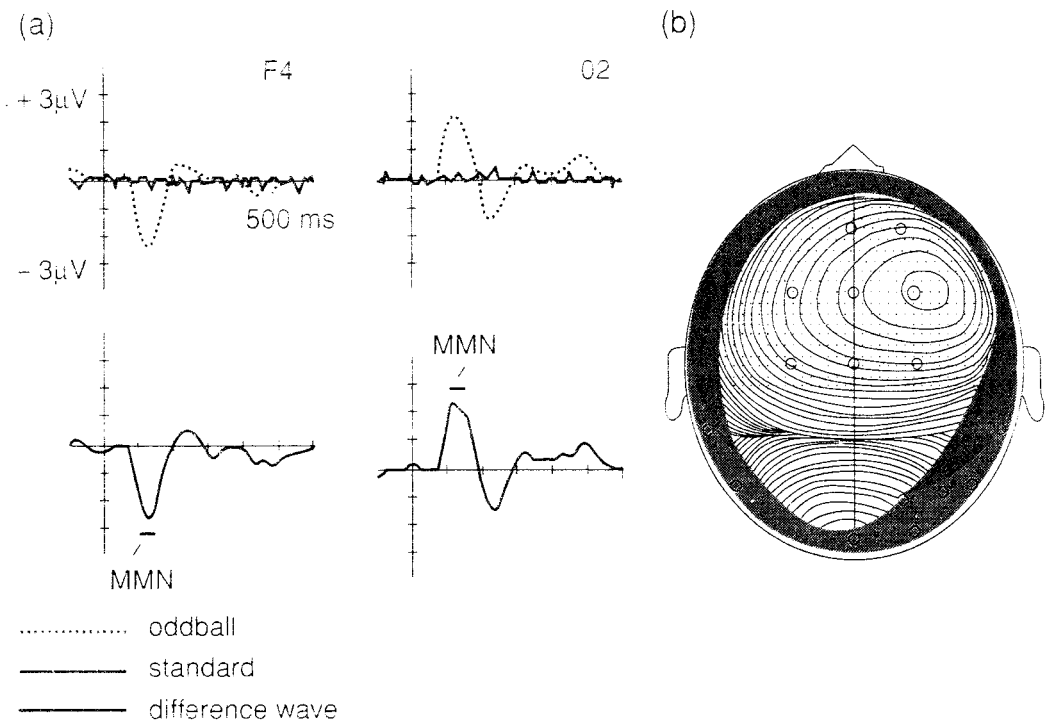

Figure 3.3. Mismatch negativity response in adults to a change in the location of a sine wave tone (1000 Hz, 50 ms; SOA = 104 ms). Standards (90% of trials) were presented in front of the listener and oddballs (10%) from 90° to the left. MMN is often illustrated by the difference wave obtained by subtracting the average ERP generated by the frequent standard stimuli from that generated by the infrequent deviant sound. (A) With the rapid presentation rate, no N1 can be seen in the standard waveforms. However, a prominent MMN is present in the difference waves. Note the reversal in polarity above (right frontal site, F4) and below (right occipital site, O2) the sylvian fissure, consistent with a source in auditory cortex. Bars represent regions of the difference waves that are significantly different from zero. (B) Isovoltage contour map of the MMN peak, showing the right focus of the MMN when the sound changes to a location 90° to the left. Data are from Sonnadara et al. (2006).

response to changes in basic sound features such as frequency, intensity, and duration, as well as to derived sound features such as pitch, timbre, and location (Näätänen et al., 2001; Picton et al., 2000). Initially, MMN was thought to reflect only basic sensory encoding. However, more recent research indicates that MMN also occurs to changes in patterns of sound (e.g., Näätänen et al., 2001; Picton et al., 2000; Trainor, McDonald, & Alain, 2002). N1 and MMN are affected differently by the rate of stimulation, with N1 diminishing in amplitude and MMN increasing in amplitude as the stimulus onset asynchrony (SOA) becomes smaller. Figure 3.3 shows MMN to a change in sound location (Sonnadara, Alain, & Trainor, 2006). The SOA is very short at 104 ms, and the standard waveforms therefore show virtually no N1 component. However, the MMN is readily apparent.

In humans, the detection of changes in different sound features appears to localize to slightly different cortical regions (e.g., Alain, Achim, & Woods, 1999; Alho et al., 1996; Takegata, Paavilainen, Näätänen, & Winkler, 1999). In monkeys, MMN in response to an intensity change is generated in the superficial layers of primary auditory cortex (Javitt et al., 1994), but it is not known whether this generalizes to humans or to other sound features. The MMN component is obligatory in the sense that it occurs regardless of whether the person is paying attention to the sounds. Interestingly, MMN appears to be less dependent on experience during a critical period than is N1b. As such, MMN readily develops in deaf patients fitted with cochlear implants whereas N1b does not (Ponton et al., 2000). These properties have made MMN of great interest to developmental researchers, the hope being that MMN will allow the investigation of auditory discrimination independent from attentional factors in infancy and childhood.

Components following the N1 and P2 are typically greatly affected by the particular task or attentional focus of the listener. For example, the N2 component, which can overlap the MMN, is very small or absent when the participant is not attending (Picton et al., 2000). The frontal P3a component is found when a salient sound in a stream of unattended sounds captures the attention of a listener (Escera, Alho, Winkler, & Näätänen, 1998; Squires, Squires, & Hillyard, 1975); thus, P3a is thought to reflect the inadvertent capture of attention. The parietal P3b component, which can peak anywhere between 300 and 600 ms depending on task difficulty, is typically only clearly present when a participant listens for and identifies a particular sound in a sequence of non-target sounds. An N4 component appears to reflect linguistic semantic mismatch, occurring in response to a sentence such as "He spread the warm bread with socks" (Kutas & Hillyard, 1980).

Researchers are interested in linking stages of processing with particular ERP components (e.g., P1 represents sensory encoding, P3 represents memory updating, N4 represents semantic encoding, etc.), but this linkage is not entirely straightforward. There are a number of reasons for this issue. First, electrical activity will only be visible in the ERP waveform if enough neurons pointing in the same direction have fired synchronously. The percentage of neural activity captured by the ERP waveform is not known, but clearly much goes on in the brain that is never seen through ERP measurement. Second, the generators of the components measured at the scalp must overlap to some extent in time, and perhaps to some extent in brain location as well, adding greatly to the complexity of identifying individual components. Obviously, one component may mask another if it is larger and occurs during the same time period. Worse, a component may be seen at the scalp that does not

actually reflect the activity of any particular neural generator in the brain. For example, if two neural generators individually give rise to similar-amplitude peaks somewhat before and somewhat after 100 ms, their sum will look like a single peak at 100 ms, and a false conclusion may be drawn that there is a single neural process at 100 ms.

To some extent these problems can be overcome through the use of source modeling that takes into account not only the peaks and latencies of components at single electrodes, but also the spatial-temporal distribution of measured activity across the scalp across time (Picton et al., 1999; Scherg, 1990). If the location of a neural generator is known, the propagation of the electrical fields through the brain and skull can be modeled, and a predicted ERP potential derived. Source modeling techniques attempt to reverse this process. Starting with the measured ERP waveforms across time and scalp locations, the sources of activation that would yield that pattern of activity can be estimated. Although in theory, there is no unique solution to the number and locations of the sources giving rise to the observed activity at the scalp, simplification constraints (e.g., a limited number of generators, symmetry between hemispheres) and constraints based on prior anatomical knowledge, perhaps derived from animal studies, often yield reasonable solutions that account for most of the variance in the recorded data. However, as will be discussed below, we are not yet able to perform accurate source modeling with human infants.

ISSUES IN RECORDING ERPS IN INFANTS AND CHILDREN

Getting the Electrodes On and Keeping the Infant Still

The first challenge when recording from infants is to apply the electrodes while maintaining the infant's good mood. The next challenge is to keep the infant still, attentive, and happy during the recording. This task can be easier in younger than in older infants. Once infants reach 5 or 6 months, their behavior becomes more purposeful (e.g., they are more likely to try to remove the electrodes), and more coordinated (and hence more likely to succeed in removing the electrodes). The most challenging period in this regard is between about 1 and 2 years of age. It often works best to have one researcher devoted to keeping the infant distracted with toys, peek-a-boo games, and soap bubbles while one or two other researchers apply the electrodes and run the equipment. Beyond the newborn period, infants are often happiest when held by their mothers. If the infant is on the mother's lap, the mother can also help by holding the infant's hands.

A related issue concerns the number of electrodes that can be applied to the scalp. Obviously, the more electrodes used, the more information that can be collected, and the greater the choice of analysis procedures. However, with systems that require conducting electrogel application and impedance checking for each electrode, it is better to record from only a few electrodes in the interest of increasing signal-to-noise ratios. Because the infant will only cooperate for a short time, the more time that can be spent collecting data rather than applying the electrodes, the better. On the other hand, with high impedance systems, adequate conductivity can be obtained with nets of electrodes imbedded in sponges after the nets are simply dipped in a saline solution. In this case, 128 or even 256 electrodes can be applied in a few minutes. The use of high impedance systems allows for quick application, but such a system is more subject to electrical noise. Which system is most suitable depends on the particular application.

Choosing Reference Electrodes

EEG signals must always be referenced to something. The choice of reference has been discussed at great length in the adult literature over the past few decades (Dien, 1998), with choice locations including the ears, mastoids, nose, and base of the neck. However, as none of these locations is neutral with respect to brain activity, and with the increasing capability of recording simultaneously from many sites, a common average reference is now typical. In this case, a single site reference is used during recording (e.g., the Cz vertex), but during data analysis, the reference (or zero value) for each time point is taken as the averaged activity across all electrodes at that time. If one electrode is bad and hence excluded from the average, the homologous electrode on the other side of the head should also be excluded if hemispheric effects are to be examined. A common average reference works well if about 30 or more electrodes are used and they are spread across the scalp and face, including sites below the sylvian fissure. The activity at each site then reflects whether that site is more positive or more negative than the average. Care must be taken when using a common average reference with infants, however, because sites around the periphery of the cap or net, particularly at the back of the head, tend to be noisy. The cap may fit least well at the back, and infants sometimes flex the muscles at the back of their head because their neck control is poor. If electrodes that capture this muscle activity are included in the common average reference, the data may appear quite noisy. Bad electrodes can be interpolated and replaced, but these estimates will be worst at the periphery because there are fewer surrounding electrodes. It may

be better to discard them from the common average reference calculation, although they are important for modeling the sources of the activations.

When only a few electrode sites are available, a common average reference does not work well (Dien, 1998). In this case, the choice of reference electrode may be different for different applications. For example, in adults, with a common average reference, MMN reflects activity in auditory cortex, which propagates through the brain to produce a negativity at frontal sites and a positivity at mastoid and posterior sites. Thus, if the mastoid sites are used as the reference, the MMN peak at frontal sites will be maximum. However, in this case, it will not be possible to test whether there is a reversal from negative to positive voltage across the sylvian fissure. On the other hand, if Pz (midline parietal site) is used as the reference, this reversal should be apparent.

Artifact Elimination with Children

Measured at the scalp, the electrical signals generated from muscle movement are very large compared to those generated by neurons in the brain. Adults can typically remain still, so the major artifact is usually from eye blinks and eye movements. As adults are instructed to minimize these movements, they tend to be few in number and executed quickly. With infants, verbal instructions are not possible, so other means of keeping infants still must be employed. In studies of automatic processing in which attention is not important, visual stimuli that are not time-locked to the auditory events of interest can be employed. Young infants can sometimes be mesmerized by experimenters performing peek-a-boo games and blowing soap bubbles or by bright shapes appearing and disappearing on a monitor. Older infants and children often like silent cartoons. Infants also have short attention spans, with 15 to 20 min of EEG recording typically constituting a good run, so the fewer trials lost to artifact the better.

However, enchanting the visual stimulation, infant data will likely contain substantial numbers of trials with artifact. The simplest approach is to eliminate these trials. Rejection criteria in adults often focus on eliminating trials in which electrodes around the eyes contain large voltages, or large changes in voltage, as eye blinks and eye movements provide the vast majority of the noise. However, in infants, a wider range of electrodes for rejection may be more appropriate because considerable artifact can come from small movements at the back of the head. There is no simple answer to the question of how large a voltage is needed for a trial to be rejected as containing artifact. If there is a very large number of trials, a few trials with artifact will not change the average substantially. Unfortunately, with infants, there are typically few

trials, and so a few noisy ones can have a large effect. Too strict a criterion, however, may result in most trials being rejected, and the remaining data will also be very noisy because there are not enough trials to average out the brain activation not due to processing the sound event. The amount of noise that can be tolerated will also depend on the size of the components of interest. The larger the component, the more noise that can be tolerated.

Given how precious every trial is in infant data, it would be helpful to develop a technique whereby artifact could be eliminated through signal processing means while keeping all, or most, trials. This procedure is possible with adult data, if ERP eye movement and eye blink responses are recorded separately in each individual subject (see Picton, Lins, & Scherg, 1995). Source models of eye movements and eye blinks can be made, and the modeled activity from these sources eliminated from the data. It is not clear, however, that taking the time to elicit and record infant eye movements and eye blinks would leave enough time for conducting the experiment of interest. Furthermore, this method does not account for artifact from the back of the head due to movement. In addition, we do not yet have a good head model for infants on which to base source modeling (see below), so at the present time, this approach is not possible. However, given how important every trial is in infant data, the development of techniques for eliminating artifact while keeping the trial should be a priority.

Averaging Infant Data

As discussed in the previous section, many similar trials must be averaged together in order to distill out the parts of the ERP waveform that are due to the sound event of interest. This process assumes that the "noise" (i.e., the rest of the brain activity) is stationary, that is, has the same mean and standard deviation statistics throughout the recording session. In adults, the stationary assumption is likely reasonable. However, infants can change their mood dramatically from the beginning to the end of the session, they may be more distracted at the end than at the beginning, they may be more sleepy at certain times than at other times, and there is probably more variance in the latency of their neural responses. All of these changes can alter the nature of the noise. To the extent that the noise is not stationary, the averaging process will be less successful at removing it. Thus, not only do we typically obtain fewer trials from infants, but eliminating noise through the averaging process is probably less effective in infants than in adults. The averaging process also assumes that the ERP generated in response to the sound is the same on every trial. In a young brain with much plasticity and much to learn quickly,

the neural response to a sound event may well change over the course of the study. This point is very important because when we examine an averaged infant ERP waveform and a component appears spread out in time, we are unsure whether the infant takes a long time to perform the operation giving rise to that component, or whether there is simply a lot of noise and latency variation from trial to trial.

Individual electrodes are more likely to become bad part way through a session with infants than with adults because infants squirm. Individual electrodes can also contain artifact on particular trials that does not affect the rest of the electrodes (e.g., if one electrode is temporarily pushed). Normally, with adults, if the data from one electrode contain artifact and should be eliminated on a particular trial, the whole trial is discarded. If enough trials are bad, the electrode is eliminated entirely from the dataset. Similarly, when averaging together different adult participants, only electrodes for which data exist for all participants are included. However, these rules should probably be relaxed somewhat with infant data. First, the sources of the artifact are likely somewhat different and more independent in infants than in adults. Second, because so few trials can typically be obtained in infants, it does not make sense to throw away data from good electrodes when one isolated electrode is bad or, once averaging is complete, to not include an electrode in statistical analyses across participants because that electrode was eliminated in one individual. Additionally, it may be the case that all electrodes should be monitored for artifact, not just eye electrodes. In sum, it is particularly important with infant data to consider carefully all rules for averaging in order to obtain the cleanest signals possible.

Filtering Infant and Child Data

Filtering is important because it can clarify the components of interest and increase the signal-to-noise ratio. As with adult data, a band-pass filter is typically used with infant data. A zero-phase shift filter should be used, or different frequency components can be shifted different amounts in time, and virtually all EEG analysis packages use either a zero-phase shift FIR (finite impulse response) filter, or an IIR (infinite impulse response) filter both forward and backward in order to ensure a zero-phase shift. Adult studies examining late auditory ERP components typically use a bandpass filter of around 0.1 to 30 Hz. The steepness of the filter roll-off (related to the size of the window over which the filtering is done) is of major importance for maintaining the integrity of the data. Although a steep roll-off is desirable from the perspective of signal-to-noise ratio, very steep filters can introduce

ringing artifact into the signal. Furthermore, the software associated with different EEG analysis packages specify filters in different ways, so care must be taken when comparing data collected and analyzed in different systems. For example, in some systems the cutoff frequency is specified (the frequency beyond which filtering begins), and the roll-off is expressed in dB/octave (i.e., intensity decrease per doubling of frequency). In other systems, a pass band and stop band gain are expressed in percentage (e.g., a pass band gain of 95% passes 95% of the power over the pass band frequencies; a stop band gain of 5% only passes 5% of the power over the frequencies that are almost entirely filtered out), and roll off is expressed in linear Hz units (e.g., 20 Hz to 40 Hz), which specifies the frequency region over which the signal goes from 95% to 5% power.

There are additional issues that need to be considered with respect to infant data. Infant data often contain very slow wave components. If these are of interest, the cutoff frequency for the high pass filter should be fairly low (e.g., 0.1 Hz). However, these slow waves may obscure the faster components of interest, such as MMN. The faster components will be more apparent if the high pass filter has a higher cut off (e.g., 1 or 3 Hz, depending on the speed of the component of interest; see Figure 3.4). Thus, in choosing the cutoff frequency, it is important to examine the frequency characteristics of the components that are to be analyzed.

Performing Statistics on Individual and Group Waveforms

The most common group statistical analyses of developmental ERP data use the amplitude or latency of a particular component as the dependent variable. If the question of interest is whether the component is present or not, the mean and standard deviation of the peak amplitude can be analyzed using a t-test to see whether the mean is significantly different from zero. A generalization of this procedure is to perform a t-test at every time point across the entire epoch from the onset of the sound. Although this approach is very common, it does involve a large number of t-tests (for a 500 ms epoch with a sampling rate of 500 Hz, this is 250 t-tests) and, therefore, a large probability of false positives. With this in mind, most researchers look for a series of adjacent time points surrounding a peak of interest that are all significantly different from zero before concluding that the component is reliably present. Such a procedure can be formalized through the use of Monte Carlo simulations to determine how many adjacent time points are necessary to achieve a particular significance level (e.g., $p = 0.05$ or $p = 0.01$). An alternative to the multiple t-test approach is to determine the latency of a peak in the grand average

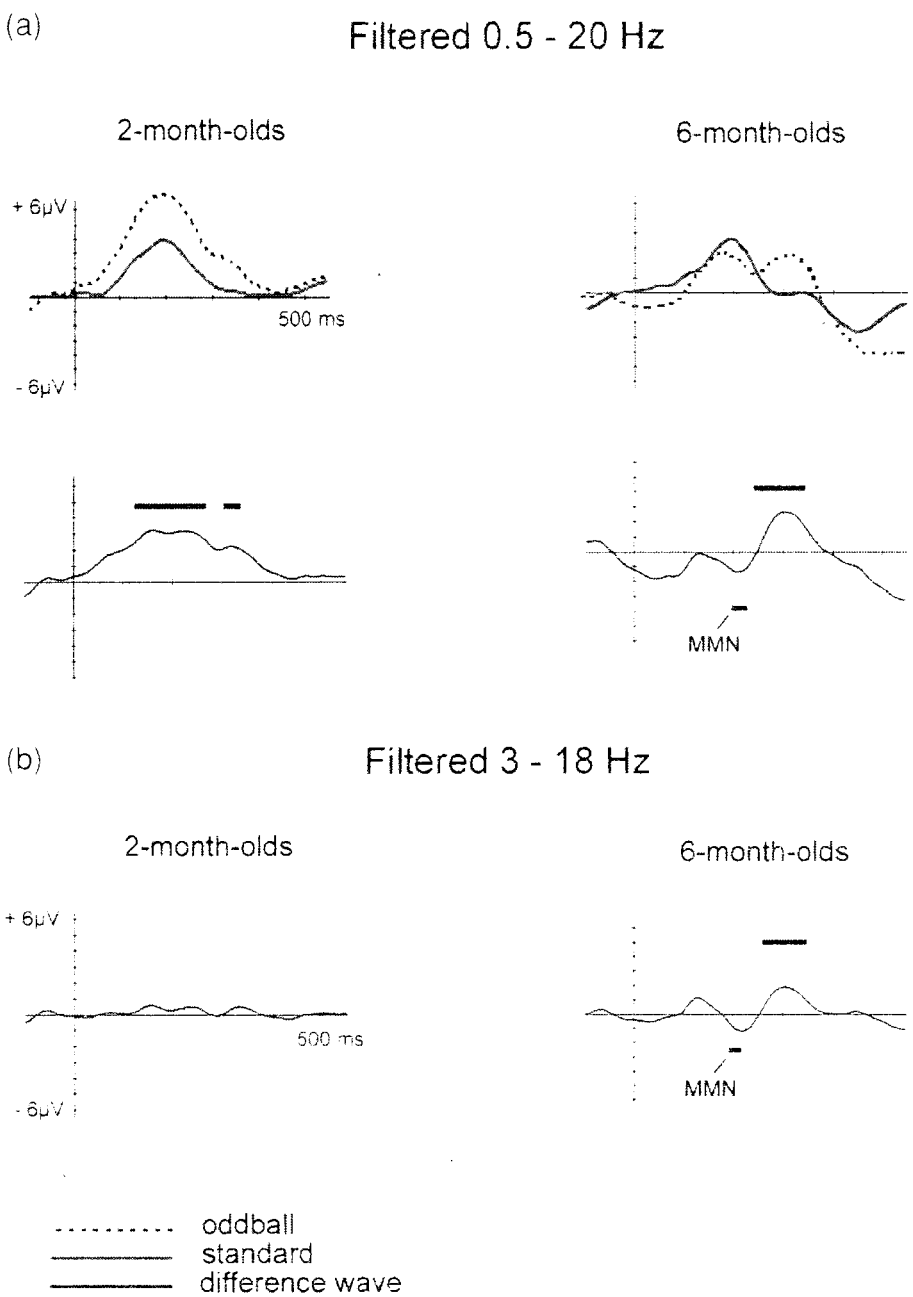

Figure 3.4. Responses from 2-month-old and 6-month-old infants at a right frontal site (F4) to standard (80%) tone pips (Gaussian-enveloped 2000 Hz sine tones) and occasional oddball (20%) tone pips (matched in overall intensity) containing short silent intervals of 12 or 16 ms. Bars represent regions of the difference waves that differ significantly from zero. (A) Standard, deviant, and difference waves are shown filtered between 0.5 and 20 Hz. Note that in 2-month-old infants, oddball waveforms are more positive than standard waveforms, whereas 6-month-olds show a significant negative difference (MMN) and the following positive difference. (B) When the data are filtered between 3 and 18 Hz no components are apparent in the difference wave at 2 months, but MMN and P3a remain at 6 months, indicating that no significant fast components are present at 2 months. Data are from Trainor, McFadden and colleagues (2003).

waveform (the average of all subjects), take a region around this peak, (e.g., 20 or 50 ms on each side), and calculate the area under the ERP waveform across this time period for each subject. These measures then form the dependent variable for a single t-test. For both approaches, Analysis of Variance (ANOVA) can be used to examine other independent variables, such as different test conditions, sex, age, and so on, although care must be taken to normalize data where appropriate. If more than one electrode is being analyzed concurrently, the electrode site may be entered as a variable in the ANOVA. However, for large numbers of electrodes, false positive errors will tend to be high. One alternative is to average several nearby sites (e.g., left frontal, right frontal, left posterior, right posterior) to reduce the number of levels in the electrode site variable. If the measure of interest is the overall strength of a component, global field power is a good approach. In this case, at every time point, the average of the square of activation across all electrodes is taken. Global field power across time is calculated by taking the square root of this value at each time point. The global field power waveform will contain only positive values, and the overall strength of a component will be reflected in the size of its peak.

One significant problem encountered by developmental researchers in analyzing infant ERP data is the large amount of variation from infant to infant. There are likely many reasons for this variation. First, infant data are inherently more noisy than adult data, as discussed above. More importantly, however, there are tremendous individual differences in the age at which infants reach various developmental milestones. For example, some infants speak in sentences soon after their first birthday, while others do not do so until three years of age. ERP waveforms change dramatically over the first year after birth (see below). Given that infants of a particular age demonstrate large differences in brain maturation, they would be expected to produce very different ERP waveforms. In some cases, the differences can be seen mainly in terms of the latencies of the components. In less severe cases, latency variation will simply result in the grand average peaks looking smaller and more spread out than in individual infants. In more severe cases, where the peaks of a component may appear to vary by 100 ms or more across infants, it is difficult to determine with certainty that the same component is present across infants, and the grand average waveform will tend to be flat with no statistically significant regions. In the worst case, different infants appear to produce completely different waveforms, with some infants showing a positivity during the same time period at which others demonstrate a negativity (Kushnerenko et al., 2002; Trainor, McFadden et al., 2003). In such cases, it is difficult to determine with certainty whether the individual waveforms

represent noise, or whether they represent very different stages of cortical maturation. Several approaches to this problem are possible. One approach is to test infants multiple times. If test-retest reliability is good, then it can be assumed that the individual differences are real and reflect different cortical maturation. A second approach is to try to relate the individual differences to other variables such as performance on a behavioral test. A third approach is to conduct longitudinal studies and show that all infants go through the same stages of ERP waveform development, but do so at different ages. For the field to progress, studies are needed that outline basic ERP development and individual differences across the first years of life.

ERPs hold the potential to provide diagnostic tools for determining perceptual/cognitive problems earlier than can be determined with behavioral testing. For this possibility to become a reality, the reliability of ERP components in individual infants needs to be assessed. Statistical tests can only be performed when multiple samples are available in order to estimate the variance of the dependent variable. One approach to obtaining measures in individual infants is to use t-tests as noted above, but with individual trials within a single subject.

In sum, analysis of infant data presents a challenge because of the small number of trials, inherent noise, and large individual differences between infants. The field will not progress rapidly until these challenges are met and systematic methods of data analysis become routine.

PCA and Source Modeling with Infant Data

Because the identification of components and the association of them with brain processes are fraught with difficulties as discussed above, some researchers have taken a more atheoretic approach to the analysis of infant data. For example, Molfese and Molfese (1985) have used principal component analysis to identify factor waveforms that together account for a high percentage of the variance in the original ERP waveforms. Although each principal component waveform may not correspond to a single identifiable process in the brain, they have been used to predict, for example, which infants will have above and below average language performance at 5 years of age (Molfese & Molfese, 1997), and which infants will become dyslexic, poor, or normal readers at age 8 (Molfese, 2000).

As it becomes more common to obtain data from 128 or even 256 channels in infants, data analysis techniques that take into account spatio-temporal properties of the ERP waveforms will also become more common. In its simplest form, isovoltage contours (i.e., lines joining positions on the scalp with equal voltage amplitude taken at a particular time point such as the

peak of a component) can illustrate the center and extent of activation on the scalp for different components (see Figure 3.3). Current source density contours are obtained by approximating the spatial derivative of the scalp field, and give information about the effective sources and sinks in the radial direction (see Picton et al., 1995 for a discussion). Techniques for estimating the location and direction of the sources of activation in the brain that give rise to the potentials seen at the surface of the scalp are being refined (e.g., Picton et al., 1999; Scherg, 1990), and often work quite well for adult data, especially for earlier ERP components that result from few sources of brain activation. However, at present it remains difficult to perform source analysis with infant data. Infant data do tend to be noisy, but the major limitation is that a good head model for infants is not yet available. In particular, the fontanels are still open in infants, which will have a considerable effect on how electrical fields propagate to the scalp (Flemming et al., 2005). Furthermore, as with many developmental processes, the age at which the fontanels close is variable across infants, so an individual structural MRI scan might be necessary for accurate source fitting. Despite these difficulties, it is imperative that source models be developed for infants as, to date, EEG is the main technique we have for studying the infant brain in action.

DEVELOPMENT OF ERP RESPONSES TO SOUND IN INFANCY

Basic Components of the Infant ERP Response

Auditory ERPs change dramatically across the first months after birth. The newborn response to speech sounds and tones is dominated by large, slow, positive waves, and shows little of the complex series of positive and negative deflections seen in the adult waveform (Kurtzberg, Hilpert, Kreuzer, & Vaughan Jr., 1984; Kushnerenko et al., 2002b; Kushnerenko et al., 2001a; Molfese & Molfese, 1985; Novak, Kurtzberg, Kreuzer, & Vaughan Jr., 1989; Thomas & Lykins, 1995; Thomas et al., 1997). In response to a sound, newborns show a large positivity at fronto-central sites beginning about 100 ms after stimulus onset and peaking around 250 to 300 ms. With a mid occipital reference site, coincident with this positivity, mastoid and temporal sites show a small negativity (Novak et al., 1989). As age increases, the negativity between 100 and 400 ms at temporal sites becomes more positive, with virtually all 3-month-old infants showing a positivity in response to sounds across frontal, central, and temporal regions. Following this widespread positivity, a negative slow wave is apparent between about 400 and 800 ms.

The positive wave is reported to dominate infant auditory ERPs between 2 and 4 months of age (Friederici, Friedrich, & Weber, 2002; Thomas et al.,

1997; Trainor, McFadden et al., 2003; Figure 3.4). However, several studies report a negative trough in the positive slow wave by 3 or 4 months of age, leading to two positive peaks. Novak et al. (1989) reported peaks at 160 and 300 ms to speech syllables; Kushnerenko et al. (2002a) reported peaks at 150 and 350 ms to complex tones; Dehaene-Lambertz and Dehaene (1994) reported peaks at 220 and 390 ms to speech syllables; and Dehaene-Lambertz (2000) reported peaks at 176 and 328 ms to tones, and at 258 and 402 ms to speech syllables. The negative trough suggests that there may be overlapping processes, although it is not clear where or in what layers these processes may be generated. The large variance in peak latency across studies is not related to the stimulus or to stimulus onset asynchrony (SOA) in any obvious way. The question also arises as to why some studies report a double peak while others do not. As discussed above, infant waveforms can be highly variable. It is possible that the variance in peak latency across individual infants obscures the presence of a double peak in some grand average waveforms. In fact, most reports only include figures of grand average waveforms, likely because individual infant data tend to be rather noisy. However, Kushnerenko et al. (2002) include both grand average and individual data, even if it is only from 4 of the 15 infants in the study. For these 4 infants, the presence of two positive peaks can be seen in the individual traces at 2 to 4 days and at 3 months, but a double peak cannot be seen in the grand averages until 6 months. In general, it is possible that much ERP development is not currently seen because latency variation obscures it in the grand average waveforms, and individual traces are too noisy.

By 6 months, there are clear faster components present (e.g., Kushnerenko et al., 2002a; Novak et al., 1989; Trainor, Samuel, Desjardins, & Sonnadara, 2001), likely reflecting the presence of more mature, faster synaptic connections (Moore & Guan, 2001). However, the waveforms still do not resemble those of adults. As will be outlined below, adult waveforms are not fully achieved until well into the teenage years.

Development of MMN in Infancy

Recent infant auditory ERP research has been dominated by studies of mismatch negativity (MMN). Because MMN reflects the brain's response to change, it appears to be an ideal component for the study of infants' perception of, encoding of, and memory for sound features. MMN also appears well suited for the study of discrimination, categorization, and learning of linguistic and musical sounds. Indeed, studies of preterm to 12-month-old infants report MMN responses to changes in duration (Friederici et al., 2002; Kushnerenko et al., 2001b; Leppänen, Pihko, Eklund, & Lyytinen, 1999;

Trainor et al., 2001; Trainor, McFadden et al., 2003), pitch (Alho et al., 1990; Čeponiené et al., 2002; Dehaene-Lambertz, 2000; Leppänen, Eklund, & Lyytinen, 1997; Morr, Shafer, Kreuzer, & Kurtzberg, 2002), and phonemic identity (Cheour et al., 1997; Cheour et al., 1998; Cheour, Leppänen, & Kraus, 2000; Dehaene-Lambertz, 2000; Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz & Dehaene, 1994).

However, an examination of the literature indicates that very different-looking components are being labeled as MMN. Some studies report an increased negativity to occasional deviant stimuli, as is the case with adults (Alho et al., 1990; Čeponiené, Kushnerenko et al., 2002; Cheour et al., 1997; Cheour et al., 1998; He, Hotson, & Trainor, 2007; Kushnerenko et al., 2001a; Morr et al., 2002; Pang et al., 1998; Trainor et al., 2001). However, where individual data are shown, these negativities are highly variable (e.g., Cheour et al., 1998), and the presence of MMN is defined in rather different ways in different studies. For example, in a study of vowel discrimination, Cheour et al. (1998) defined MMN as "a negative deflection peaking between 200 and 500 ms in the difference waves" (p. 222). With this broad definition, individual differences were large, and it was thus impossible to perform statistics on group averages. Rather, the authors report that 9 out of 11 preterm, and 8 out of 12 full term, infants met this criterion for demonstrating MMN. On the other hand, Cheour-Luhtanen and colleagues (1995) report greater consistency across infants, with statistically significant MMN to vowel change in newborns at 200 ms. Kushnerenko and colleagues (2001a) report two negativities in the difference waves to changes in consonant duration, one at 150 ms (similar to adults) and the other at 350 ms. They report that all newborns showed at least one of the two negativities. Čeponiené and colleagues (2002b) also report two negativities in the difference waves to changes in the frequency or duration of complex tones. Kushnerenko and colleagues (2002a) defined MMN in their study of pitch change as "the largest negative deflection in the difference waveform between 80 and 300 ms after stimulus onset, greater than the average baseline voltage by 1.0 μV at any two of the four fronto-central electrodes" (p. 1844). By this definition, 10 of the 12 infants showed MMN at birth, but 3 of these infants did not have a MMN at 3 months, and another 3 infants did not have a MMN at 6 months, leading to the conclusion that MMN is inconsistent at best. With infants 6 months of age and older, the studies seem to be somewhat more consistent, with the majority reporting an MMN around 200 ms (e.g., Cheour et al., 1998; Morr et al., 2002; Pang et al., 1998; Trainor et al., 2001).

Perhaps most surprising is that a number of studies report increased positivities to occasional changes in a sequence of sounds in infants (Dehaene-Lambertz, 2000; Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz &

Dehaene, 1994; Dehaene-Lambertz & Pena, 2001; Leppänen et al., 1997; Leppänen et al., 1999; Morr et al., 2002). For example, in a series of studies examining 4-month-olds' vowel discrimination, Dehaene-Lambertz and colleagues report that changes in a repeating vowel result in an increased positivity around 400 ms (Dehaene-Lambertz, 2000; Dehaene-Lambertz & Baillet, 1998; Dehaene-Lambertz & Dehaene, 1994). Friederici and colleagues (2002) report a significant increase in positivity between 400 and 600 ms in 2-month-olds in response to an increase in vowel duration. The increased positivity was followed by an increased negativity between 800 and 1000 ms. Trainor, McFadden and colleagues (2003) reported an increase in positivity around 150 to 400 ms in 2- to 4-month-olds to the insertion of a 16-ms silent gap in tone pips. Leppänen et al. (1999) reported a positive difference between 130 and 400 ms to a change in vowel duration in newborns and a positive difference between 250 and 350 ms to a change in pitch (Leppänen et al., 1997). He et al. (in press) also report a positive difference in the same time range to a pitch change in 2-month-olds.

How can one make sense of these seemingly contrary findings, with some studies reporting mismatch negativities and others reporting "mismatch positivities"? To answer this question, consideration needs to be given to data collection methods, analysis techniques, and the special challenges posed by infant data. Sleep state of the infant (Friedrich, Weber, & Friederici, 2004), task difficulty (Morr et al., 2002), and neurological condition of the infant (Cheour et al., 1999; Čeponiené et al., 2002; Leppänen et al., 2004; Pihko et al., 1999) have all been proposed as possible explanations; however, in a review of the literature, He, et al. (2007) found that none of these factors can explain the inconsistencies across studies. Part of the problem undoubtedly arises because infant data are so variable, and the results obtained will depend greatly on the criteria by which infants are included and excluded from the analysis. In many studies, more than half the infants tested are excluded because the data are too noisy. Obviously, this point raises questions as to how generalizable the data are, and underlines how very important it is that better testing and analysis methods for infants are developed so that cleaner individual ERP data can be obtained.

It is also possible that the positive and negative difference components represent different processes that emerge at different ages (see He et al., 2007, for a detailed discussion). As discussed above, infant data, particularly during the earliest months, are dominated by slow wave activity, which may obscure the presence of faster components of interest. To separate slower and faster components, filtering techniques can be useful. For example, by filtering their 6-month-olds' gap-detection data between 3 and 18 Hz, Trainor and colleagues

(2001) found significant MMN that resembled that of adults. When they applied the same filter to their 2-month-old gap-detection data (Trainor, McFadden et al., 2003), they were unable to see any fast negative components (Figure 3.4). Furthermore, they found that the waveforms of 3- and 4-month-olds were more variable than those of 2- or 6-month-olds. At 3 months, 31% of infants showed the 6-month pattern, whereas at 4 months, 58% of infants showed the 6-month pattern. These results suggest that both the increased positivity and the increased negativity reported in different studies may be real, but represent different neural processes that overlap in time.

A further complication is that different sound features may show different developmental trajectories, with adult-like negativities emerging at different ages for different sound features. Although fewer than half of the 3-month-olds in Trainor, McFadden et al. (2003) showed a negativity around 200 ms to a temporal deviant, He et al. (2007) found that virtually all 3-month-olds showed an MMN-like negativity to a change in pitch (Figure 3.5). Under a filter setting of 3–20 Hz, they found that MMN emerged between 2 and 4 months of age, with increases in the amplitude and decreases in the latency of the MMN with increased age (Figure 3.5). Under a filter setting of 0–3 Hz, they found that the slow positive difference wave was significant at 2 and 3, but not at 4 months of age. Interestingly, at 3 months, both the slow wave response and the MMN response were clearly present, again suggesting that these components represent different neural processes.

The neural generators of the slow positive waves seen in young infants remain unclear. However, given the immature state of neurofilament expression in all layers except layer I, and the temporal spread of the ERP response, it may be that the response reflects EPSP or IPSP rather than action potentials. According to a simple model, a surface positivity could reflect either a sink associated with an EPSP with a more superficial passive circuit-completing source, or it could reflect a superficial IPSP. Given that only layer I contains mature neurofilament expression, and that layer I is increased in thickness in early infancy (Moore & Guan, 2001), another possibility is that this response in infants involves layer I.

In monkeys, MMN involves the depolarization of apical dendrites in superficial layer II creating a sink, accompanied by a passive circuit-completing source in layer III (although an active source representing recurrent inhibition in layer III may also be involved; Javitt et al., 1994). A similar process may take place in young infants. However, the immaturity of these layers makes it difficult to see how an MMN of similar latency to that of adults could be generated. Alternatively, mature microfilaments in deeper cortical layers begin to develop after 4.5 months of age (Moore & Guan,

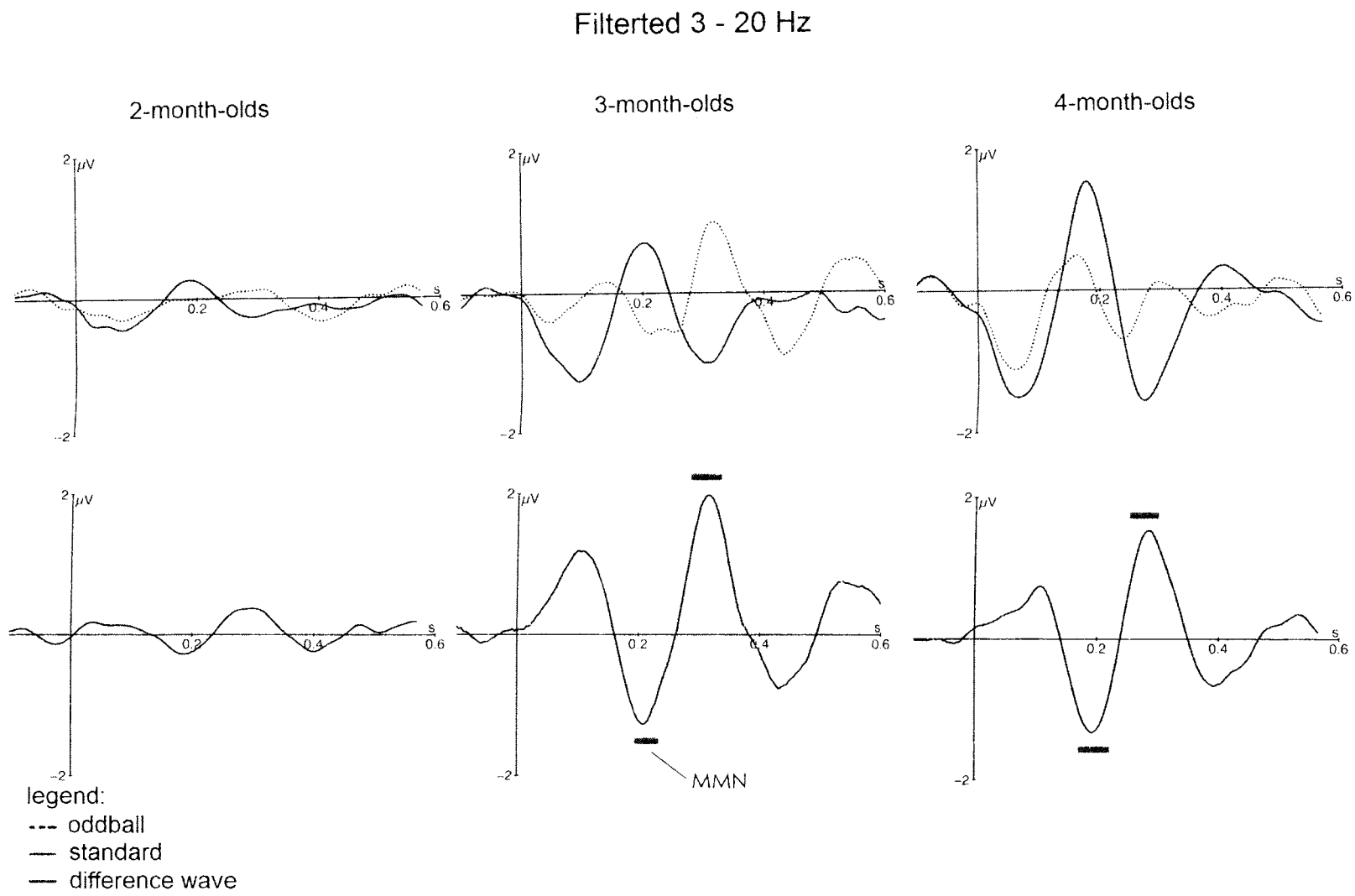

Figure 3.5. Responses from 2-, 3-, and 4-month-old infants at a central frontal site (Fz) to a piano tone with standard pitch (80%) and a deviant pitch (20%). Bars represent regions of the difference waves that differ significantly from zero (filtered between 3 and 20 Hz). Note that by 3 months of age a robust MMN is present, which gets larger and earlier by 4 months of age. Data are from He, Hotson, and Trainor (2007).

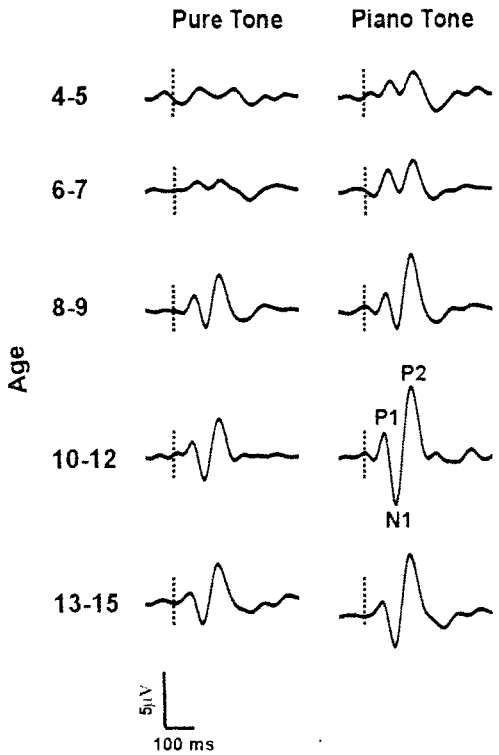

Figure 3.6. Late ERP responses of children between 4 and 15 years of age to a pure tone and piano tone. N1 and P2 emerge after 4 years of age and reach a maximum around 12 years. Responses to the spectrally rich piano tone are larger than to the sine tone. Data are from Shahin et al. (2004).

2001), so another possibility is that the infant MMN response somehow involves sources in deeper layers (Trainor, McFadden et al., 2003). It remains for future work to sort out which of these mechanisms is involved in the various MMN responses reported in the literature. Part of this process will be to test at what ages and under what specific stimulation conditions increased positivities and increased negativities are consistently seen, but developmental animal models will likely be of greatest utility.

DEVELOPMENT OF P1, N1, AND P2 RESPONSES TO SOUND IN CHILDREN

A number of studies indicate that the basic P1/N1/P2 complex continues to develop well into adolescence. Figure 3.6 shows ERP responses to musical tones between 4 and 15 years of age. In general, P1 is present early on but decreases in latency well into the teenage years (Kraus et al., 1993; McArthur & Bishop, 2002; Ponton et al., 2000; Sharma, Kraus, McGee, & Nicol, 1997; Shahin et al., 2004; Trainor, Shahin et al., 2003). The vertex N1b cannot be seen in children younger than 6 years of age unless a slow stimulation rate is used (Čeponienė et al., 2002b; Pang & Taylor, 2000; Ponton et al. 2000; Shahin et al., 2004; Trainor, Shahin et al., 2003). N1b increases in amplitude until about 10 to 12 years of age, and then decreases until adult levels are reached

in the late teenage years. N1b also decreases in latency with increasing age (Johnstone et al., 1996; Kraus et al., 1993; Ponton et al., 2000; Sharma et al., 1997). The T-complex and associated N1c components, seen at temporal leads, appear to mature earlier than the N1b, and they decrease in latency and amplitude between 6 and 12 years of age (Gomes et al., 2001; Pang & Taylor, 2000). Less work has been done on the P2, but it appears to follow the development of the N1b (Johnstone et al., 1996; Shahin et al., 2004; Trainor, Shahin et al., 2003). Furthermore, as can be seen in Figure 3.6, N1 and P2 are more clearly elicited by the piano tones than the pure tones, suggesting that learning, familiarity, and/or greater spectral complexity affect this maturation.

The P1 latency decrease is likely due to its overlap with the emerging N1b, and not primarily a change in the P1 process itself. MMN also appears to change relatively little after 6 years of age (Kraus et al., 1993). Thus, the major ERP changes between 6 years and adulthood involve the N1b/P2 complex. In adults, N1b is associated with recurrent activation in the superficial layers (II and upper III; Eggermont & Ponton, 2003; Fishman et al., 2000; Mitzdorf, 1994). These layers do not begin to show mature microfilament expression until after 6 years of age, and do not reach adult levels until about 12 years of age (Moore & Guan, 2001). Therefore, the age ranges coincide over which N1 develops and layers II and upper III mature. Furthermore, the generation of N1b is associated with input from other cortical areas. As this input may be coming from regions undergoing protracted maturation, such as frontal areas, it makes sense that layers II and upper III maintain protracted plasticity. Furthermore, the N1 component is modulated by attention, an executive function that has a long developmental period. The evidence strongly suggests, then, that N1b emerges with the maturation of neurofilaments in superficial layers and allows such behaviors as sophisticated auditory attention, deciphering degraded signals, and hearing signals in noise. Interestingly, musicians show larger amplitude N1m (N1 measured with MEG) than non-musicians, and the N1m amplitude is greater the earlier they began lessons (Pantev et al., 1998). Furthermore, the increase is specific to the timbre of their instrument of practice (Pantev et al., 2001).

Less work has been done on the P2 component. Of great interest is the fact that P2 amplitude is affected by specific experience, even in adulthood, whereas N1 amplitude appears relatively stable in adulthood (Bosnyak, Eaton, & Roberts, 2004). P2 responses to musical tones are larger in musicians than in non-musicians (Shahin et al., 2003), and frequency discrimination training in adulthood increases the P2 response for the trained frequencies (Bosnyak et al., 2004), as does speech sound discrimination training (Tremblay et al., 2001). Furthermore, children as young as 4 years of age

who are beginning Suzuki music lessons show larger P2 responses than non-musician children (Shahin et al., 2004). The difference in N1b and P2 plasticity in adulthood is not yet understood. However, some studies locate N1b activity primarily in the planum temporale (secondary auditory cortex), but P2 activity closer to primary areas (see Eggermont & Ponton, 2002), and the latter areas may retain more plasticity than the former. In any case, the dramatic development of the N1/P2 complex through childhood allows for the emergence of very sophisticated auditory processing by adulthood.

SUMMARY

Although developmental ERP data are still limited by recording and analysis problems, and indeed there are some discrepancies across studies, it is clear that ERPs change from predominantly slow positive waves in the newborn to the complex series of faster components seen in the adult. Furthermore, the layer-specific maturation of cortex, with mature connections beginning in deeper layers after 4.5 months, and in superficial layers after 5 years, can be linked in a meaningful way not only to the emergence of ERP components, but also to the behavioral competencies of the child. A complete review of the developmental literature is beyond the scope of this chapter. However, ERPs are now being used to address many interesting developmental questions including how basic sound properties are encoded, how speech sounds are encoded, how attention develops, how words are learned, how foreign languages are processed, and how music is learned.

At the same time, in order for the ERP field to advance, more attention will have to be paid to how ERPs can better be recorded in infants and young children in order to maximize the number of trials obtained and minimize the artifact present. Careful attention to referencing, artifact rejection, averaging, and filtering can enhance signal-to-noise ratios. Ultimately, however, new recording and/or signal processing techniques need to be developed to ensure that results are reliable and replicable.

Finally, auditory ERPs hold great promise in the clinical diagnostic realm (e.g., Escera, Alho, Schröger, & Winkler, 2000; Hyde, 1997; Leppänen & Lyytinen, 1997). Beyond simply identifying hearing loss, ERPs recorded in newborns have been shown to predict, for example, reading competency at 8 years of age (Molfese, 2000). ERPs are of particular interest because different components in the waveform are associated with different stages of processing. Therefore, abnormalities in particular components may not only diagnose that a problem exists, but also elucidate the nature of the problem and indicate the type of remediation that is most likely to be effective. For

example, Connolly, D'Arcy, Newman, and Kemps (2000) have shown that different components are associated with phonological and semantic stages of word processing. However, reliable measurement and interpretation of individual ERPs are critical issues for clinical tests. It remains difficult to distinguish between normal variation in the age at which ERP component milestones are reached and pathological conditions in which normal adult development will never be realized. Thus, much work on developmental norms needs to be done before ERP measures can become standard clinical tests. However, despite current limitations, ERPs are expanding the nature of questions that we can ask about complex developmental processes, and their use is likely to increase greatly in the future.

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References

Alain, C., Achim, A., & Woods, D. L. (1999). Separate memory-related processing for auditory frequency and patterns. *Psychophysiology, 36*, 737–744.

Albrecht, R., Suchodoletz, W., & Uwer, R. (2000). The development of auditory evoked dipole source activity from childhood to adulthood. *Clinical Neurophysiology, 111*, 2268–2276.

Alho, K., Sainio, K., Sajaniemi, N., Reinikainen, K., & Näätänen, R. (1990). Event-related brain potentials of human newborns to pitch change of an acoustic stimulus. *Electroencephalography and Clinical Neurophysiolology, 77*, 151–155.

Alho, K., Tervaniemi, M., Huotilainen, M., Lavikainen, J., Tiitinen, H., Ilmoniemi, R. J., Knuutila, J., & Näätänen, R.et al. (1996). Processing of complex sounds in the human auditory cortex as revealed by magnetic brain responses. *Psychophysiology, 33*, 369–375.

Anderson, A. W., Marois, R., Colson, E. R., Peterson, B. S., Duncan, C. C., Ehrenkranz, R. A., Schneider, M. P. H., Gore, J. C., & Ment, L. R., et al. (2001). Neonatal auditory activation detected by functional magnetic resonance imaging. *Magnetic Resonance Imaging, 19*, 1–5.

Bosnyak, D. J., Eaton, R. A., & Roberts, L. E. (2004). Distributed auditory cortical activations are modified when nonmusicians are trained at pitch discrimination with 40-Hz amplitude modulated tones. *Cerebral Cortex, 14*, 1088–1099.

Ceponiené, R., Kushnerenko, E., Fellman, V., Renlund, M., Suominen, K., & Näätänen, R. (2002a). Event-related potential features indexing central auditory discrimination by newborns. *Brain Research: Cognitive Brain Research. 13*, 101–113.

Čeponiené, R., Rinne, T., & Näätänen, R. (2002b). Maturation of cortical sound processing as indexed by event-related potentials. *Clinical Neurophysiology, 113*, 870–882.

Cheour, M., Alho, K., Sainio, K., Reinikainen, K., Renlund, M., Aaltonen, O., Eerola, O., & Näätänen, R.., et al. (1997). The mismatch negativity to changes in speech sounds at the age of three months. *Developmental Neuropsychology, 13*, 167–174.

Cheour, M., Čeponiené, R., Hukki, J., Haapanen, M. -L., Näätänen, R., & Alho, K. (1999). Dysfunction in neonates with cleft palate revealed by the mismatch negativity. *Electroencephalography and Clinical Neurophysiology, 110*, 324–328.

Cheour, M., Čeponiené, R., Lehtokoski, A., Luuk, A., Allik, J., Alho, K., & Näätänen, R., et al. (1998). Development of language-specific phoneme representations in the infant brain. *Nature Neuroscience, 1*, 351–353.

Cheour, M., Leppänen, P. H., & Kraus, N. (2000). Mismatch negativity (MMN) as a tool for investigating auditory discrimination and sensory memory in infants and children. *Clinical Neurophysiology, 111*, 4–16.

Cheour-Luhtanen, M., Alho, K., Kujala, T., Sainio, K., Reinikainen, K., Renlund, M., Aaltonen, O., Eerola, O., & Näätänen, R., et al. (1995). Mismatch negativity indicates vowel discrimination in newborns. *Hearing Research, 82*, 53–58.

Connolly, J. F., D'Arcy, R. C., Newman, L., & Kemps, R. (2000). The application of cognitive event-related brain potentials (ERPs) in language-impaired individuals: Review and case studies. *International Journal of Psychophysiology, 38*, 55–70.

Creutzfeldt, O., & Houchin, J. (1974). Neuronal basis of EEG waves. In A. Remond, (Ed.), *Handbook of electroencephalography and clinical neurophysiology* (pp. 5–55). Amsterdam: Elsevier.

Dehaene-Lambertz, G. (2000). Cerebral specialization for speech and non-speech stimuli in infants. *Journal of Cognitive Neuroscience, 12*, 449–460.

Dehaene-Lambertz, G., & Baillet, S. (1998). A phonological representation in the infant brain. *Neuroreport, 9*, 1885–1888.

Dehaene-Lambertz, G., & Dehaene, S. (1994). Speed and cerebral correlates of syllable discrimination in infants. *Nature, 370*, 292–295.

Dehaene-Lambertz, G., & Pena, M. (2001). Electrophysiological evidence for automatic phonetic processing in neonates. *Neuroreport, 12*, 3155–3158.

Dien, J. (1998). Issues in the application of the average reference: Review, critiques, and recommendations. *Behavior Research Methods, Instruments and Computers, 30*, 34–43.

Eggermont, J. J., & Ponton, C. W. (2002). The neurophysiology of auditory perception: From single units to evoked potentials. *Audiology and Neuro-Otology, 7*, 71–99.

Eggermont, J. J., & Ponton, C. W. (2003). Auditory-evoked potential studies of cortical maturation in normal hearing and implanted children: Correlations with changes in structure and speech perception. *Acta Otolaryngologica, 123*, 249–252.

Escera, C., Alho, K., Schröger, E., & Winkler, I. (2000). Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiology and Neuro-Otology, 5*, 151–166.

Escera, C., Alho, K., Winkler, I., & Näätänen, R. (1998). Neural mechanisms of involuntary attention to acoustic novelty and change. *Journal of Cognitive Neuroscience, 10*, 590–604.

Fishman, Y. I., Reser, D. H., Arezzo, J. C., & Steinschneider, M. (1998). Pitch vs. spectral encoding of harmonic complex tones in primary auditory cortex of the awake monkey. *Brain Research, 786*, 18–30.

Fishman, Y. I., Reser, D. H., Arezzo, J. C., & Steinschneider, M. (2000). Complex tone processing in primary auditory cortex of the awake monkey. II. Pitch vs. critical band representation. *Journal of the Acoustical Society of America, 108*, 247–262.

Flemming, L., Wang, Y., Caprihan, A., Eiselt, M., Haueisen, J., & Okada, Y. (2005). Evaluation of the distortion of EEG signals caused by a hole in the skull mimicking the fontanel in the skull of human neonates. *Clinical Neurophysiology, 116*, 1141–1152.

Friederici, A. D., Friedrich, M., & Weber, C. (2002). Neural manifestation of cognitive and precognitive mismatch detection in early infancy. *Neuroreport, 13*, 1251–1254.

Friedrich, M., Weber, C., & Friederici, A. D. (2004). Electrophysiological evidence for delayed mismatch response in infants at-risk for specific language impairment. *Psychophysiology, 41*, 772–782.

Gomes, H., Dunn, M., Ritter, W., Kurtzberg, D., Brattson, A., Kreuzer, J. A., & Vaughan Jr., H. G., et al. (2001). Spatiotemporal maturation of the central and lateral N1 components to tones. *Brain Research Developmental Brain Research, 129*, 147–155.

Hattori, H., Yamano, T., Tsutada, T., Tsuyuguchi, N., Kawawaki, H., & Shimogawara, M. (2001). Magnetoencephalography in the detection of focal lesions in West syndrome. *Brain and Development, 23*, 528–532.

He, C., Hotson, L., & Trainor, L. J. (2007). Mismatch responses to pitch changes in early infancy. *Journal of Cognitive Neuroscience, 19*, 878–892.

Hillyard, S. A., & Kutas, M. (1983). Electrophysiology of cognitive processing. *Annual Review of Psychology, 34*, 33–61.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology, 387*, 167–178.

Hyde, M. (1997). The N1 response and its applications. *Audiology and Neuro-Otology, 2*, 281–307.

Javitt, D. C., Steinschneider, M., Schroeder, C. E., Vaughan Jr., H. G., & Arezzo, J. C. (1994). Intracortical mechanisms of mismatch negativity (MMN) generation. *Brain Research, 667*, 192–200.

Johnstone, S. J., Barry, R. J., Anderson, J. W., & Coyle, S. F. (1996). Age-related changes in child and adolescent event-related potential component morphology, amplitude and latency to standard and target stimuli in an auditory oddball task. *International Journal of Psychophysiology, 24*, 223–238.

Konig, N., & Marty, R. (1974). On function and structure of deep layers of immature auditory cortex. *Journal of Physiology, 68*, 145–155.

Konig, N., Pujol, R., & Marty, R. (1972). A lamina study of evoked potentials and unit responses in the auditory cortex of the postnatal cat. *Brain Research, 36*, 469–493.

Kral, A., Hartmann, R., Tillein, J., Heid, S., & Klinke, R. (2000). Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cerebral Cortex, 10*, 714–726.

Kraus, N., McGee, T., Carrell, T., Sharma, A., Micco, A., & Nicol, T. (1993). Speech-evoked cortical potentials in children. *Journal of the American Academy of Audiology, 4*, 238–248.

Kurtzberg, D., Hilpert, P. L., Kreuzer, J. A., & Vaughan Jr., H. G. (1984). Differential maturation of cortical auditory evoked potentials to speech sounds in normal fullterm and very low-birthweight infants. *Developmental Medicine and Child Neurology, 26*, 466–475.

Kushnerenko, E., Čeponiené, R., Balan, P., Fellman, V., Huotilainen, M., & Näätänen, R. (2002a). Maturation of the auditory event-related potentials during the first year of life. *Neuroreport, 13*, 47–51.

Kushnerenko, E., Čeponiené, R., Balan, P., Fellman, V., & Näätänen, R. (2002b). Maturation of the auditory change detection response in infants: A longitudinal ERP study. *Neuroreport, 13*, 1843–1848.

Kushnerenko, E., Čeponiené, R., Fellman, V., Huotilainen, M., & Winkler, I. (2001a). Event-related potential correlates of sound duration: Similar pattern from birth to adulthood. *Neuroreport, 12*, 3777–3781.

Kushnerenko, E., Cheour, M., Čeponiené, R., Fellman, V., Renlund, M., Soininen, K., Alku, P., Koskinen, M., Sainio, K., & Näätänen, R., et al. (2001b). Central auditory processing of durational changes in complex speech patterns by newborns: An event-related brain potential study. *Developmental Neuropsychology, 19*, 83–97.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*, 203–205.

Leppänen, P. H. T., Eklund, K. M., & Lyytinen, H. (1997). Event-related brain potentials to change in rapidly presented acoustic stimuli in newborns. *Developmental Neuropsychology, 13*, 175–204.

Leppänen, P. H., Guttorm, T. K., Pihko, E., Takkinnen, S., & Lyytinen, H. (2004). Maturational effects on newborn ERPs measured in the mismatch negativity paradigm. *Experimental Neurology, 190*, 91–101.

Leppänen, P. H., & Lyytinen, H. (1997). Auditory event-related potentials in the study of developmental language-related disorders. *Audiology and Neuro-Otology, 2*, 308–340.

Leppänen, P. H., Pihko, E., Eklund, K. M., & Lyytinen, H. (1999). Cortical responses of infants with and without a genetic risk for dyslexia: II. Group effects. *Neuroreport, 10*, 969–973.

Liégeois-Chauvel, C., Musolini, A., Badier, J. M., Marquis, P., & Chauvel, P. (1994). Evoked potentials recorded from the auditory cortex in man: Evaluation and topography of the middle latency components. *Electroencephalography and Clinical Neurophysiology, 92*, 204–214.

McArthur, G., & Bishop, D. (2002). Event-related potentials reflect individual differences in age-invariant auditory skills. *Neuroreport, 13*, 1079–1082.

Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: Investigation of evoked potentials and EEG phenomena. *Physiology Review, 65*, 37–100.

Mitzdorf, U. (1994). Properties of cortical generators of event-related potentials. *Pharmacopsychiatry, 27*, 49–52.

Miyata, H., Kawaguchi, S., Samejima, A., & Yamamoto, T. (1982). Postnatal development of evoked responses in the auditory cortex of the cat. *Japanese Journal of Physiology, 32*, 421–429.

Molfese, D. L. (2000). Predicting dyslexia at 8 years of age using neonatal brain responses. *Brain and Language, 72*, 238–245.

Molfese, D. L., & Molfese, V. J. (1985). Electrophysiological indexes of auditory-discrimination in newborn infants: The bases for predicting later language development. *Infant Behavior and Development, 8*, 197–211.

Molfese, D. L., & Molfese, V. J. (1997). Discrimination of language skills at five years of age using event-related potentials recorded at birth. *Developmental Neuropsychology, 13*, 135–156.

Moore, J. K., & Guan, Y. L. (2001). Cytoarchitectural and axonal maturation in human auditory cortex. *Journal of the Association for Research in Otolaryngology, 2*, 297–311.

Morr, M. L., Shafer, V. L., Kreuzer, J. A., & Kurtzberg, D. (2002). Maturation of mismatch negativity in typically developing infants and preschool children. *Ear and Hearing, 23*, 118–136.

Muir, D. W., Clifton, R. K., & Clarkson, M. G. (1989). The development of a human auditory localization response: A U-shaped function. *Canadian Journal of Psychology, 43*, 199–216.

Muir, D., & Field, J. (1979). Newborn infants orient to sounds. *Child Development, 50*, 431–436.

Näätänen, R. (1992). *Attention and brain function*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Näätänen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology, 24*, 375–425.

Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., & Winkler, I. (2001). 'Primitive intelligence' in the auditory cortex. *Trends in Neuroscience, 24*, 283–288.

Näätänen, R., & Winkler, I. (1999). The concept of auditory stimulus representation in cognitive neuroscience. *Psychological Bulletin, 125*, 826–859.

Neijenhuis, K., Snik, A., Priester, G., van Kordenoordt, S., & van den Broek, P. (2002). Age effects and normative data on a Dutch test battery for auditory processing disorders. *International Journal of Audiology, 41*, 334–346.

Novak, G. P., Kurtzberg, D., Kreuzer, J. A., & Vaughan Jr., H. G. (1989). Cortical responses to speech sounds and their formants in normal infants: Maturational sequence and spatiotemporal analysis. *Electroencephalography and Clinical Neurophysiology, 73*, 295–305.

Pang, E. W., Edmonds, G. E., Desjardins, R., Khan, S. C., Trainor, L. J., & Taylor, M. J. (1998). Mismatch negativity to speech stimuli in 8-month-old infants and adults. *International Journal of Psychophysiology, 29*, 227–236.

Pang, E. W., & Taylor, M. J. (2000). Tracking the development of the N1 from age 3 to adulthood: An examination of speech and non-speech stimuli. *Clinical Neurophysiology, 111*, 388–397.

Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L. E., & Hoke, M. (1998). Increased auditory cortical representation in musicians. *Nature, 392*, 811–814.

Pantev, C., Roberts, L. E., Schulz, M., Engelien, A., & Ross, B. (2001). Timbre-specific enhancement of auditory cortical representations in musicians. *Neuroreport, 12*, 169–174.

Picton, T. W., Alain, C., Otten, L., Ritter, W., & Achim, A. (2000). Mismatch negativity: Different water in the same river. *Audiology and Neuro-Otology, 5*, 111–139.

Picton, T. W., Alain, C., Woods, D., John, M. S., Scherg, M., Valdes-Sosa, P., Bosch-Bayard, J., & Trujillo, N. J. et al. (1999). Intracerebral sources of human auditory-evoked potentials. *Audiology and Neuro-Otology, 4*, 64–79.

Picton, T. W., Lins, O. G., & Scherg, M. (1995). The recording and analysis of event-related potentials. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 10, pp. 3–73). New York: Elsevier.

Pihko, E., Leppänen, P. H. T., Eklund, K. M., Cheour, M., Guttorm, T. K., & Lyytinen, H. (1999). Cortical responses of infants with and without a genetic risk for dyslexia: I. Age effects. *Neuroreport, 10*, 901–905

Pisoni, D. B., Lively, S. E., & Logan, J. S. (1994). Perceptual learning of nonnative speech contrasts: Implications for theories of speech perception. In J. C. Goodman & H. C. Nusbaum (Eds.), *The development of speech perception: The transition from speech sounds to spoken words* (pp. 121–166). Cambridge, MA: The MIT Press.

Ponton, C. W., & Eggermont, J. J. (2001). Of kittens and kids: Altered cortical maturation following profound deafness and cochlear implant use. *Audiology and Neuro-Otology, 6*, 363–380.

Ponton, C. W., Eggermont, J. J., Don, M., Waring, M. D., Kwong, B., Cunningham, J., & Trautwein, P. et al. (2000). Maturation of the mismatch negativity: Effects of profound deafness and cochlear implant use. *Audiology and Neuro-Otology, 5*, 167–185.

Ponton, C. W., Eggermont, J. J., Kwong, B., & Don, M. (2000). Maturation of human central auditory system activity: Evidence from multi-channel evoked potentials. *Clinical Neurophysiology, 111*, 220–236.

Scherg, M. (1990). Fundamentals of dipole source potential analysis. In F. Grandori, M. Hoke, & G. L. Romani (Eds.), *Auditory evoked magnetic fields and electric potentials, advances in audiology* (Vol. 5, pp. 40–69). Basel: Karger.

Scherg, M., & von Cramon, D. (1986). Psychoacoustic and electrophysiologic correlates of central hearing disorders in man. *European Archives of Psychiatry and Neurological Sciences, 236*, 56–60.

Schröger, E. (1998). Measurement and interpretation of the mismatch negativity. *Behaviour Research Methods, Instruments and Computers, 30*, 131–145.

Segalowitz, S. J., & Berge, B. E. (1995). Functional asymmetries in infancy and early childhood: A review of electrophysiologic studies and their implications. In R. J. Davidson & K. Hugdahl (Eds.), *Brain asymmetry* (pp. 579–615). Cambridge: MIT Press.

Shahin, A., Bosnyak, D. J., Trainor, L. J., & Roberts, L. E. (2003). Enhancement of neuroplastic P2 and N1c auditory evoked potentials in musicians. *Journal of Neuroscience, 23*, 5545–5552.

Shahin, A., Roberts, L. E., & Trainor, L. J. (2004). Evidence for enhancement of auditory cortical development by musical experience. *NeuroReport, 15*, 1917–1921.

Sharma, A., Kraus, N., McGee, T. J., & Nicol, T. G. (1997). Developmental changes in P1 and N1 central auditory responses elicited by consonant-vowel syllables. *Electroencephalography and Clinical Neurophysiology, 104*, 540–545.

Sonnadara, R. R., Alain, C., & Trainor, L. J. (2006). Effects of spatial separation and stimulus probability on event-related potentials elicited by occasional changes in sound location. *Brain Research, 1071*, 175–185.

Souweidane, M. M., Kim, K. H., McDowall, R., Ruge, M. I., Lis, E., Krol, G., & Hirsch, J. et al. (1999). Brain mapping in sedated infants and young children with passive-functional magnetic resonance imaging. *Pediatric Neurosurgery, 30*, 86–92.

Squires, K. C., Squires, N. K., & Hillyard, S. A. (1975). Two varieties of long latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography and Clinical Neurophysiology, 38*, 387–401.

Stapells, D. R., Galambos, R., Costello, J. A., & Makeig, S. (1988). Inconsistency of auditory middle latency and steady-state responses in infants. *Electroencephalography and Clinical Neurophysiology, 71*, 289–295.

Steinschneider, M., & Dunn, M. (2002). Electrophysiology in developmental neuropsychology. In S. J. Segalowitz and I. Rapin (Eds.), *Handbook of neuropsychology* (Vol. 7, pp. 91–146). Amsterdam: Elsevier.

Takegata, R., Paavilainen, P., Näätänen, R., & Winkler, I. (1999). Independent processing of changes in auditory single features and feature conjunctions in humans as indexed by the mismatch negativity. *Neuroscience Letters, 266*, 109–112.

Tharpe, A. M., & Ashmead, D. H. (2001). A longitudinal investigation of infant auditory sensitivity. *American Journal of Audiology, 10*, 104–112.

Thomas, D. G., & Lykins, S. M. (1995). Event-related potential measures of 24-hour retention in 5-month-old infants. *Developmental Psychology, 31*, 946–957.

Thomas, D. G., Whitaker, E., Crow, C. D., Little, V., Love, L., Lykins, M. S., & Letterman, M. et al. (1997). Event-related potential variability as a measure of information store in infant development. *Developmental Neuropsychology, 13*, 205–232.

Trainor, L. J., McDonald, K. L., & Alain, C. (2002). Automatic and controlled processing of melodic contour and interval information measured by electrical brain activity. *Journal of Cognitive Neuroscience, 14*, 430–442.

Trainor, L., McFadden, M., Hodgson, L., Darragh, L., Barlow, J., Matsos, L., & Sonnadara, R. et al. (2003). Changes in auditory cortex and the development of mismatch negativity between 2 and 6 months of age. *International Journal of Psychophysiology, 51*, 5–15.

Trainor, L. J., Samuel, S. S., Desjardins, R. N., & Sonnadara, R. R. (2001). Measuring temporal resolution in infants using mismatch negativity. *Neuroreport, 12*, 2443–2448.

Trainor, L. J., Shahin, A., & Roberts, L. E. (2003). Effects of musical training on the auditory cortex in children. *Annals of the New York Academy of Sciences, 999*, 506–513.

Tremblay, K., Kraus, N., McGee, T., Ponton, C., & Otis, B. (2001). Central auditory plasticity: Changes in the N1-P2 complex after speech-sound training. *Ear and Hearing, 22*, 79–90.

Vaughan Jr., H. G., & Arezzo, J. C. (1988). The neural basis of event-related potentials. In T. W. Picton (Ed.). *Human event-related potentials* (pp. 45–96). Amsterdam: Elsevier.

Vaughan Jr., H. G., & Ritter, W. (1970). The sources of auditory evoked responses recorded from the human scalp. *Electroencephalography and Clinical Neurophysiology, 28*, 360–367.

Werker, J. F., & Tees, R. C. (1984). Cross language speech perception: Evidence for perceptual reorganization during the 1st year of life. *Infant Behavior and Development, 7*, 49–63.

Werner, L. A., & Marean, G. C. (1996). *Human Auditory Development.* Boulder, CO: Westview.

Woldorff, M., & Hillyard, S. (1991). Modulation of early auditory processing during selective listening to rapidly presented tones. *Electroencephalography and Clinical Neurophysiology, 79*, 170–191.