Introduction to infant EEG and event-related potentials

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It is many decades since investigators first employed the electroencephalogram (EEG) to study the function of infants’ central nervous systems (for reviews see Bell, 1998; Schmidt & Fox, 1998). While initially investigators focused on how changes in the ongoing EEG related to the behavioural states of sleep and wakefulness (Lindsley, 1939; Smith, 1938), in subsequent years they also began to study event-related activity including evoked (e.g., Galambos & Despland, 1980; Sokol & Dobson, 1976) and endogenous responses (e.g., Courchesne, Ganz, & Norcia, 1981; Vaughan, 1975). In recent years, with the growing interest in understanding the neural bases of human perception, cognition, and emotion, there has been increased interest in use of EEG and event-related potentials (ERPs) to study these processes as they develop in human infants. This is because EEG and ERPs are among the only ways to study brain activity in healthy infants (see Meek, 2002, for discussion of another method that can be used with healthy infants, optical imaging). Other brain-imaging methods commonly used with adults and older children pose significant risks or would require sedation in young infants, making them unsuitable unless required for clinical purposes.

That there is now a sufficient body of literature in the field of infant EEG and ERPs to warrant an entire volume on this topic is testament to how quickly the field has grown in the last few years. This is in spite of the fact that these data can be quite challenging to collect from young infants. Cooperation with placement of the electrodes and leaving them in place for the duration of the experiment, minimising movement during the experiment to prevent artefacts, and ensuring that the baby participates in the experiment as needed (e.g., by attending to visual stimuli) can all represent challenges (see DeBoer et al., Chapter 1, for discussion of practical aspects of recording infant EEG and ERPs). Once these challenges are overcome, others present themselves in analysis and interpretation of the data, as in many instances the relationship between components observed in infant ERPs and those known in adults is not obvious.

The chapters in this volume demonstrate that these challenges can be overcome and reliable EEG and ERP data can be recorded from infants in a variety of paradigms and ages. Chapter 1 (DeBoer et al.) provides an
overview of methods for recording and analysing EEG and ERP, with an emphasis on the special issues related to using these techniques with infants. Chapters 2–4 focus on visual potentials, from visual evoked responses (McCulloch, Chapter 2) to face-sensitive components (de Haan et al., Chapter 3) and components related to visual attention and memory (de Haan, Chapter 4). In Chapter 2, McCulloch outlines techniques for recording visual evoked potentials (VEPs) and describes the picture they provide of the development of the visual system in infancy, in both typical and atypical development. In Chapter 3, de Haan, Johnson, and Halit describe ERP components related to infants’ processing of faces, how these relate to components in the adult ERP, and how developmental changes in these components inform theories of the development of face processing. In Chapter 4, de Haan focuses on ERP components related to infant recognition memory and attention, describing the development of the negative central (Nc) component and various slow waves.

Chapters 5–7 focus on auditory potentials, including those related to auditory recognition (de Regnier, Chapter 5), the mismatch negativity (Cheour, Chapter 6), and those related to speech and language (Molfese et al., Chapter 7). In Chapter 5, de Regnier outlines the brain circuits involved in auditory recognition memory and presents data demonstrating differences in ERP response to the mother’s vs a stranger’s voice in neonates. When the same auditory recognition paradigm is used with infants at risk for later memory impairment, there is evidence of atypical auditory ERP memory responses very early in life. In Chapter 6, Cheour describes what is perhaps one of the most well-studied ERP components, mismatch negativity (MMN). She discusses issues in identifying the infant MMN, and its differences from and similarities to the adult component, as well as its usefulness in detecting cognitive impairment early in life. In Chapter 7, Molfese, Molfese, and Pratt discuss the use of infant ERPs to predict later language and reading development. They present impressive findings indicating that ERPs to speech and non-speech sounds in neonates and young infants can predict a sizeable amount of the variance in language and reading skills at school age.

Chapters 8–10 focus on other aspects of the EEG, with Chapter 8 (Marshall & Fox) examining ERP and EEG emotion-related responses, Chapter 9 (Stroganova & Orekhova) focusing on EEG and infants’ states, particularly different states of wakefulness, and Chapter 10 (Csibra & Johnson) reporting on event-related oscillations in perceptual-cognitive tasks. In Chapter 8, Marshall and Fox report on individual differences in both EEG and ERP responses and how they relate to individual differences in emotion and temperament. Their findings suggest that temperamental differences among infants may be an important factor to consider in interpreting results from ERP group studies. In Chapter 9, Stroganova and Orekhova discuss development of the EEG in relation to infant states, raising important questions regarding variations in the EEG during wakefulness and definition of infant EEG rhythms (e.g., alpha) in relation to those observed in adults. In
Chapter 10, Csibra and Johnson described a relatively recent approach to analysing infant brain activity, event-related oscillations, and describe how these have been used to study the neural correlates of perceptual binding and memory for hidden objects in infancy.

Several questions and themes run throughout these chapters, including the usefulness of infant EEG/ERP in early detection of impairments in perception and cognition, and how best to define infant brain activity with respect to adult brain activity, and these and other themes are discussed further in Chapter 11 (de Haan). A glossary of terms is also provided at the end of the book, with the hope that it will make the chapters more accessible to those less familiar with the field and its terminology.

The main purpose of creating this volume was to provide a reference useful to both those active in the field and those new to it. For those already involved in infant EEG and ERP research, the chapters in this book will provide a very useful reference drawing together numerous studies, and may also help to broaden their outlook, as often researchers tend to focus on a particular type of ERP and may not be fully aware of work that is related but carried out in another domain. For those new to the field, it is hoped that the introduction provided by Chapter 1 and the glossary will form the background for informed reading of the remaining chapters devoted to more specific topics. Ideally, the exciting findings reported here will recruit new researchers into the field and help to take the field forward in the decades to come.

REFERENCES


1 Methods for acquiring and analyzing infant event-related potentials

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A primary goal of developmental cognitive neuroscience is to elucidate the relation between brain development and cognitive development (see Nelson & Luciana, 2001). The study of this relation in children older than 5–6 years lends itself to many of the same tools used in the adult, such as functional magnetic resonance imaging (fMRI). However, in children younger than this, limitations in motor and linguistic abilities, coupled with abbreviated attention spans, make the use of such tools impractical. In contrast, electroencephalography (EEG) and event-related potentials (ERPs) provide some of the only noninvasive methodological techniques in the armamentarium of cognitive neuroscientists that allow researchers to examine the relation between brain and behavior beginning at birth. Both EEG and ERPs measure electrical activity of the brain recorded from scalp electrodes and can be utilized across the entire lifespan, thereby permitting one to use the same methodological tool and dependent measure across a broad range of ages (although comparisons across large age spans may be challenging due to qualitative differences in the EEG and ERP response). In addition, EEG and ERPs do not require an overt behavioral or verbal response and therefore permit the study of phenomena that cannot be studied with behavioral methods (e.g., responses to the simultaneous presentation of multiple stimuli or stimuli presented so briefly as to preclude a behavioral response). However, when a behavioral response is obtainable, EEG and ERPs can also provide an invaluable complement and an additional level of analysis to that behavioral measure by permitting one to glimpse (albeit imperfectly) the neural circuits underlying the behavior.

EEG and ERPs both reflect the electrical activity of the brain, and both are collected in a similar manner; however, they represent slightly different aspects of brain function. Whereas EEG is a measure of the brain’s ongoing electrical activity, ERPs reflect changes in electrical activity in response to a discrete stimulus or event. ERPs are collected from several trials and then
averaged in order to eliminate background noise that is not related to the stimulus of interest. Thus, ERPs are said to be “time-locked” to the stimulus. Both EEG and ERPs contribute to the understanding of brain maturation and cognitive development. EEG provides information regarding the resting state of the brain (as indexed by various EEG patterns or rhythms), synchrony between regions (coherence), or spectral changes in response to a cognitive event (Event-related Synchronization/Desynchronization). In contrast, deflections in the ERP (referred to as components) reflect specific aspects of sensory and cognitive processes associated with various stimuli. Due to the high temporal resolution (on the order of milliseconds), ERPs are well suited to index changes in the mental chronometry of a given neural response.

Although sources have discussed aspects of electrophysiological research including the historical and neurophysiological background of EEG and ERPs, issues concerning experimental design, data acquisition, analysis, and interpretation in adult populations in great detail (e.g., Handy, 2004; Regan, 1989), few have addressed utilization of these measures in developmental populations (for an important exception see Taylor & Baldeweg, 2002). This is unfortunate because recording EEG and ERPs in infants and young children differs from that of adults in some unique ways. Thus, in this chapter we elaborate on the idiosyncrasies of using EEG and ERPs in developmental populations, provide the reader with some practical methodological advice, and call attention to some caveats that arise when using EEG and ERP techniques to investigate the developmental progression in brain–behavior relations early in life. The chapter is designed for the novice developmental EEG/ERP researcher and focuses on issues regarding study formation, experimental design, data collection, and data analysis. The heart of the chapter reviews issues regarding practical acquisition topics such as data acquisition systems, participant selection, data collection (e.g., recording electrophysiological data, artifact rejection, and averaging), and statistical analysis. The chapter closes with an introduction to source separation and localization, and challenges and future directions for developmental electrophysiological research.¹

¹ The field of developmental electrophysiology is continually evolving; subsequently, what is considered “developmental” electrophysiological research remains broad. At this point in time, the term “developmental” is used not only to refer to authentic change over time (e.g., changes in components, changes in brain structures, or changes in children’s behavior) but also to refer to research that, ultimately, will contribute to knowledge regarding such change. Therefore, in this chapter, the term “developmental” will be used to refer to both circumstances (e.g., studying the development of actual entities such as components and the utilization of ERP components in developmental, or child, populations to better understand development more generally).
Hypotheses

Despite increases in the use of EEG and ERPs with developmental populations, several obstacles remain that prevent testable hypotheses from appearing more often in the literature. First, since relatively little is known about the specifics of human brain development, it can be challenging to derive concrete hypotheses based on the development of discrete neural circuits. Second, almost nothing is known about how physiologic activity in the developing brain propagates to the scalp surface, and thus we do not know what the relation is between activity in the brain vs at the scalp. Third, the field has only begun to define ERP components of interest and normative and abnormal patterns of EEG across development; thus much discontinuity remains between age groups and across areas of investigation.

With these caveats in mind, in this chapter we attempt to illustrate the kinds of questions that are particularly amenable to an electrophysiological investigation with developmental populations. We also challenge researchers to perform the appropriate exploratory investigations to ensure that more theoretically driven experiments with testable hypotheses can be conducted.

Task design

Due to the limited attentional capacity and restricted behavioral repertoire of infant populations, several considerations may be necessary when designing an experiment. Some developmental EEG/ERP tasks can be derived from tasks used with adults that are adjusted to take developmental differences into consideration (e.g., decreasing the length of the trials, the number of independent variables, or the complexity of the stimuli). However, as accommodations such as these are made, it must be acknowledged that infants are not typically tested under the same conditions as adults (e.g., infants do not benefit from instructions, whereas older children do) and, therefore, direct comparisons across large age differences are often difficult to interpret. Other age-appropriate tasks can arise from modified versions of behavioral tasks known to tap certain cognitive functions of interest (e.g., speech discrimination tasks, approach–withdrawal tasks, habituation tasks, or recognition memory tasks).

Many developmental EEG studies to date have compared spectral activity of children with typical cognitive development to that of clinical groups under a variety of circumstances. Common paradigms involve recording resting EEG while infants watch objects such as brightly colored balls tumbling around a bingo wheel, abstract patterns on a video display, or bubbles, for various amounts of time (e.g., Calkins, Fox, & Marshall, 1996; Marshall, Bar-Haim, & Fox, 2002). Additionally, EEG can be recorded during prolonged events such as games of peek-a-boo or a stranger entering the
room (e.g., Buss, Malmstadt Schumacher, Dolski, Kalin, Hill Goldsmith, & Davidson, 2003; Dawson, Panagiotides, Klinger, & Spieker, 1997) or emotion-eliciting videos or musical clips (Jones, Field, Fox, Daivalos, & Gomez, 2001; Schmidt, Trainor, & Santesso, 2003) as long as precautions are made to minimize movement on the part of the participant.

On the other hand, as mentioned above, ERPs are by definition time-locked to the presentation of a stimulus. Therefore, in both adult and developmental populations, more stringent constraints are placed on the types of tasks amenable to ERP experiments. To date, most developmental ERP studies have used either the standard oddball paradigm or a combination of the oddball paradigm with an infant habituation paradigm. In the former, two or more discrete stimuli (i.e., typically 500 milliseconds in duration) are presented repeatedly, but with different frequencies. For example, in one study 4- to 7-week-old infants were shown pictures of checkerboard patterns and geometric shapes. ERPs were recorded while one stimulus was repeated frequently (80% of the time) and the other stimulus was presented infrequently (20% of the time, Karrer & Monti, 1995). In contrast, the combined oddball/habituation paradigm involves first familiarizing or habituating an infant to a stimulus (e.g., a face), and then presenting a series of stimuli, consisting of the now familiar stimulus and a novel stimulus (e.g., a new face) repeatedly with equal frequency (i.e., 50% of the time for each) while ERPs are recorded (e.g., Pascalis, de Haan, Nelson, & deSchonen, 1998).

**IMPORTANT CONSIDERATIONS IN DEVELOPMENTAL POPULATIONS**

Beyond paradigm considerations, one must also consider (1) age-related changes in EEG or the morphology and timing of ERP components of interest, and (2) changes in behavioral measures, including the availability, quality, and validity of these measures.

Developmental changes, which are apparent in both EEG rhythms and the morphology of the ERP waveform, are often difficult to describe, and increasingly difficult to explain due to their complex and multifaceted nature. For instance, major developmental changes in synaptic density, myelination, and other physical maturational processes (e.g., changes in skull thickness and closing of the fontanel) may combine to influence amplitude and latency increases and decreases across different ages (Nelson & Luciana, 1998; see also Chapter 11, this volume, for further discussion).

Although great strides have been made in documenting changes in EEG over the first few years of life, much less is known about the developmental trajectories of ERP components (although see Webb, Long, & Nelson, 2005, for an exception). For example, the same EEG frequency bands are typically present throughout development, yet high-frequency bands tend to increase in relative power with increases in age (especially in the band of 6–9Hz:
Marshall et al., 2002; Schmidt et al., 2003; see also Taylor & Baldeweg, 2002, for a review). ERP components tend to vary considerably in both form and function across development. Unexpectedly, ERPs of adults and newborns are similar to each other in amplitude, but very dissimilar compared to ERPs from older infants and young children (see Figure 1.1 for illustration). Furthermore, in the first two years of life, reduced synaptic efficiency results in greater slow wave activity rather than peaked activity, the latter being more typical of adult ERPs. Thus, the infant ERP does not show as many well-defined peaked responses (especially in anterior components) when compared to adult responses. The characteristics of the peaked adult waveform typically begin to emerge when children reach 4 years of age, and continue to develop well into adolescence (Friedman, Brown, Cornblatt, Vaughan, & Erlenmeyer-Kimling, 1984; Nelson & Luciana, 1998). In fact, because the distribution of activity across the scalp (i.e., topography) changes with age, we can infer that important changes are still taking place in the neural substrate generating the components of interest throughout development.

Amplitudes may also vary as a function of differing task demands imposed on the participant. Presumably the easier the task, the less effort expended, and the less cortical activation required, which may ultimately result in smaller amplitudes (Nelson & Luciana, 1998). Finally, the general heuristic for changes that take place from early adulthood to later adulthood is that, overall, latencies of several ERP components appear longer and amplitudes appear smaller (see Kurtzberg, Vaughan, Courchesne, Friedman, Harter, & Putnam, 1984; Nelson & Monk, 2001; and Taylor & Baldeweg, 2002 for further discussion).

A major change that also occurs with increasing age is the ability to “ground” the measure in behavior or correlate the brain’s electrophysiological response with task performance. Infant EEG/ERP paradigms by necessity do not involve issuing instructions, nor do they require an overt behavioral response. However, most adult ERP paradigms include both instructions and a behavior response (even if only to ensure continued attention to the task). Therefore, due to the differences in testing conditions it is possible that, at some level, differences in ERP morphology are due to differences in task requirements.

The “passive” viewing paradigm (i.e., one in which no instructions are given) is useful for two reasons. First, developmental populations can be tested and their data can be compared to those of adults without modification to the paradigm. Second, passive paradigms may evoke basic perceptual components, without the added activity (or noise) that may be recorded when the participant is engaged in some task and/or a behavioral response is required. The drawback to using a passive task is that it is difficult to determine whether participants maintain attention throughout the task, or whether they are doing the task at all. Depending on the specific hypotheses, one must use other means of monitoring attention, for example in visual paradigms, videotaping participants to ensure they were looking at the
Figure 1.1 (A) Grand averaged ERPs from posterior, inferior temporal electrodes P9 (left parietal lobe) and P10 (right parietal lobe) in response to face stimuli for seven age groups. (B) Grand averaged ERPs from midline electrodes taken from a pilot study in which 8-month-olds, 4-year-olds, and adults passively viewed images of their own face in the context of a face recognition task. Figure 1.1A kindly provided by Dr Margot Taylor (Centre National Cerveau et Cognition, Toulouse, France) and Figure 1.1B provided by Lisa S. Scott (Institute of Child Development, University of Minnesota, USA.)
stimuli, and/or repeating trials in which it was obvious the participants were not attentive. For auditory studies, attention may be a different issue, as ERPs are often recorded during sleep (e.g., deRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000). During these paradigms, infants may need to be monitored continuously if changes in sleep states (active versus passive) are thought to influence the ERP response (cf. Martynova, Kirjavainen, & Cheour, 2003).

Although below the age of 4 to 5 years traditional button-press responses cannot be used, there are some behavioral measures that have been used previously in developmental populations in conjunction with EEG and ERPs. The most informative behavioral measures are those that can be recorded concurrently and therefore directly correlated with the electrophysiological response. For example, in one EEG investigation (Dawson et al., 1997), infants were exposed to several conditions designed to elicit positive and negative emotions while EEG activity was measured (e.g., peek-a-boo with their mothers versus being approached by a stranger). EEG activity was subsequently analyzed during periods when infants were displaying prototypic expressions of emotions. Results from this investigation indicated that, compared with infants of nondepressed mothers, infants of depressed mothers exhibited increased EEG activation in the frontal but not parietal regions when they were expressing negative emotions.

Due to temporal limitations, recording behavior in conjunction with ERP recording has been a slightly greater challenge, although a number of paradigms have been able to record behavior concurrent with ERP recording. For example, following a visual oddball paradigm using two stimuli with different presentation frequencies, Karrer and Monti (1995) immediately presented infants with four additional trials during which visual fixations were recorded, analogous to a post-test after a traditional behavioral habituation paradigm. Specifically, one of the two stimuli was presented repeatedly until the infant looked away; followed by the presentation of the other stimulus until the infant again looked away, and so on (Karrer & Monti, 1995). Similarly, Snyder (2002) employed a design analogous to a habituation/dishabituation procedure that consisted of recording ERPs during an initial exposure to a stimulus (the habituation phase), and then recording the duration of infants’ visual fixations during a dishabituation phase. Snyder’s study is unique in that it reflects a composite between ERP methodology and stimulus exposure during a conventional infant controlled habituation procedure. During the familiarization phase, trials were continuously presented until the infant either became fussy, or looked away from the screen three times for at least 3 or more seconds each time. After the familiarization phase, infants were shown serial presentations of familiar and novel stimuli and allowed one continuous look at each. Infants’ visual preferences for test stimuli were computed as the proportion of fixation to the novel stimulus versus the total fixation time. Infants were subsequently divided into three groups: infants who showed a novelty preference at test (looked at the novel stimulus 55% or more of the time),
those who showed a familiarity preference (looked at the novel stimulus 45% or less of the time), and those who did not show a preference.

This method of combining EEG/ERPs with behavioral measures (facial display of affect or preferential looking) permits researchers to more directly examine relations between behavior and brain activity. A combination of techniques such as these provides information not accessible by either method alone.

Unfortunately, due to the highly constrained testing environment required by EEG and ERPs (e.g., movement restrictions) it is not always feasible to record behavioral measures during or immediately following EEG/ERP data collection. Therefore, some researchers have elected to record behavioral measures separately (e.g., after removing the electrodes when the infant is more attentive or better able to perform a required task). For example, EEG data have been associated with measures of object permanence (Bell & Fox, 1992, 1997), motor development (Bell & Fox, 1996), joint attention (Mundy, Card, & Fox, 2000; Mundy, Fox, & Card, 2003), temperament (Henderson, Fox, & Rubin, 2001), cortisol levels, and withdrawal-related behaviors (Buss et al., 2003) all of which were collected either prior to or sometime after EEG data collection.

Similarly, Carver, Bauer, and Nelson (2000) combined ERP responses with behavioral performance on a deferred imitation task (which has been purported to tap explicit memory functions; see Bauer, 1995; Nelson, 1995). Specifically, before recording ERPs, 9-month-old infants were behaviorally exposed to a unique sequence of events (e.g., the experimenter places a red cylinder into a wooden block, which is then pushed into the base of the apparatus causing a green dinosaur puppet to “pop up”). After a 1-week delay, the infants’ ERP responses to photographs of the now familiar event sequence and a novel event sequence were recorded. Four weeks later the infants’ delayed recall performance on the deferred imitation memory task was assessed. Infants were split into groups based on their behavioral performance: those who recalled the sequence and those who did not. Based on these groupings, Carver and colleagues (2000) examined the electrophysiological responses and found differentiation between the familiar and novel conditions for the infants who demonstrated recall after a 1-month delay, but no such differentiation for the infants who did not display delayed recall.

In sum, although challenging, it is important that researchers continue to ground EEG/ERP measures in behavior. Such a combination will yield converging evidence and lead to more reliable results in predominately exploratory studies typical of the field at this time.

DATA COLLECTION SYSTEMS

Currently, there are several commercial electrophysiological data collection systems available for purchase and use. These systems differ on features such
as electrode and montage type, quantity, location, and placement. A major
distinction between systems available to date is whether they are high- or low-
density electrode montages. A low-density montage provides less coverage
over the scalp (ranging from 3–32 electrodes), whereas high-density montages
refer to greater coverage across the scalp (ranging from 32–256 electrodes).
The main advantages of high-density systems are increased opportunity for
source localization, the use of the average reference, and the relative increased
ability to detect subcortical electrical activity. When deciding whether to use a
high- or low-density system in developmental populations there are several
considerations to be made, such as: (1) where the data will be collected (e.g., a
MRI scanner that does not permit the presence of metal), (2) what hypoth-
eses will guide data analysis (e.g., how important is spatial information), (3)
what are the components of interest (i.e., what is their distribution across the
scalp), (4) the proposed dependent measures for data analysis (e.g., amplitude
differences at one electrode site or source localization procedures).

There are two different methods of recording low-density EEG/ERPs that
we have utilized in our developmental laboratory. These methods differ in the
number of electrodes and the method by which the electrodes are placed on
the scalp. For both methods, the location of electrode placement follows the
international 10–20 system of electrode placement commonly used in adults
(Jasper, 1958). Each electrode is placed a percentage of the distance between
the inion and nasion to ensure the ERPs are being recorded from approxi-
mately the same neural structures across all individuals regardless of age or
head size. In addition, these low-density systems require slight scalp abrasion
and the use of conductance cream in order to conduct the signal into the
electrode on the scalp. Abrading the scalp may increase the risk of infection,
and although it is not likely to occur, certain precautions are necessary
(see Ferree, Luu, Russell, & Tucker, 2001; Putnam, Johnson, & Roth, 1992).

The first low-density approach is derived from methods with adults, in
which a form of glue (collodion) is used to fix single electrodes filled with
conductance cream to the scalp, and a solvent (acetone) is used to remove
them. The advantage to this method is that the electrodes remain in the same
place throughout the duration of the experiment; however, the disadvantage
is that safety glasses, rubber gloves, and ventilation are recommended when
using these products due to the fact that they may be irritating to the nose and
throat. The modification we have used involves first slightly abrading the
scalp with a cleansing solution such as NuPrep© and holding single elec-
trodes filled with conductance cream (EC2 cream©) in place with adhesive-
backed foam pads, which in turn are held in place with Velcro headbands
(see Figure 1.2A). In studies with newborns or when fewer electrodes are
required, disposable electrodes, which stick directly to the infant’s scalp, can
be used instead of the single electrodes and foam (Figure 1.2B). The advan-
tage is that this procedure is typically no more aversive than putting on a hat.
However, the disadvantage is that the foam pads can stick poorly to infants
who have a great deal of hair or where the hair is braided, and thus have the
Figure 1.2 Infant wearing (A) 16 electrodes held in place with adhesive foam pads and Velcro headbands, (B) single disposable electrodes typically used in the newborn and NICU nurseries, (C) a 32-channel Electro-Cap®, and (D) a 64-channel Electro Geodesic Sensor net®.
potential to move around on the scalp unless extra care is taken. Typically 6–12 electrodes are used with this procedure, and are most appropriate for infants under 12 months of age.

The second approach utilizes an electrode cap. Such caps are made out of Spandex-like material that has electrodes sewn into it at standardized coordinates (this method is also commonly used with adults, see Figure 1.2C). The advantage to this procedure is that a greater number of electrodes may be positioned on the scalp in relatively little time in comparison with the Velcro headband procedure, or with using single disposable electrodes. The scalp is lightly abraded and conductance jelly is inserted under each electrode site after the placement of the cap (this is typically done through the use of a blunt-tip syringe and cotton swab). This may be bothersome to some infants as it produces an uncommon sensation of a light scratching on the scalp. The cap is held in place by a chin or chest strap. Although this strap does not wholly ensure that the cap will not shift on the head during the experiment, it does greatly reduce the risk of electrodes moving out of position. A disadvantage is that some infants’ heads are asymmetrical and varied in size, which makes it difficult to ensure that the electrodes are fixed in the same location. In addition, the chin or chest strap used to hold the electrodes in place may bother some infants. Typically, electrode caps have 16–32 electrodes and, in our laboratory, have been found to be appropriate for use with infants as young as 9 months of age and through to adulthood.

Recording high-density EEG/ERPs in developmental populations has been made possible by the Geodesic Sensor Net© (GSN), which allows a very large number of electrodes (ranging from 64–256) to be applied quickly to the surface of the scalp (Tucker, 1993). The GSN consists of an array of electrodes arranged in an elastic tension structure, which can be relatively quickly and easily slipped on and off the participants’ head (see Figure 1.2D). The arrangement of electrodes does not follow the international 10–20 system due to the fact that the tension structure conforms to the geometry of each individual’s head, but ensures that the electrodes are all equidistant from one another, even on a variety of head shapes (which is a requirement for localization of underlying dipoles). One advantage of the GSN is its high-operating impedance level, which, when combined with amplifiers that allow high-input impedance, removes the need for scalp abrasion and conductance cream. The net is soaked in an electrolyte solution prior to application, which allows the signal to be conducted, recorded, and amplified by the high-input impedance amplifiers. A second advantage is the use of the average reference, which results in an unbiased estimate of noise across the scalp and thus unconfounds estimates of the amplitude and topography of components with the location of the reference electrode. A third advantage is that high-density montage arrays provide greater coverage of the scalp and thus are able to pick up activity in superficial cortical tissue (which, due to its proximity to the scalp, tends to produce smaller, more discrete patterns of activity, in addition
to deeper subcortical structures). Finally, it takes a relatively short amount of time to apply the net (e.g., 5 minutes) in comparison to other procedures (e.g., 15–20 minutes; see Johnson et al., 2001). However, there are a few disadvantages worth mentioning. First, due to the fact that the electrodes are not fixed rigidly to the scalp, movement artifacts are common, and in some cases infants (6 months of age and older) may attempt to grab the net, frequently causing displacement and possible damage to the net (Johnson et al., 2001). A second disadvantage is that high-density systems are considerably more expensive than low-density systems due to the increased cost of equipment and the need for several different net sizes to accommodate small differences in head size among participants. Nets are available in many different sizes that can be used with newborns (64 or 128 electrodes), children up to 6 years of age (64 or 128 electrodes), and children aged 6 years to adults (64, 128, or 256 electrodes). (For a complete review of recording high-density ERPs and strategies for analyzing high-density data with infants using the GNS, see Johnson et al., 2001.)

Thus far, comparisons of ERP data collected from high- and low-density systems appear similar in quality (Carver et al., 1999; Johnson et al., 2001) and the overall advantage of high-density montages is that they may allow for the use of the average reference, source separation, and source localization. Furthermore, due to greater spatial coverage of the scalp, high-density montages may be able to better pick up superficial cortical and subcortical activity. In contrast, low-density systems are more widespread in their use and are less expensive.

**PARTICIPANTS**

**Ages**

When selecting participants for a study, rationale should be provided for the selected age group of interest. Common sources of rationale are related to (1) known changes occurring at the neurological or physiological level during some period in development or (2) changes in behavior that are hypothesized to be related to changes in neurological substrates during a specific time in development. It is important, however, to keep in mind that the relation between EEG/ERPs and behavior is associative and not causal (Hood, 2001). Furthermore, as Hood (2001) argues, caution should be used when interpreting EEG/ERP data, due to the fact that EEG/ERPs do not reflect the cause of the behavior nor do they provide an adequate explanation of the behavior. Areas may become activated simply as a consequence of connections with other more relevant areas. Nonetheless, once an age of interest has been selected for a given study, a specific age range must be set, due to changes in the electrophysiological responses that occur with increases in age. The previous discussion of the complex changes in ERPs should help with the
conceptualization of the fact that averaging over a wide age range may obscure developmental changes resulting from response variability (Taylor & Baldeweg, 2002). In fact, it is recommended that, in developmental studies, averages of group EEG/ERPs should not be combined over more than 1–2 month intervals in infant studies, 1–2 years in childhood, and 2–3 years in adolescence (Picton et al., 2000; Taylor & Baldeweg, 2002). Our laboratory (based on knowledge regarding both brain and child development) typically recommends that averages should not be combined over more than 10 days in infants, 1 month in childhood, and 1 year in adolescence. Final decisions regarding age ranges of participant groups must be based on the specifics of each study, including considerations of task demands, task difficulty, and components of interest.

Screening

As in any research study, participants should be screened for several factors that are thought to influence the dependent variable of interest, although specific exclusion criteria may vary depending on the hypotheses, population, and age group of interest. For most populations it is recommended that the following be described and/or documented, due to presumed or unknown influences that these factors have on the EEG or ERP response: age, gender (Hirayasu, Samura, Ohta, & Ogura, 2000; Lavoie, Robaey, Stauder, Glorieux, & Lefebvre, 1998; Oliver-Rodriguez, Guan, & Johnston, 1999), sensory problems, medications, neurological and psychiatric disorders, and handedness (including handedness of first degree relatives; see Oldfield, 1971, for an example of a handedness assessment). In addition, the following are relevant for developmental populations: pre- or postnatal difficulties, including prematurity (Lavoie et al., 1998; Stolarova, Whitney, Webb, deRegnier, Georgieff, & Nelson, 2003), iron deficiency (deRegnier et al., 2000), head size (circumference, inion to nasion and ear to ear measurements, Polich, Ladish, & Burns, 1990), memory span or intelligence assessment (Polich et al., 1990; Stauder, Van Der Molen, & Molenaar, 1998), time of day (especially in relation to feeding, see Geisler & Polich, 1990), and the main source of nutrition in early months of life (i.e., breast milk or formula).

Sample size

An additional consideration in developmental EEG/ERP studies is the number of participants required to obtain enough power to detect significant results. First, although collecting EEG/ERPs is considered a noninvasive procedure, preparation and participation in an ERP study does require a considerable amount of patience and cooperation on the part of the participant. In developmental populations this requirement is not easily realized. The behavioral and emotional state of young infants and children is extremely variable; many participants are unable to tolerate the preparation procedure
or recording and therefore do not produce utilizable data due to extreme fussiness or excessive movement artifacts.

It is currently thought that it is this excessive movement (of the eyes and/or head) that accounts for much of the increased variability in developmental ERP components, although other sources of variability are suspected. Given this increased variability in the ERP response, both between and within participants at younger ages, care must be taken to ensure adequate power. Thus, typical infant ERP studies in our lab have enrollment numbers of 50 participants, with an expected 50–75% retention rate that is highly age dependent (e.g., 65% at 9 months, 50% at 12 months; see also Chapter 4, Table 4.1 for more comparisons of attrition rates over age and in different paradigms).

However, every attempt is made to increase the amount of useable data from every session, such as by using toys to distract the infant during electrode placement, having multiple testing partners who are experienced with children, and testing at a time of day that is best for the infant (see the next section on data collection for more specific suggestions broken down by age group). Due to high and variable rejection rates of developmental data, one must be mindful of differences that may arise due to the differential ability of infants and young children to successfully complete one condition versus another. Therefore, we strongly recommend that manuscript method sections include complete descriptions of rejection criteria including the number of participants indicated by the specific reasons for their exclusion.

DATA COLLECTION

Recording

Due to developmental changes in skull thickness (including closure of fontanels in infancy) and variation in cell density, synaptic efficiency, and other physiological parameters, developmental groups require differences in the set up of the data acquisition system. Specifically, amplifier gain settings (i.e., resolution settings) must be altered in order to adequately resolve the ERP signal; sampling rates (i.e., the analog to digital conversion rate) may need to be adjusted in order to register signals of differing frequencies (with the minimum rate being twice the highest frequency of the signal to be measured); and filtering and scoring parameters need to be specified. For instance, in an ERP experiment with 9-month-olds using a low-density Grass-Astromed© amplifier, we commonly use a gain of 20,000 µV, a sampling rate of 200 Hz, a notch filter at 60 Hz, and headroom of ± 250 µV. However, for the same study in adults, we would use a gain of 50,000 µV, a sampling rate of 200 Hz, a notch filter at 60 Hz, and headroom of ± 100 µV.

In short, headroom is a function of the range of values accepted by the A/D board and the gain. For adults, data are typically collected with a ± 100 µV headroom, and this usually does not need to be reduced (or “scored down”)

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any further offline since normal adult brain activity falls within these bounds. However, for infants, due to the large variability and increased amount of movement artifacts, a wider headroom range may be used for data collection. This range is then reduced offline, in order to remove large artifact signals. Although there is still debate about the range of amplitude of typical infant and child brain activity, current consensus is somewhere between ±100 to 150 µV. We have provided guidelines for ERP data collection in Table 1.1 from our laboratory; however, these values may differ for various recording systems and in EEG research (which requires a higher sampling frequency). Furthermore, these settings may be changed depending on how the data are to be used. For example, if 6- and 9-month-olds were to be directly compared, it would be appropriate to have the same recording specifications for both ages.

Testing session specifics

There are several factors in developmental EEG/ERP testing sessions that differ from adult testing sessions. For groups of all ages, session length (including preparation) and the number of trials attempted and expected to be completed should be considered. In our laboratory we have found the following recommendations useful regardless of the age of the participant group, whereas in the sections following we make additional recommendations that apply to specific age groups. First, experience with infants and children is desirable, due to the fact that the procedure is often a very novel experience to infants and children and it is important to make the participants and their caregivers comfortable. Second, a welcoming preparation room with many toys and “distractor” items will also help both the child and the caregiver feel comfortable in the unfamiliar surroundings during the introduction to the procedure and preparation. In the actual testing room we

<table>
<thead>
<tr>
<th>AGE</th>
<th>Amplification factor* (Gain)</th>
<th>Sampling rate</th>
<th>Headroom</th>
<th>Scoring parameters (A/D units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 months and 6 years and above</td>
<td>50,000</td>
<td>200 Hz***</td>
<td>± 100 µV</td>
<td>± 100 µV</td>
</tr>
<tr>
<td>3 months to 6 years</td>
<td>20,000</td>
<td>200 Hz</td>
<td>± 250 µV</td>
<td>± 100 to ± 225 µV**</td>
</tr>
</tbody>
</table>

* High-density systems, such as the EGI© system, have high input impedance amplifiers and gain settings may vary.

** For example, using the following equations: Minimum A/D units: 0 + (headroom/2) − X µV / precision) and Maximum A/D units: 4096 − (headroom/2) − X µV / precision). If headroom is ± 250 µV, the gain is 20,000, and data that exceed ± 100 µV need to be rejected, the calculation (using a 16-bit data acquisition board) is: Min A/D units: 0 + (250 − 100) µV / (500/4096)) = ~1229, Max A/D units: 4096 − (250 − 100) µV / (500/4096)) = ~2867.

*** Sampling rates in EEG paradigms are typically higher (500 Hz) as the minimum rate required is twice the highest frequency of the signal to be measured.
recommend placing a screen around the area where the infant or child is sitting and removing any distracting items from the room in order to keep their attention focused on the computer screen. This will help to minimize movement artifacts. Finally, for all age groups, we recommend that the experimenter(s) have some means, either during data collection or during data analysis, to ensure that data are accepted only when the infants are motionless and attending to the stimuli. For example, experimenters could monitor infants’ looking during the task and have access to both a repeat button and a pause button. This will reduce artifacts due to either movement or eye blinks, and will allow the experimenter to take short breaks from testing if the infant becomes fussy.

**Newborns**

Data collection with newborn infants involves “passive” viewing or listening paradigms. During auditory tasks newborns are typically in an active state of sleep or awake, and artifacts are uncommon, due to the newborn’s limited range of movement. In fact, most newborn infants are able to complete 50–200 trials, as the experiment can usually be paused to accommodate changes in the newborn’s state (e.g., if the newborn becomes fussy). One important consideration when studying newborns is the portability of the data collection system. Often it is desirable to record electrophysiological data within a day of birth and thus requires that these studies take place in a hospital setting, preferably in different hospital rooms so that disturbance of baby and mother is minimal.

**Infants**

Data collection in infants also typically involves “passive” viewing or listening paradigms. For the most part, infants are easily distracted during preparation by playing with a second experimenter or engaging with toys. Depending on the age and locomotor abilities of the child, we recommend the use of a highchair or self-contained walker to keep the infant from crawling around the room during preparation. During recording, it is preferable if infants remain in a highchair or car seat in front of the computer screen presenting stimuli, with the caregiver seated a little behind and to the side of the infant. It is important to minimize the amount the infant turns to look at his/her caregiver. In some cases, infants may be more comfortable sitting on their caregiver’s lap during stimulus presentation and ERP recording but this typically increases movement artifact. If the infant sits on the caregiver’s lap, we recommend instructing the caregiver to let the infant move around only as much as necessary, but request that the caregiver not bounce the infant on his/her knee, as such movement creates artifacts in the data. Furthermore, in looking paradigms (such as habituation paradigms) we suggest that the parent be blindfolded to reduce possible biases.
Often, during data collection, infants become inattentive, restless, or fussy. Therefore, in visual experiments an experimenter typically sits next to the infant and directs the infant’s attention to the stimuli by tapping or pointing at the screen. (Note: To decrease potential biases in the data due to artifacts that result from consistent movements to only one side, the side on which the experimenter sits should be counterbalanced or randomized.) Additionally, the experimenter who is directing the infants’ attention to the stimuli should be naive to stimuli or conditions of interest in order to reduce possible biases. In auditory ERP studies or during resting EEG data collection, it is also important to achieve eye fixation and reduce movement in order to minimize artifacts. In such cases, providing an interesting screen saver or object (e.g., bubbles) for the infant to watch can be quite useful (for other examples see the section on Task Design earlier in this chapter).

Visual stimuli can either be presented by the computer at a constant rate, with the option to repeat a trial or pause the experiment if the infant is not attending to the stimuli, or the experimenter can control stimulus presentation and only present stimuli when the infant is attending. One experimenter may be needed to control the stimulus presentation and determine when the infant is attending to the stimulus while the other experimenter directs the infants’ attention. If necessary, the infant may have a pacifier, bottle, Cheerios™, cookie, or teether, although there is some concern that sucking on such objects may result in movement artifacts and thus should be well documented and examined to determine any influence such items have on the data (cf. Johnson et al., 2001; Picton et al., 2000).

In sum, there are several ways to create a more comfortable atmosphere for infant and child participants and their caregivers both during preparation and EEG/ERP recording. We encourage researchers to try several of the suggestions mentioned above and create new strategies that are appropriate for different types of studies. However, we conclude this section by acknowledging that there is a trade-off between introducing exogenous factors that may influence data (e.g., pacifiers, short breaks, etc.) and keeping participants comfortable and happy in order to acquire usable data.

Reference montages

The appropriate type of recording reference depends largely on the inter-electrode distance. Typically, low-density montages (32 electrodes or less) use a common bipolar. The difference in amplitude between the scalp electrode of interest and a reference electrode that is equidistant from all other electrodes (commonly the vertex or Cz in the 10–20 system) is recorded during data collection, and then the data are re-referenced offline to a mathematically linked reference recorded separately from two single sources (e.g., the ear lobes or mastoids). With high-density montages such as the EGI system (64, 128, 256 electrodes) an average reference is typically used. The average reference is calculated by subtracting the mean of all electrodes from each
channel. An important note here is that it is not the density that determines the type of reference per se, but instead the inter-electrode distance. An average reference can be used when the inter-electrode distance is less than 2–3 cm. Junghöfer and colleagues (1997) suggest that the optimal number of electrodes on an adult head is approximately 256 and on the infant head about 128 (although 64, and possibly 32, electrodes can yield a sampling density of less than 3 cm in infants depending on the age of the infant and size of the infant’s head; Junghöfer, Elbert, Leiderer, Berg & Rockstroh, 1997 cited in Johnson et al., 2001).

In our experience, the best way to record a mathematically linked reference is by affixing electrodes to an adhesive foam pad and placing them behind the infant’s or child’s ears on the mastoid bone. However, this is problematic if the infant has a great deal of hair; the adhesive pad may stick to the hair and not remain in place. Ear clips are also available which clip to the infant’s ear lobes, yet our lab has found that these do not consistently remain on the infant’s ears and have to be replaced frequently during the recording session. When using the average reference, the data are referenced online to one of the electrodes on the scalp (usually the vertex) and then later re-referenced to the average. The original online recording does not present any unique problems except that one must ensure this essential electrode has a low-impedance connection with the scalp.

It is important to note that different referencing configurations can influence the amplitude and latency of the components of interest. Depending on the distribution of the components and the reference used, amplitudes can be smaller or larger and latencies slower or faster. A recent investigation using a face-processing paradigm in adults reported that both the amplitude and latency of several adult components (VPP, N170, and P300) were influenced by reference type (Abrams, Westerlund, Hersey, Gustafson, & Nelson, 2004). As illustrated in Figure 1.3A, the adult vertex-positive potential (VPP), commonly observed over fronto-central sites, showed a smaller amplitude when an average reference was used compared to either a linked mastoid, linked earlobes, or left mastoid reference. However, as illustrated in Figure 1.3B, the adult N170, which is maximal over posterior-temporal sites, was larger when an average reference was used. Thus, when choosing the referencing montage for any particular study, the components of interest must also be taken into consideration, as a reference proximal to the sources may reduce the ability to distinguish significant differences.

It has also been noted that because activity recorded at the mastoid electrodes may include background noise as well as cephalic activity, using the linked mastoids re-reference can add variability to the data (Abrams et al., 2004). This increased variability may influence the ability to observe consistent differences between conditions or groups. Therefore, caution must be used when comparing data between investigations utilizing different references.
Figure 1.3 Effects of four different references on adult components elicited during a face-processing paradigm. (A) Components with a fronto-central distribution, such as the vertex-positive potential (VPP) and P300, show decreases in amplitude when an average reference is used compared to either a linked mastoid, linked earlobes, or one left mastoid. (B) In contrast, components that are maximal over posterior-temporal sites, such as the N170, show increases in amplitude when an average reference is used. (Figure 1.3 kindly provided by and reproduced with permission from Abrams et al., 2004.)
Data reduction

Artifact rejection

Artifacts refer to unwanted noise in the electrophysiological signal that can result from many sources. The largest source of artifact in infant ERPs is movement artifact unrelated to EMG (i.e., high-amplitude or offscale activity as opposed to high-frequency activity of electromyogram, or EMG). However, artifacts can also be caused by EMG (e.g., head or body movements) and eye movements (e.g., blinking). In the previous section we made several suggestions as to how to reduce artifacts and ensure that the infant attends to the stimuli. Far more challenging are artifacts resulting from eye movements, which may disproportionately contaminate anterior recording electrodes. These artifacts may result in the misattribution of the component source to the frontal region of the brain, when it rightly belongs in the eyes and should be excluded from data analysis (Nelson, 1994). Fortunately, the amplitudes of infant ERPs tend to be much larger than adult ERPs (most likely due to physiological differences such as thinner skulls, and less dense cell packing in brain tissue). As a result, developmental researchers have found that it takes considerably more eye activity to contaminate the ERP signal in infants compared to adults (see Nelson, 1994, for further discussion). However, to ensure against contamination due to electrooculogram (EOG) activity, we recommend recording eye movements, using computer algorithms, and visual inspection of the data to identify and delete corrupted trials (see Nelson, 1994, for details).

Specifically, our lab uses a bipolar recording for the EOG recording (i.e., the upper eye electrode is referenced to the lower eye electrode), which provides us with a measure of the eye activity itself. Typically, the recording configuration consists of two electrodes placed on the supra and inferior orbital ridges of the eye. This configuration allows for the detection of blinks and, with somewhat less precision, horizontal eye movements (e.g., saccades). In an ideal situation, recording both vertical and horizontal eye movements is preferable, but from a practical perspective, if participants are not able to tolerate multiple electrodes near the eye, vertical eye movements are considered relatively more problematic and should be recorded. However, if the study involves presenting stimuli in the periphery, it is necessary to record both vertical and horizontal eye movements. Although it is becoming increasingly common with adult participants to use mathematical routines for identifying and subtracting artifacts due to eye movements to preserve the trial for averaging and analysis, this technique should only be used when it is ensured that the infant’s eyes were not moving during the time the stimulus was being presented. Moreover, given differences in head size and shape between infants and adults, different propagation factors may dictate the utilization of different algorithms for subtracting EOG artifacts. In practice, our lab has adopted the following procedures for dealing with infant EOG
activity. If the slope of the EOG activity is less than 250 \( \mu V/100 \text{ ms} \) and the infant’s eyes were fixated during the stimulus presentation, we apply a blink correction algorithm (Gratton, Coles & Donchin, 1983). After the data have been edited for EOG artifacts, each individual participant’s data are visually inspected; if it appears that eye movements were occurring consistently and appear to distort the ERP signal, especially at the anterior electrode sites, we reject those trials from the average and subsequent analyses.

When editing data for artifacts, many benign sources of activity can be detected (e.g., head movements, eye movements, blinks, and so on). In addition, sources of abnormal activity, such as seizure activity, may also become apparent during data collection or data analysis. A final recommendation is that researchers be generally familiar with the appearance of seizure activity and establish procedures for reporting such activity if and when it is suspected (either during or after data collection). Although this is very rare, due to the young age of some participants many seizure disorders may not yet be detected because of the ambiguous way they present themselves behaviorally (situations such as this are similar to incidental findings of structural abnormalities in the brains of normal or typical participants in fMRI studies and should be handled in a similar manner). Notifying the parents of such a possible concern should be done with great care and accompanied with a referral to a competent physician.

**Averaging**

One issue alluded to above that is highly pertinent to developmental ERP data concerns the large variability in waveforms (both between and within participants). Indeed, Nelson and colleagues report more between-participant variability in infants than in adults and children tested under the same conditions (Nelson, 1994). Although part of this variability is the result of increases in artifacts (as discussed above), there is a great deal of variability between participants as a function of the total number of trials contributed by each infant during the ERP session (Snyder, Webb, & Nelson, 2002). Infants vary widely in the number of trials they complete in an ERP session, with some completing as few as 20 trials and others completing over 100. Importantly, between-participant differences that arise from differences in the number of completed trials have been associated with both amplitude and latency differences in certain components (e.g., the Nc component in 6-month-olds; see Snyder et al., 2002).

In addition to the differences that lead to increased between-participant variability, there is often a great deal of within-participant variability in developmental ERP data. In fact, variability in the infant’s brain response to the same stimulus over time has been reported. Differences in topography (of both the Nc and slow wave activity) have been detected in the same participant’s data depending on whether the first half or the second half of their data from one testing session was included in their final data set. These
differences may depend on the infant’s familiarity with the stimulus (Snyder et al., 2002); however, they also may arise from state changes in the infant during data collection (e.g., changes in sleepiness, fussiness, or comfort levels).

Such individual differences are important and can be analyzed separately to answer a different line of questions. However, these differences can result in an extraordinary amount of variability in group data sets. In fact, it is not uncommon to fail to find statistical differences between two experimental conditions that visually appear to be vastly dissimilar from one another. These findings may, of course, reflect the actual equivalence of two experimental conditions. However, null findings can also be due to insufficient power to detect differences due to large between- and within-participant variability. Although methods for analyzing such variability exist (e.g., analyzing variances instead of means) these methods are not common in the literature due to the fact that they are mathematically complex and not easily implemented or interpretable (Nelson, 1994; Taylor & Baldeweg, 2002). Ideally, the signal-to-noise ratio should be maximized both within individual participants, by including a large number of individual trials in a cross average (see Figure 1.4), and between participants, by including a large number of participants in each group (see Figure 1.5). Although it varies from study to study, our current heuristic is to require that an infant contribute at least 10 to 20 artifact-free trials to their individual average and at least 10 infants contribute data for each experimental condition. This same general principle applies to EEG data as well. To obtain stable estimates of spectral power, a minimum of 10–15 seconds of artifact-free EEG is recommended (Davidson, 1995). Without these or more stringent criteria, the signal-to-noise ratio is often compromised and significant results remain elusive despite genuine differences between experimental conditions (i.e., a Type II error). Therefore, we recommend that investigators report estimates of effect size and conduct power analyses to determine the number of participants required to obtain significant effects, and caution the interpretation of null findings with small sample sizes.

STATISTICAL ANALYSIS

In the following sections we comment on the utilization of different techniques used to statistically analyze developmental data, including ANOVA and MANOVA, hierarchical linear modeling (HLM), independent components analysis (ICA), and principal components analysis (PCA). For a full discussion, we refer the reader to other sources regarding these topics (e.g., Handy, 2004; Johnson et al., 2001; Reynolds & Richards, 2003; Richards, 2003a, 2003b), as our discussion will highlight concepts that are especially relevant when working with developmental data.

In EEG studies the dependent variables consist of absolute power, relative power, coherence, or hemispheric asymmetry. More specifically, absolute
power is calculated through fast Fourier transform and divided up by spectral frequency for each electrode site. Relative power reflects the percentage of power in a specific frequency bin at each electrode site, relative to total power in all frequency bins. EEG coherence between two electrode sites reflects the power and phase dynamics between two signals, the covariation of which reflects the strength of the relationship (Taylor & Baldeweg, 2002). Finally, hemispheric asymmetries in power reflect the difference in the degree of activation between the left and right hemispheres of the brain (e.g., frontal lobe asymmetries; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). It is also important to note the common practice of applying a log transformation to the measure of power to normalize the distribution before analyses are conducted.

In adult ERP studies, the typical dependent or response variables include: average or peak amplitude, area below or above the curve, and latency to peak measurements. The independent or predictor variables include condition or task factors. Average amplitude measurements and area measures are typically used with components that do not exhibit a distinctly peaked component. For example, some investigators have used average amplitude to analyze the N400 component (e.g., Bentin & Deouell, 2000; Eimer, 2000). For data occurring in longer latency windows, such as slow wave activity, measurements of area under the curve are typically used. Area measurements tend to be less sensitive to noise but may also underestimate differences between participants, conditions, and electrodes (van Boxtel, 1998). For clearly defined components, such as the N170 or the P300, peak amplitude and corresponding latency measures are often used with similar criteria to those used in adult data (Carmel & Bentin, 2002; Donchin, McCarthy, Kutas, & Ritter, 1983).

Currently, statistical analyses that use the appropriate dependent variables mentioned above are similar if not the same as those analyses conducted with adult ERP data. Both Picton and colleagues (2000) and van Boxtel (1998), provide guidelines for statistical analyses with ERP data that we summarize briefly, but we also refer readers to other relevant sources (e.g., Handy, 2004). It is suggested that the experimenter use statistical analyses that are appropriate to both the nature of the data and the goal of the study. Typically, repeated measures ANOVA models are used to test hypotheses with ERP data. As with any ANOVA, repeated measures ANOVAs test the equality of means. This type of analysis is used when all members of a random sample are measured under a number of different conditions. As the sample is exposed to each condition, the measurement of the dependent variable is repeated (i.e., amplitude or latency at different leads). Using ANOVA techniques is not appropriate in this case because they fail to model the correlation between the repeated measures (the psychophysiological data often violate the ANOVA assumption of independence). To compensate for such violations, the degrees of freedom can be reduced by calculating epsilon as described by Greenhouse and Geisser (1959) or Huynh and Feldt (1970).
MANOVA analyses can also be used to analyze ERP data. As long as the sample size exceeds the number of repeated measures by “a few,” MANOVA analyses will range from being slightly less powerful than the adjusted method (described above) to infinitely more powerful (Davidson, 1972). Davidson
(1972) suggests that the MANOVA approach is the best in cases when one expects small but reliable effects. Furthermore, Davidson (1972) suggests that when using MANOVA, a sample size that exceeds the number of repeated measurements by 20 or more be chosen. Thus, the only case when one should use adjusted ANOVA tests is when the sample size becomes as small as the number of repeated measurements in the design. These typical statistical methods used with ERP data in adults (ANOVA, MANOVA, etc.) which can also be utilized for the statistical analysis of developmental ERP data, have several assumptions. For instance, (1) there cannot be any missing data (cases are deleted listwise), (2) all participants must be measured at the same equally spaced time points (e.g., using the same leads across all participants), (3) the
response variable must be normally distributed, and (4) there is homogeneity of variance (either across time or across measurements). Violations in the above assumptions that, unfortunately, are common in developmental ERP data, result in deletion of cases and an unbalanced design. However, recent
statistical advances such as the use of hierarchical linear modeling (HLM) to analyze longitudinal and repeated measure data sets may be especially relevant for developmental ERP data, due to the fact that it is not constrained by these assumptions. For example, HLM can accommodate unbalanced designs or data sets by estimating missing data. This accommodation may allow researchers to include more data that ultimately results in an increase in the retention rate. HLM can be used to include data from participants who may have unusable or artifact-contaminated data at specific electrode locations (e.g., participants with data that were selectively contaminated at anterior electrode sites by eye artifacts). Furthermore, infants will often only finish one of two experimental conditions (e.g., due to fussiness). The use of HLM may

Figure 1.5 Example of a grand mean waveform (at Cz) containing cross averages from (A) 2 participants, (B) 4 participants, (C) 6 participants, (D) 8 participants, and (E) 10 participants. Note how the variability in the waveform decreases as the number of participants increases. Figure 1.5 kindly provided by Dr Charles Nelson and Alissa J. Westerlund (Developmental Medicine Center, Boston Children’s Hospital, Harvard Medical School).
allow one to keep data from the first condition for subsequent data analysis, as opposed to deleting all of the participant’s data.

**SOURCE SEPARATION AND LOCALIZATION TECHNIQUES IN ERPs**

An increase in the number of electrodes, and a concomitant decrease in inter-electrode distances, results in increased spatial resolution in high-density recording methods. Conventional methods of analyzing electrophysiological data do not take advantage of this added spatial information, thus several investigators have used source separation and localization techniques to statistically identify source generators in the brain (for further illustration see Johnson et al., 2001; Reynolds & Richards, 2003; Richards, 2000).

A well-known challenge in ERP research is localizing activity that is volume conducted to the scalp surface. This problem, known as the inverse problem, refers to the relative difficulty we have in calculating the distribution of electrical current in the brain from surface measurements. Electrical recordings taken from the scalp reflect a mixture of the activity of a number of underlying neural sources (dipoles) in the brain. Source separation consists of identifying sources that account for the largest portion of variance in ERP data. One method of source separation is independent component analysis (ICA), which decomposes spatiotemporal data into separate, or independent, components. ICA can be thought of as an extension of a more commonly applied method, principal component analysis (PCA). PCA uses factor analysis to identify the components that account for the largest amount of variance in the data, then the next largest, and so on. Compared to ICA, which is not restricted to normally distributed components, PCA yields statistically independent components if they are normally distributed (Johnson et al., 2001). ICA assumes that electrical activity recorded at scalp electrode sites represents a linear combination of the concurrent electrical activity evoked by networks of neurons within the brain. It is assumed that these networks are spatially fixed and operate independently in time. However, the “sources” of ICA components may be (one or more) distributed brain networks rather than modularly active brain regions. Source localization procedures assume that brain networks (or dipoles) are physically isolated from one another, whereas ICA procedures only assume that brain networks act independently. Therefore, ICA may be useful as a preprocessing step prior to attempting source localization (Makeig, Bell, Jung, & Sejnowski, 1996). However, this does not solve the problem of source localization. Johnson and colleagues (2001) suggest that ICA may be useful in reducing intertrial variability in analyses of infant ERP data. They state that ICA may be able to extract components from more noisy data (common in infant data) that are similar to those extracted from a data set that has been previously corrected for artifacts. In sum, for developmental ERP data, ICA
could provide a method for examining both intersubject and intertrial variability.

Source localization is a different process from source separation. Source localization attempts to identify the location, orientation, and magnitude of dipoles in the brain that may be responsible for specific ERP components (Nunez, 1990). The software package, Brain Electrical Source Analysis (BESA©) identifies candidate dipoles in the brain by analyzing the distribution of electrical activity recorded at the scalp (Scherg & Berg, 1996). This activity is applied to simplified models of the head in order to determine neural sources. Johnson and colleagues (2001) voice several concerns regarding the use of source localization methods in infants. First, skull thickness, density, and fontanel closure are different in adults relative to infants. Thus, localization techniques used with adults may not be applicable to all developmental populations. Second, the spherical head model used in source localization may be less appropriate for developmental populations, as factors such as skull thickness and head circumference may be more variable in infant compared to adult populations. There are currently no software packages (such as BESA) that attempt to compensate for these differences. Developmentally appropriate head models may increase the feasibility of source localization in developmental populations. Although high-density ERP techniques appear to provide researchers with the ability to estimate sources of neural activity, it is recommended that source localization only be combined with strong theoretical foundations concerning anatomical localization (e.g., Richards, 2003a). In fact, Hood argues that although relatively specific areas may “light up” under some conditions, such localization is of limited value on its own as explanation, and provocatively claims that “in most cases it [source localization] simply confirms the experimenter’s expectation that there is event-related activity occurring in the brain” (Hood, 2001, p. 215).

FUTURE DIRECTIONS

There are several areas of developmental EEG/ERP research in need of improvement. First, further headway in grounding developmental EEG/ERP research in behavior is needed. New behavioral measures need to be utilized (especially in conjunction with ERP measures), and new paradigms, which facilitate a convergence of behavioral and electrophysiological data, need to be designed. Second, future research should aim to explore the development of ERP components (e.g., Webb et al., 2004). Such knowledge can be combined with our increasing knowledge of the development of EEG rhythms and the brain in order to refine data collection parameters. This will allow ERP recordings to accurately capture the dynamic development of the brain. Third, statistical methods, which accommodate missing data, should be applied to developmental data sets. This strategy will help to ensure that
valuable information is not lost due to insufficient statistical techniques. In addition, algorithms used to identify artifacts in adult EEG/ERP data analysis should be altered to accommodate the wide variability in infant data. This will ensure that similar techniques can be used across age groups. Finally, if researchers continue to use source localization techniques, parameters suitable for infant and child data need to be developed and established in available software.

In conclusion, the challenges of developmental research include issues ranging from designing studies that are sufficiently interesting in order to recruit and sustain infants’ attention, to successfully placing the desired number of electrodes on infants’ heads, to the careful reduction of variability in data and rejection of artifact-contaminated data. However, the ultimate challenge in conducting developmental EEG/ERP research is to take what is known from other areas of research, which utilize different methodologies, and combine this information with electrophysiological data in innovative ways to produce converging evidence, which supports theoretical claims. The use of consistent and appropriate methods will, we hope, contribute to this goal. Furthermore, we hope that methods for developmental EEG/ERP research will continue to be refined after the publication of this chapter. We underscore the importance of a collaborative approach that will prove to be the most powerful tool in examining complex developmental changes in the brain from infancy through the lifespan.

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Visual evoked potentials (VEPs) are used to assess the integrity and maturity of the visual system in infants and young children (Fulton, Hartmann, & Hansen, 1989; Hartmann, 1995; Mackie & McCulloch, 1995; Mellor & Fielder, 1980; Skarf, 1989; Taylor & McCulloch, 1992). The retinae and visual pathways develop very rapidly during the last trimester of gestation and the early months of life, which is reflected in dramatic changes in VEPs. Following this period of very rapid development, maturation of VEPs proceeds more gradually throughout infancy and childhood. VEPs are particularly useful in infants as they are easily recorded and precise normal limits have been established for a range of functions.

By convention, VEPs are defined as cortical potentials that are time-locked to repeated presentations of a visual stimulus, in the absence of a defined task and without significant cognitive content. However, the distinction between VEPs and event-related potentials to visual targets is never absolute, as both visual and cognitive processing mature in tandem. In this chapter, it is presumed that VEPs to repetitive visual stimuli reflect visual functions such as resolution, contrast, colour, and motion, while cognitive processing such as novelty and memory make minimal contributions to the resulting VEP.

In adults, the first major component of VEPs to commonly used pattern stimuli likely arise from surface negative activity of the primary visual cortex around the calcarine sulcus, V1. The generators of the other early components, those within 200 ms of the stimulus, are generated in V1 and in several visually active cortical areas in the occipital and parietal cortex (Di Russo et al., 2005; Schroeder, Teneke, Givre, Arezzo, & Vaughn, 1991; Vanni, Warnking, Dojat, Delon-Martin, Bullier, & Segebarth, 2004). Infant VEPs have relatively few components with broad scalp distributions and there is very little information available regarding their cortical origins. It seems likely that the cortical sources of immature VEPs would be relatively extended. Source locations for individual components in infants may overlap and may evolve during the maturation process.
VEP STIMULATION AND RECORDING IN INFANTS

VEP stimuli

VEPs are classified according to both the rate and the type of visual stimulation. Those elicited by abrupt stimulation followed by relatively long inter-stimulus intervals are called transient VEPs and consist of a series of components that are usually labelled according to their peak time relative to the stimulus onset. In adults, stimulation below four times per second will elicit a transient VEP. In infants, transient VEP stimuli are typically presented twice per second in healthy infants after 10 weeks of age, and once per second for very young infants or those at risk for abnormal development.

Rapid repeated visual stimulation elicits VEPs that overlap in time producing a continuous oscillating waveform. These are called steady-state VEPs. The oscillating components of steady-state VEPs coincide with the frequency of the stimulation and its harmonics so that this type of VEP is usually analysed in the frequency domain (Bach & Meigen, 1999). Most strategies for rapid VEP signal detection and threshold estimation use steady-state VEPs.

Although virtually any type of visual stimulus will elicit a VEP, stimuli are selected to isolate an underlying visual function. Luminance VEPs can be elicited by transient luminance stimuli (flash, onset or offset of light) or by steady-state luminance stimulation (flicker).

Stimuli that isolate pattern vision are usually designed with constant average luminance so that the resulting VEP depends solely on processing of pattern information. Pattern VEPs can be designed to test a wide range of visual functions, such as resolution, orientation tuning, contrast detection, motion, and binocular visual functions.

VEP testing strategies for infants

Although infants do not follow instructions about fixation and attention, they are naturally attracted to visual stimuli. Thus, VEP recording is straightforward in alert, attentive infants. Infant VEP amplitudes are larger than those of adults allowing good quality VEP recording with shorter recording times. These large amplitudes are in part due to the thin infant skull that allows the electrode to be positioned close to the cortex with much lower electrical insulation than that of the thicker adult skull. Additionally, neural synchrony may be greater in the infant visual cortex compared with that in a more developed brain.

To facilitate recording VEPs in infants, the stimulus should be positioned away from distracting objects and people: a testing booth or moveable screens are useful. Fixation should be monitored and VEP recording interrupted during fixation losses. Useful strategies to improve fixation include dangling and tapping the fixation screen with small objects (usually keys) and superimposing or interrupting the stimulus with interesting pictures, animation,
or input from a live camera (for example, a parent encouraging fixation). Although such strategies introduce random interruption or degradation of the stimulus, the attention and fixation greatly outweigh the disadvantages (Fulton et al., 1989; Kriss & Russell-Eggitt, 1992; Skarf, 1989). Finally, young infants are best tested using a flexible approach that allows the infant to adopt his/her preferred position (sitting, reclining, over a shoulder) and ensures appropriate breaks for feeding, changing, or rest (Figure 2.1).

**Standard VEP tests**

Standardised VEPs are the basic tests used to assess the integrity of an infant’s visual system. Standard VEP stimuli and recording methods are defined in the VEP standard of the International Society of Clinical Electrophysiology of Vision (ISCEV) (Odom et al., 2004). This standard as well as guidelines for calibration (Brigell, Bach, Barber, Moskowitz, & Robson, 2003) and standards for other electrophysiological tests of the visual system are regularly updated <www.iscev.org/standards>. The standards specify recording conditions and define standard flash and pattern stimuli.

For flash VEPs the standard stimulus is brief flash from an extended source (strobe or screen flash of at least 20 degrees of visual angle) with a flash luminance between 1.5 and 3 candela seconds per metre squared. Although standard flash VEPs demonstrate high inter-subject variability, they are particularly useful for those with poor fixation, reduced vision, or defects affecting the optics of the eyes.

For flash VEPs, the standard stimulus is brief flash from an extended source (strobe or screen flash of at least 20 degrees of visual angle) with a flash luminance between 1.5 and 3 candela seconds per metre squared. Although standard flash VEPs demonstrate high inter-subject variability, they are particularly useful for those with poor fixation, reduced vision, or defects affecting the optics of the eyes. For pattern VEPs, the standard stimulus is high-contrast, black and white checkerboards with large checks (check width, 1 degree of visual angle) and small checks (check width, 0.25 degree). Checkerboards are visually complex but have been adopted as the standard because they are used widely and because they elicit large amplitude VEPs. The preferred presentation mode for standard checkerboards is pattern-reversal, abrupt alternation of black and white checks without a change in average luminance. This ensures that there will be no stimulus present if the pattern is not resolved. Pattern-reversal VEPs have low intra-subject variability in waveform and in peak latencies, particularly of the major positivity, P100, which peaks approximately 100 ms after pattern reversal in adults. The alternative mode of presentation for standard check stimuli is onset/offset, in which the pattern is abruptly substituted for a diffuse grey background. As the onset and offset must be achieved with no absolute or transient change in the average luminance or colour, this stimulus is technically more difficult to achieve compared with pattern reversal. Onset/offset VEPs have greater inter-subject variability.

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1 A brief flash is within the neural integration time of the retina, which varies with background and adaption levels but should be no longer than 0.5 ms. Brief flashers are specified by the “total luminance integrated over the flash duration”, often abbreviated “flash luminance”.
Figure 2.1 Infants prepared for VEP testing. In this case, disposable orthopaedic wrap is used to keep the electrodes secure. The young infant has adopted his preferred position, looking over the adult’s shoulder (upper). When older the infant prefers to be seated with an object to keep his attention.
compared with pattern reversal VEPs, but they are more robust in cases of poor fixation and nystagmus (Apkarian, 1994a; Hoffman, Seufert, & Bach, 2004; Saunders, Brown, & McCulloch, 1998).

An ISCEV standard VEP is, in general, quick and easy to record in most infants. All paediatric laboratories should incorporate standard VEP testing into every protocol to document the integrity of the visual system in a way that is comparable with other laboratories and with published normative data.

MATURATION OF LUMINANCE VEPs
(FLASH AND FLICKER)

The earliest indication of an intact visual pathway from the retina to the brain is a transient VEP to flash stimulation, which can be recorded from the occipital scalp in premature infants from approximately 24 weeks after conception (Ellingson, 1960; Gross, Harding, Wilton, & Bissenden, 1989; Taylor, Menzies, MacMillan, & Whyte, 1987a). The premature flash VEP is dominated by a slow, broad negativity, usually called N3, at about 300 ms. Between 30 and 36 weeks after conception, N3 is typically a bifid peak (Ellingson, 1986; Tsuneishi, Casaer, Fock, & Hirano, 1995). From 35 weeks after conception, the flash VEP of healthy infants typically has several components with a prominent positivity, P2, preceding the N3. Between term age and 15 weeks after term, there is a phase of rapid maturation of the flash VEP. This phase is characterised by the emergence of an earlier positivity (P1), an overall shortening and sharpening of all peak latencies, and the disappearance of the N3 component. The waveform of the flash VEP during early maturation is illustrated in Figure 2.2. After 15 weeks of age, flash VEP maturation progresses much more slowly and the mean peak latencies for infant VEPs fall within the range of adult values (McCulloch, Skarf, & Taylor, 1993).

Flash VEPs in young infants have generally been studied in hospital settings often without calibrated, standard flash stimuli. Hand-held strobes and LED flashing goggles give qualitatively similar VEPs with overlapping normal ranges for peak latencies (Taylor et al., 1987a). However, even within a single study, the flash VEP has a broad normal range in healthy infants so that only gross delays or non-recordable flash VEPs are associated with increased visual or neurological risk (Shepherd, Saunders, McCulloch, & Dutton, 1996b).

Sleep is a confounding factor in the study of the flash VEP of young infants. Quiet sleep is a convenient and artifact-free opportunity to test very young infants but VEPs recorded during sleep differ from those of alert infants with both longer peak latencies and smaller amplitudes (Apkarian, 1993; Apkarian, Mirmiran, & Tijssen, 1991b; Shepherd, Saunders, & McCulloch, 1999a; Shepherd et al., 1999b).

Steady-state luminance stimulation (flicker) elicits optimal VEP amplitude at a stimulation frequency of 4–5 Hz in young infants from birth to 3 months.
of age (Ellingson, 1960; Pieh, McCulloch, Shahani, & Bach, 2005; Regal, 1981). Infants show maturation of this optimum stimulus frequency in the first year of life, but the adult value for optimum frequency of 12 to 15 Hz is not reached by 15 months of age (Pieh et al., 2005; Regan, 1986). The temporal resolution limit—that is, the highest flicker frequency that elicits a detectable VEP—is more difficult to determine and shows high inter-subject variability. At birth, the highest values for this limit are around 15 Hz in infants during quiet sleep (Ellingson, 1986). Apkarian (1993) used bright sinusoidally modulated flicker in alert infants and reported that the temporal resolution limit is below 20 Hz for young infants and matures to over 50 Hz by 8 months of age. Maturation proceeded slowly in the first month of life, rapidly between 2 and 6 months, and more gradually thereafter.

Figure 2.2 Maturation of the flash VEP waveform is illustrated for pre-term (<40 weeks gestation) and post-term infants. Traces are overlaid to show reproducibility. The major components N3, P2, and P1 are labelled at their first occurrence and indicated by an arrow thereafter. (Figure courtesy of Margot J. Taylor.)
MATURATION OF STANDARD PATTERN VEPs

The dominant feature of the standard pattern reversal VEP is a major positive peak centred at Oz on the occipital scalp (Figure 2.3). This peak, conventionally labelled P100 based on its nominal peak latency in adults, has a large amplitude and low inter-subject variability. The pattern reversal VEP waveform remains dominated by this positive component throughout the developmental period. P100 peaks at 250 to 300 ms in full-term neonates and in premature infants from 32 weeks gestation (Harding, Grose, Wilton,

![Figure 2.3](image.png)

Representative pattern reversal VEPs are illustrated for standard high-contrast large checks (1°) and small checks (0.25° = 15 min. of arc) in healthy infants aged 3 weeks, 10 weeks, and 22 weeks after birth at full term. Overlaid traces show reproducibility. The P100 peak for the averaged traces, indicated by an arrow (↓) for the large checks is at 247, 136, and 108 ms after pattern reversal respectively from youngest to oldest. For the small checks, P100 is not recordable in the youngest infant and is at 153 and 118 ms for the older two infants.
It is widely held that normative data for VEPs may not be comparable across laboratories, and guidelines recommend that laboratories collect their own normative data (American EEG Society, 1984; Odom et al., 2004). However, collection of sufficient normative data for testing young infants throughout the period of early maturation is impractical for many laboratories, as pattern VEP components mature by as much as 10 ms per week during the first 4 months of life. Although none of the published studies of pattern VEP maturation matches the current standards on all of the relevant parameters (i.e., reversal rate, check size, luminance, field size, reference electrode location, and band pass filtering) studies show remarkable agreement when methods broadly similar to standard VEPs are used (McCulloch, Orbach, & Skarf, 1999). The general agreement among laboratories is illustrated for eight published studies (Figure 2.4). However this masks small systematic differences in the VEPs. Specifically, the P100 has a shorter peak latency for larger stimuli (Crognale, Kelly, Chang, Weiss, & Teller, 1997; McCulloch & Skarf, 1991) and lower contrast produced longer latencies (Fiorentini & Trimarchi, 1992).

Several laboratories have also reported data for infant VEPs elicited by small checks similar to those of the ISCEV standard 0.25-degree checks (Birch, Birch, Petrig, & Uauy, 1990; McCulloch & Skarf, 1991; Moskowitz & Sokol, 1983; Porciatti 1984). For very young and premature infants no data for small checks are available because these VEPs are not detectable before 8 to 10 weeks post term age (McCulloch & Skarf, 1991). Smaller patterns give consistently longer P100 peak times but follow a similar pattern of maturation as for large patterns: early rapid maturation followed by a more gradual change. For both standards, the logistic curve provides an efficient description of the maturation of P100 (McCulloch et al., 1999).

ASSESSMENT OF VISUAL THRESHOLDS FROM VEPs

The basic question “How well does the infant see?” requires not only confirmation of an intact visual pathway but also a measure of visual threshold. Measuring visual acuity, the visual resolution threshold for high-contrast stimuli, is the aim of most studies of visual threshold in infants. However, VEPs have been used to measure contrast thresholds and a range of other visual functions.

Using conventional signal averaging, near-threshold visual stimuli do not elicit VEPs that are recognisable and reproducible to an experienced observer. In good recording conditions the critical stimulus of the conventional VEP (i.e., the weakest stimulus that elicits a detectable VEP is two to three times
stronger than the psychophysical threshold) and there are large variations from this in some individuals (Katsumi, Kronheim, Mehta, Tetsuka, & Hirose, 1993; Mackie et al., 1995). In conditions of elevated noise or limited cooperation the disparity between thresholds for conventional VEPs and subjective thresholds is greater.

Strategies to estimate thresholds from steady-state VEPs are based on extrapolation, quantitative signal detection, or both. Extrapolation is possible because the amplitude of steady-state VEPs decreases in a linear fashion as the stimulus approaches threshold. When vision is good, extrapolation to zero amplitude or to the noise level is a useful strategy to estimate visual thresholds in both infants and adults (Jenkins, Douthwaite, & Peedle, 1985; Katsumi, Hirose, Larson, Skladzien, & Tsukada, 1986; Marechal & Faidherbe, 1990; Marg, Freeman, Peltzman, & Goldstein, 1976; Ohn, Katsumi, Matsui,
Tetsuka, & Hirose, 1994). However, extrapolation may be unreliable when vision is poor and VEPs to supra-threshold stimuli are small in amplitude (Bane & Birch, 1992; Ridder, McCulloch, & Herbert, 1998; Sokol 1978). Extrapolation using components of transient VEPs is not recommended as there are non-linearities near threshold and success rates for linear fitting are low (McCormack & Tomlinson, 1979; McCulloch & Skarf, 1994; Sokol & Jones, 1979).

Signal detection of steady-state VEPs can be approached quantitatively using the frequency spectra (Bach & Meighen, 1999; Regan, 1985). Steady-state stimuli evoke cortical activity at the stimulation frequency and at its harmonics. Using a noise estimate, usually calculated from nearby frequencies, steady-state VEP signals can be quantified in terms of a specific signal-to-noise ratio. Signal detection is further enhanced with adaptive filters that estimate the phase of the VEP signal and by considering the VEP at more than one harmonic frequency (Tang & Norcia, 1995; Zemon, Hartmann, Gordon, & Prunte Glowazki, 1997). The signal-to-noise ratio is improved further by recording from appropriately placed surrounding electrodes and calculating the differential signal (Laplacian derivation). Using some or all of these strategies, the VEP is detectable at or near the psychophysical threshold (Bach, 2005; Beers, Riemslag, & Spekreijse, 1992; Eizenman, McCulloch, Hui, & Skarf, 1989; Mackay, Hamilton, & Bradnam, 2003; Tang & Norcia, 1995).

The step VEP is technique that uses steady-state VEPs to measure acuity (see Figure 2.5). Real-time analysis of EEG allows automated reduction of stimulus size on detection of a steady-state VEP using a successive approximation, staircase protocol to find a threshold (Bach, Wolfe, & Maurer, 2005; Eizenman et al., 1989; Mackay et al., 2003). Threshold is determined in less than a minute for patients with good fixation. To this end, the step VEP spends minimal time testing below the acuity threshold.

The method known as the sweep VEP is more widely applied to the study of infant visual thresholds (Norcia & Tyler, 1985a, 1985b). The sweep VEP is elicited by a continuous sequence of steady-state visual stimuli, each presented for a few seconds. The stimuli are ordered in an increasing or decreasing sequence. For example, in a typical “visual acuity sweep” black and white gratings are presented in either pattern reversal or onset–offset modes, beginning with very fine gratings and progressing through medium to wide gratings. The VEP elicited by this “swept” stimulus sequence is then analysed using extrapolation of the steady-state VEP amplitudes to rapidly estimate visual thresholds (Regan, 1977). Figure 2.6 illustrates sweep VEPs for typically developing infants.

VEP measures of infant visual thresholds usually record greater sensitivity levels than those derived from behavioural techniques. Although part of this difference can be attributed to differences between static and reversing stimuli, thresholds based on VEPs also show a different time course of development from that measured from behaviour (Sokol, Hansen, Moskowitz,
Figure 2.5  Step VEP records from normal infants and children are illustrated. A total of 27 check sizes were available from 10.8° (650 min. of arc) to 1.8 minutes of arc (check diagonal) in approximately 0.1 log units. Using real-time analysis of EEG the check size was automatically reduced on detection of a steady-state VEP. Check size was reduced in 0.4 log steps following detection, increased in 0.2 log steps following non-detection, then reduced again in 0.1 log steps until the critical check size (shaded grey here) was found. Equivalent behavioural acuity is estimated using data from artificially fogged adults tested both behaviourally and with the step VEP. (a) 10-week-old infant, critical check 23 min. of arc (1.35 log), estimated acuity 6/56. (b) 6-month-old infant, critical check 11.3 min. of arc (1.05 log), estimated acuity 6/24. (c) 8-year-old child, critical check 3.6 min. of arc (0.56 log), estimated acuity 6/7.5. (Figure courtesy of Alison M. Mackay and Ruth Hamilton.)
Greenfield, & Towle, 1983; Sokol & Moskowitz, 1985; Sokol, Moskowitz, & McCormack, 1992a). When acuity thresholds derived from sweep VEPs are compared in adults with visual acuity measured using eye charts, the results are correlated but are not equivalent. In general, acuity charts record better acuity in those with good vision and sweep VEP acuity is better in those with poor vision (Bane & Birch, 1992; Hoyt, 1986; Katsumi, Denno, Arai, Faria, & Hirose, 1997). When comparing VEP thresholds with infant visual acuity based on fixation preference behaviour, there is even greater uncertainty (Katsumi, Mehta, Larsonpark, Skladzien, & Hirose, 1994; Westall, Ainsworth, & Buncic, 2000).

Success rates are generally high for recording visual thresholds in infants with sweep VEPs (Birch & Petrig, 1996; Norcia & Tyler, 1985a; Norcia, Tyler, & Hamer, 1988) and validity is similar to that for adults (Suttle, Banks, & Candy, 2000). However, accuracy is limited so that the sweep VEP is a good method to estimate vision in populations but caution should be used for assessing individuals (Lauritzen et al., 2004; Ridder et al., 1998).

MATURATION OF VISUAL RESOLUTION AND CONTRAST SENSITIVITY THRESHOLDS

At birth, visual resolution (visual acuity) is limited by both the optical and neural systems (Candy & Banks, 1999; Odom & Green, 1984; Skoczenski & Norcia, 1998). However, very young infants resolve large contours and show evidence of selective adaptation based on spatial frequency (Suter, Armstrong, Suter, & Powers, 1991; Shahani, Manahilov, & McCulloch, 2001). Poor visual acuity in young infants is reflected in the absence of a VEP to small patterns such as the standard small checks (15 min of arc). Early rapid improvement is indicated by emergence of the small check VEP in the majority of healthy infants before 11 weeks of age (Crognale et al., 1997; McCulloch & Skarf, 1991; Moskowitz & Sokol, 1983).

Visual acuity thresholds in infants are usually measured from black and white gratings and expressed as either the angular size of a “stripe” at threshold or as grating spatial frequency in cycles per degree of visual angle. Regardless of the pattern used, the VEP amplitude near threshold relates to the fundamental or largest spatial frequency element in the pattern (Tobimatsu et al. 1993). Threshold detection strategies, like those described in the previous section, are used to define a visual acuity threshold and characterise the time course of its maturation.

Studies of VEP acuity in infants show rapid improvement in the early months of life (Fiorentini, Pirchio, & Spinelli, 1983; Norcia & Tyler, 1985a; Sokol 1978). Figure 2.6 illustrates maturation of visual acuity derived from standard VEPs, from extrapolation of steady-state VEPs and from sweep VEPs. Acuity plotted on a logarithmic scale improves in an approximately linear fashion throughout the first 7 months of life. Differences in VEP
threshold values reflect not only differences in extrapolation methods but also differences in the temporal stimulation rate, which interacts with the VEP amplitude (Orel-Bixler & Norcia, 1987; Norcia, Pettet, Candy, Skoczenski, & Good, 1999; Norcia & Tyler, 1985b).

Figure 2.6 also illustrates that behavioural thresholds are substantially poorer than those derived from VEPs. Part of this difference can be accounted for by differences in the stimuli (behavioural studies usually use static stimuli), but even with matched stimuli behavioural thresholds are different from VEP thresholds (Katsumi et al., 1993, 1997; Sokol et al., 1992a). Behavioural methods require attention and motor responses as well as sensory input to meet the threshold criterion, so equivalence is not expected.

Visual acuity defines the upper resolution limit for high-contrast patterns, whereas the contrast sensitivity function is a comprehensive description of contrast thresholds in spatial vision. Thresholds for contrast detection vary with stimulus size (i.e., with the spatial frequency of the stimulus). Extrapolation of steady-state VEPs can be used to calculate the contrast thresholds across a range of spatial frequencies (Atkinson, Braddick, & French, 1979; Parker & Salzen, 1977; Pirchio, Spinelli, Fiorentini, & Maffei, 1978; Porciatti, Vizzoni, & vonBerger, 1982). With rapid VEP techniques such as the sweep VEP, it is feasible to measure the entire contrast sensitivity function in infants within a single visit (Norcia et al., 1988, 1990).

Contrast sensitivity matures rapidly in the early months of life in tandem with maturation of visual acuity (Atkinson et al., 1979). Young infants under 10 weeks of age show maximal contrast sensitivity for large patterns (low spatial frequencies). The optimum then shifts to higher spatial frequencies, accompanied by an overall increase in contrast sensitivity, which is more marked at the higher spatial frequencies. By 6 months of age the contrast sensitivity function parallels that of adults but is approximately one octave below adult sensitivity levels. Both visual acuity and contrast sensitivity decline rapidly away from the centre of the visual field. In the paracentral field (8 to 16 degrees from fixation) maturation of both contrast sensitivity and visual acuity proceed at similar rates to those in the central field (Allen, Tyler, & Norcia, 1996).

**VEP ASSESSMENT OF OTHER VISUAL FUNCTIONS IN INFANTS**

A number of important elements of infant visual perception have been investigated using VEPs, including chromatic (colour) perception, orientation selectivity, motion perception, binocular functions, and maturation of the functional subsystems in the visual pathways.
Figure 2.6 Sweep VEP data are shown for three healthy children aged 11 months, 23 months, and 8 years, respectively. To produce these graphs, ON/OFF high-contrast grating stimuli were presented at 15 Hz and the amplitude of the VEP at this fundamental stimulus frequency was plotted. Gratings were presented from invisible to visible (high spatial frequency to low spatial frequency as shown in cycles per degree along the abscissa). The straight line used to estimate threshold is fitted through the ascending portion of the amplitude curve to the point of the maximal signal to noise ratio (SNR). Threshold (Thrsh) is recorded for the grating size corresponding to zero signal and the noise levels are indicated by small rectangles. The lower curve is signal phase. Snellen equivalent visual acuity for the three children is 6/11, 6/9.3, and 6/5.7. (Figure courtesy of Sean I. Chen, Arvind Chandna, and Anthony M. Norcia.)
Figure 2.7 Visual acuity maturation in the first 7 months of life is shown using various measurement techniques. The normal range for the behavioural method based on fixation preference is shown with dashed lines (95% confidence intervals for Teller Acuity Cards™). The smallest recordable check size using standard VEP techniques is comparable with the upper limits of this behavioural acuity range (McCulloch et al., 1992; Porciatti, 1984). Extrapolation of VEP amplitudes and other signal detection techniques usually indicate better resolution and more rapid maturation of visual acuity.
Colour vision

This can be studied using purely chromatic stimuli; specifically alternating, unpatterned light stimuli with equal luminance but different chromaticity (spectral constitution). These studies rely on first determining isoluminance for light with different chromaticity. As luminance differences evoke larger VEPs than those evoked by chromatic differences, isoluminance can be identified at the VEP amplitude minimum when luminance is varied in a chromatic stimulus series. Isoluminant stimuli in infants are generally similar to those of adults throughout the developmental period (Beiber, Volbrecht, & Werner, 1995; Pereverzeva, Chien, Palmer, & Teller, 2002). However, VEPs to isoluminant chromatic stimuli are considerably less mature than those elicited by luminance contrast throughout infancy and the time course of maturation is relatively protracted (Crognale, Kelly, Weiss, & Teller, 1998; Madrid & Crognale, 2000).

 colour vision, however, is not isolated from spatial vision and purely chromatic stimuli can also be produced with isoluminant pattern elements. Maturation of VEPs to chromatic contrast lags behind that for luminance contrast VEPs although both processes show similar shifts in spatial scale (Allen, Banks, & Norcia, 1993; Kelly 1997; Rudduck & Harding, 1994). Morrone and colleagues (Morrone, Burr, & Fiorentini, 1993; Morrone, Fiorentini, & Burr, 1996) reported that maturation of both chromatic and achromatic VEPs is slow in the early weeks of life. Others found that the chromatic VEP is undetectable before 7 weeks of age (Rudduck & Harding, 1994). After 8 weeks of age, VEP development accelerates for all stimuli but this acceleration is more rapid for contrast VEPs compared with that for isoluminant chromatic VEPs, which develop more slowly and over a longer time course (Morrone et al., 1993, 1996).

Chromatic contrast VEPs in both adults and infants are larger for isoluminant red-green stimuli than for blue-yellow chromatic contrast. Blue-yellow VEPs mature even more gradually than do the red-green responses (Crognale et al., 1998) and they are undetectable up to 4 months of age using the sweep VEP technique (Suttle, Banks, & Graf, 2002).

Orientation sensitivity and vernier offset

VEPs to large shifts in the orientation of a grating develop rapidly at around 6 weeks of age when they can be differentiated from the VEP to pattern reversal of similar gratings (Atkinson, Hood, Wattam-Bell, Anker, & Tricklebank, 1988; Braddick, Wattam-Bell, & Atkinson, 1986). Orientation tuning (sensitivity to small shifts of orientation) can be identified when pre-adaptation to gratings selectively suppresses the VEP to similarly oriented stimuli (Candy, Skoczenski, & Norcia, 2001). Orientation tuning of VEPs is broad in very young infants; double that of the tuning bandwidth in adults. This shows rapid maturation to adult levels between 6 and 12 weeks of age (Shahani et al., 2002).
Vernier acuity, the ability to detect offsets in linear stimuli, can be isolated in a rapid sweep VEP strategy (Norcia, Wesemann, & Manny, 1999b; Wesemann, Norcia, & Manny, 1996). Infants show striking immaturity in vernier acuity relative to the maturation of pattern vision and orientation sensitivity (Skoczenski & Norcia, 1999).

Motion perception

In visual neurophysiology, motion is distinguished from other dynamic aspects of vision by the criterion of directional selectivity (Braddick, Atkinson, & Wattam-Bell, 2003). When a motion reversal stimulus is alternated with pattern reversal, very young infants show no difference between the pattern and the motion reversal phases in the resulting VEP (Wattam-Bell, 1991). Between 10 and 12 weeks of age, there is a velocity-dependent emergence of the motion-reversal-specific VEP (Hamer & Norcia, 1994). This motion reversal VEP develops later than that for the orientation reversal VEP even when these similar strategies were used in the same group of infants (Atkinson, Wattam-Bell, & Braddick, 2002). Relative to adult VEP thresholds, thresholds for oscillatory motion in infants lag far behind those for contrast reversal until well into the second year of life. Although cortical motion processing has its onset before 3 months of age, aspects of this complex system such as coherence sensitivity and velocity range continue to develop throughout childhood (Braddick et al., 2003).

In normal infants, directional asymmetry in motion processing is revealed only under uniocular viewing conditions (Norcia, Garcia, Humphry, Holmes, Hamer, & Orel-Bixler, 1991). Temporalward motion elicits stronger VEPs than those elicited by nasalward motion (Mason, Braddick, Wattam-Bell, & Atkinson, 2001). This uniocular motion asymmetry constitutes only a brief developmental period; it is absent in very young infants, maximal at 2–3 months of age, and disappears around 6 months of age (Birch, Fawcett, & Stager, 2000; Braddick, Mercuri, Atkinson, & Wattam-Bell, 1998). Unilateral motion asymmetry has attracted considerable attention, not least because it persists to adulthood in those with strabismus or amblyopia who lack normal binocular vision (Birch et al., 2000; Norcia 1996; Shea, Chandna, & Norcia, 1999). The directional asymmetry in VEPs is in the opposite direction and independent of the asymmetry found in the reflex optokinetic eye movements of young infants, which are strongest for nasalward motion (Atkinson & Braddick, 1981; Naegele & Held, 1982; Wilson, Noyd, Aiyer, Norcia, Mustari, & Boothe, 1999). The apparent paradox can be explained by considering the anatomical separation of the underlying neural systems. Optokinetic eye movements for nasalward motion are processed subcortically in the midbrain nuclei, which are functional from birth. The temporalward optokinetic eye movements are mediated by cortical pathways and are functional only after the development of cortical motion processing (Braddick et al., 2003).
Binocular vision

The afferent visual pathways from each eye are segregated until they reach the primary visual cortex. In those with equal vision in the two eyes, uniocular stimulation produces very similar levels of cortical activation. For standard pattern reversal VEPs, amplitudes for left and right eye stimulation of the same individual agree within 20% and peak latencies agree within five milliseconds, similar to the trial-to-trial variations found when stimulating the same eye (Shors, Ary, Eriksen, & Wright, 1986). The fact that binocular VEPs differ from the linear sum of the uniocular VEPs is evidence for binocular interactions. In adults, binocular VEP amplitudes exceed those of uniocular VEPs and peak latencies are slightly shorter (diSumma et al., 1997; Sloper & Colins, 1998). However, during early development, binocular VEPs are relatively much larger, which could indicate less binocular interaction and greater passive summation of monocular inputs (Shea, Aslin, & McCulloch, 1987). Difficulties arise in comparing monocular and binocular VEP amplitudes, however, as both cooperation and the quality of fixation and accommodation are poorer with monocular viewing in infants (cf. Hamer, Norcia, Tyler, & Hsu-Winges, 1989; McCulloch & Skarf, 1991).

Basic binocular interaction is unequivocally demonstrated by the non-linear combination of flicker stimulation delivered to the two eyes at different temporal frequencies. In adults with normal binocular vision, the VEP to such stimuli contains components at the frequency of stimulation for each eye as well as at the sum and difference frequencies, called binocular beat frequencies (Baitch & Levi, 1989). Beat frequencies are absent when binocular interactions are abnormal in conditions such as strabismus and amblyopia (Baitch, Ridder, Harwerth, & Smith, 1991). Beat frequencies are present in infants as young as 7 weeks of age, indicating the existence of basic binocular interactions (Baitch & Srebro 1991; Stevens, Berman, Schmeisser, & Baker, 1994).

Non-linear binocular interactions also occur when patterns are presented to each eye that reverse or oscillate at different rates (Brown, Candy, & Norcia, 1999; Norcia, Harrad, & Brown, 2000). As with luminance beats, these binocular interactions in pattern VEPs are a characteristic of normal binocular vision. Although pattern VEP interactions are present in young infants, there is immaturity in the inhibitory interactions (suppression) when the gratings are cross-oriented throughout the first 15 months of life (Brown et al., 1999).

More advanced binocular functions include fusion of images in the two eyes and stereopsis (depth perception) based on disparities between fused images. These advanced binocular functions can be investigated with VEPs using dynamic random dot correlogram and stereogram stimuli (Julez, 1971; Julez, Kropfl, & Petrig, 1980). For both stimuli, correlated random dot patterns are presented separately to each eye. Regular updating of the dot patterns masks changes that are visible uniocularly. Dynamic random dot
correlograms switch between correlated and anti-correlated phases. In stereo-
grams, changes in apparent depth occur when image disparity is switched
within the correlated dot patterns. Studies of infants using correlograms have
shown that binocular fusion develops before 2 or 3 months of age. (Eizenman
et al., 1999; Birch & Petrig, 1996; Braddick, Atkinson, Julez, Kropfl, Bodis-
Wollner, & Raab, 1980; Braddick, Wattam-Bell, Day, & Atkinson, 1983;
Petrig, Julez, Lehmann, & Lang, 1982). The onset of stereopsis follows the
onset of binocular fusion and is adult-like by 5–6 months of age (Braddick,
1996; Birch & Petrig, 1996).

Functional sub-systems

The primate visual system is organised into several functional sub-systems
that are anatomically and pharmacologically distinct. These can be defined
along three dichotomous dimensions: excitatory versus lateral inhibitory, ON
versus OFF, and magnocellular versus parvocellular. Although there has
been much recent attention to the fact that the functions of these sub-systems
overlap, the basic dichotomies are clear and the substrates for maturational
differences exist (Livingstone & Hubel, 1988; Schiller, 1992). Standard VEP
stimuli do not differentiate the functional sub-systems. Zemon and Ratliff
(1984) used specially designed “windmill-dartboard” stimuli in adults to
identify VEP components associated with lateral inhibitory processing, which
are dissociated from the direct, excitatory system. In this excitatory/lateral
inhibitory sub-system, long-range lateral inhibition was shown to be well
developed at 2 months of age, while short-range inhibitory mechanisms
maturate later, at around 6 months of age (Grose et al., 1989; Sokol, Zemon,
& Moskowitz, 1992b; Zemon, Pinkhasov, & Gordon, 1989). Target and
flanking stimuli presented at different temporal frequencies have provided
evidence that non-specific lateral interactions are functional early in infancy;
lateral inhibition that is tuned to orientation develops in parallel with orienta-
tion sensitivity, between 6 and 30 weeks of age, but position-specific lateral
inhibition is immature throughout infancy (Candy et al., 2001; Hou, Pettet,
Sampath, Candy, & Norcia, 2004).

ON and OFF pathways can be investigated using contrast increments
and decrements, respectively, within a stimulus grid. Evolutionarily these ON
and OFF sub-systems can be viewed as efficient systems to detect light and
dark objects (Schiller 1992). Adults show larger VEPs to contrast decrements
(OFF stimulation) when contrasting squares are smaller than 100 minutes
of arc, but equal VEP amplitudes for ON and OFF when stimuli are larger
(Zemon, Gordon, & Welch, 1988). This asymmetry of OFF and ON path-
ways is established in infants before 2 months of age, although pattern
processing by both sub-systems is clearly immature (Hartmann, Hitchcox,
& Zemon, 1992; Sokol & Moskowitz, 1990; Zemon et al., 1988; Zemon,
Schneider, Gordon, & Eisner, 1996).

The major sub-divisions of the primary visual pathways, the magnocellular
and parvocellular pathways, are anatomically separated from the retinae to the visual cortex with separate layers in the lateral geniculate nucleus (LGN). VEP studies of these sub-systems are surprisingly scarce, perhaps because the considerable functional overlap between the pathways makes them difficult to isolate. However, the large neurons of the magnocellular pathway clearly process primarily motion, flicker, and positional information, while the smaller cells of the parvocellular pathway process primarily high-resolution and colour information. Using a range of strategies that preferentially stimulate each pathway, there is a general consensus that the magnocellular pathway matures earlier and more rapidly than the parvocellular pathway: VEPs to stimuli that are primarily parvocellular, such as chromatic or high spatial frequency stimuli, mature more slowly throughout infancy and childhood than do VEPs to stimuli that are primarily magnocellular, such as low contrast and high temporal frequency stimuli (Gordon & McCulloch, 1999; Hammerrenger, Lepore, Lippe, Labrosse, Guillemot, & Roy, 2003; Madrid & Crognale, 2000).

**CLINICAL APPLICATIONS**

VEPs are particularly valuable in paediatric clinical practice, as infants cannot report symptoms or respond to standard tests of vision. They are used to detect, quantify, and monitor dysfunction of the visual system and to provide a non-invasive, physiological measure of vision that is complementary to behavioural oculomotor and clinical assessment.

In general, standard VEPs are used to address the question “Are the visual pathways intact and developing normally?” VEP threshold measures are used to quantify visual function. VEPs depend on clear optics of the eyes as well as on the healthy functioning of the retinae, optic nerves, and visual pathways, at least to the level of the primary visual cortex. Thus, an abnormal VEP is a non-specific finding, which nonetheless may be invaluable in the differential diagnosis of conditions such as infantile nystagmus (Shawkat, Kriss, Russell-Eggitt, Taylor, & Harris, 2001). As both luminance and pattern VEPs predominantly reflect processing of the central 5 to 10 degrees of the visual field, they are of little use in detecting conditions that affect only the peripheral fields.

At least one standard VEP is required in any clinical study, although other stimuli can be added to address specific clinical questions. Results should be compared with age-matched normal ranges. Prolonged P100 peak latency of a standard VEP can reflect the presence and severity of conditions such as amblyopia, delayed visual maturation, and other forms of visual impairment (Arden & Barnard, 1979; Mackie & McCulloch, 1995a; Mellor & Fielder, 1980; Moskowitz, Sokol, & Hansen, 1987; Skarf, 1989; Sokol, 1983; Taylor & McCulloch, 1992). Amplitude measures have limited clinical utility as VEP amplitude has large variations among individuals and can be degraded by
both artifact and inattention (Cigánek, 1969; Sokol & Jones, 1979). In adults, VEPs are usually recorded separately from the right and left eyes to help identify the site of any lesion. As the relevant issue in paediatric practice is often an assessment of vision with optimal attention and fixation, binocular recording is usually the priority (Odom et al., 2004). Whenever cooperation is sufficient, at least one VEP should be recorded from each eye to assess interocular symmetry. Major clinical applications of VEPs in paediatric practice are reviewed below.

**Visual acuity**

Visual development requires early visual experience, so detection and intervention in infants with subnormal visual acuity is crucial to prevent or minimise amblyopia. Even when visual impairment is untreatable, intervention in the early developmental period improves motor and cognitive learning in visually impaired infants (Sonksen & Dale, 2002; Sonksen, Petrie, & Drew, 1991). Thus in paediatric practice, estimation of visual acuity by sweep or other methods has broad applications, as some disorders, congenital glaucoma or macular hypoplasia for example, may result in widely varied levels of visual acuity. Visual acuity is also a useful measure in infants who are at risk for visual dysfunction, such as those with cerebral palsy or developmental delays, even if normal fixation and following is present. Finally, VEP acuity measurements can aid in the diagnosis of infants with behavioural signs of visual dysfunction.

**Amblyopia**

Amblyopia, the most common visual disorder affecting infants and children, has a prevalence of 2% of the population. Amblyopia is the failure or regression of visual development, which results from poor quality or misaligned optical images. Most often amblyopia is uniconal and associated with squint or uniconal refractive error but other conditions such as congenital cataract and ptosis lead to a more severe form of deprivation amblyopia.

Although VEP testing is not currently routine in the management of amblyopia, both standard and sweep VEPs are sensitive tools for detection and monitoring of treatment regimes (Arden, Barnard, & Mushin, 1974; Odom, Hoyt, & Marg, 1981; Regan, 1977, 1985; Sokol, 1983). Amblyopia affects not only visual resolution but also a range of other visual abilities and there is an extensive literature demonstrating VEP abnormalities in functions such as binocular integration, lateral interactions, and contrast sensitivity (cf. Chadna, Pennefather, Kovacs, & Norcia, 2001; Levi & Harwerth, 1978; Norcia et al., 2000). Clinical studies often emphasise the benefits of VEP testing and monitoring in infants treated very early or particularly high-risk groups such as infants with ptosis or congenital cataract (McCulloch & Skarf, 1994; McCulloch & Wright, 1993; Salomao & Birch, 1997).
**VEPs and visual maturation**

In addition to measuring visual function, VEPs indicate the state of maturation of the visual system, which is particularly useful in clinical trials. For example, VEPs have been used as a measure of neural maturation when assessing the outcomes of infant lipid nutrition (Birch, Hoffman, Uauy, Birch, & Prestidge, 1998; Khedr, Farghaly, Amry, & Osman, 2004; Jorgensen, Hernell, Hughes, & Michaelsen, 2001; Makrides, Neumann, Simmer, & Gibson, 2000; Malcolm, McCulloch, Montgomery, Shepherd, & Weaver, 2003). Similarly, VEP studies have demonstrated maturational delays associated with prenatal exposure to drugs or other adverse conditions (Hamer, Dobson, & Mayer, 1984; Scher et al., 1998; Till, Rovet, Koren, & Westall, 2003).

Even very young infants should be visually attentive when they are alert, so that inattention is always a reason for concern. In a large series of visually inattentive infants without a diagnosed disorder of the visual system, approximately half had uncomplicated, idiopathic delayed visual maturation (Fielder, Russell-Eggitt, Dodd, & Mellor, 1985). In delayed visual maturation, VEPs are usually present but may be abnormally immature. Full recovery of VEPs in conjunction with development of normal visual function and visually guided behaviour typically occurs before 6 months of age. In visually inattentive infants with other concurrent disorders, such as developmental delays and seizure disorders, recovery may be slow or incomplete (Hartel, Holtzman, & Fiensod, 1983; Hoyt, Jastrzebski, & Marg, 1983). Infants with permanent visual impairment are differentiated from those with delayed visual maturation as they have severely abnormal or undetectable VEPs that do not recover (Derek, Leguire, Rogers, & Bremer, 1990; Weiss, Kelly, & Phillips, 2001).

**Disorders of the eye**

When ocular examination is prevented by congenital cataract or corneal opacity, luminance (flash or flicker) VEPs provide useful pre-surgical information about the integrity of the central retinae and visual pathways.

In congenital retinal dystrophies such as Leber’s amaurosis, achromatopsia, and congenital stationary night blindness, the retinal appearance in infancy is often within normal limits. Thus, it is useful to investigate retinal function using the electroretinogram (ERG) when examining paediatric patients. If retinal dystrophy is suspected the ERG is specifically indicated. Standard diagnostic ERG testing requires pupil dilation, dark adaptation, and a contact lens electrode (Marmor, Holder, Seeliger, & Yamamoto, 2004). Sedation may be required to complete standard ERGs (Fulton, Hansen, & Westall, 2003; Jandeck, Kellner, Kraus, & Foerster, 1997; Westall, Panton, & Levin, 1999), so screening ERG procedures may be useful when investigating paediatric patients (Brecelj, 2003; Brecelj & Stirn-Kranjc, 2004; Kriss,
In its simplest form, a screening ERG can be recorded from the lower eyelid with a skin electrode or from a DTL thread electrode in contact with the conjunctiva using a stroboscopic flash stimulus (Kriss, 1994). The ERG is a large retinal potential consisting of an early negative A-wave followed by a positive B-wave. The ERG to a bright flash is well developed at birth although amplitude is immature and develops throughout infancy and childhood (Berezovsky, Moraes, Nusinowitz, & Salomao, 2003; Westall et al., 1999). Full ERG testing is required to follow up an abnormal or undetectable screening ERG.

**The afferent visual pathways**

In paediatric neuro-ophthalmology, VEPs are useful to demonstrate the degree of functional loss, to monitor progression or recovery, and to monitor visual development in infants who may improve. Appropriate radiological studies are required to make a definitive diagnosis of a visual pathway lesion. Disorders of the afferent visual pathways may involve (1) the anterior pathways (optic nerves and tracts), (2) the posterior pathways (optic radiations), or (3) the entire pathway. Common paediatric disorders of the anterior visual pathways include congenital optic nerve hypoplasia, optic nerve atrophy, glioma, and compressive lesions. In general, pattern VEPs are used to give a sensitive measure of function in these disorders (Groszasser, Kriss, Halliday, & McDonald, 1985). However, flash VEPs are useful when function is seriously impaired, for example in infants with optic nerve hypoplasia (Borchert, McCulloch, Rother, & Stout, 1995). Recently, the clinical utility of flicker VEPs was demonstrated for monitoring childhood gliomas (Trisciuzzi et al., 2004).

Albinism is associated with an abnormality of optic stalk development that leads to misrouting of the anterior visual pathways. Specifically, nearly all of the optic nerve fibres from the temporal retinae anomalously decussate at the optic chiasm (Kasmann-Kellner, Schafer, Krick, Ruprecht, Reith, & Schmitz, 2003). Mapping of the visual fields in the midbrain and visual cortex is disrupted. All phenotypes of albinism have this chiasmal misrouting but the other signs, foveal hypoplasia, hypopigmentation of the skin and ocular structures, and nystagmus, overlap with those of other conditions (Apkarian, 1994a; Dorey, Neveu, Burton, Sloper, & Holder, 2003). Chiasmal misrouting can be reliably diagnosed by comparing the lateralisation of unioocular VEPs across three to five occipital electrodes. Although the VEP can be asymmetric across the scalp in individuals with normal optic routing, such individuals have very similar VEP topography from the right and left eyes. In those with misrouting, there is a characteristic asymmetry in the topography of VEPs recorded from each eye (Soong, Levin, & Westall, 2000). This intraocular VEP asymmetry test for misrouting may be reliable using flash stimulation even in the first few days of life (Apkarian, Eckhardt, & Vanschooneveld, 1991a). Pattern onset stimulation improves
accuracy for those over 3 years of age (Apkarian, 1994; Apkarian & Tijssen, 1992).

The posterior visual pathway, specifically the optic radiations around the lateral ventricles, are vulnerable in infancy. In particular, infants born prematurely are at risk for periventricular leucomalacia and those with hydrocephalus characteristically show periventricular damage. In premature infants, pattern VEP recording is difficult before 36 weeks after conception, as these infants sleep most of the time and visual resolution is limited by inaccurate fixation, poor optical quality of eye, and by retinal and neural immaturity. However the flash VEP has prognostic utility as the absence or abnormality of the simple waveform in the premature flash VEP is associated with a poor prognosis for survival and with neurological dysfunction among survivors (Pike & Marlow, 2000; Shepherd et al., 1999b).

In hydrocephalus, increased intracranial pressure can affect the periventricular visual pathways. VEPs reliably demonstrate that this damage is reversible on successful shunting in young infants (George & Taylor, 1987). In older infants and children, the association between intracranial pressure and VEPs is not as clear, perhaps because acute and long-standing tissue damage is confounded.

In generalised neurodegenerative and white matter diseases, both the anterior and posterior visual pathways may be affected. VEPs can aid in the detection, differentiation, and monitoring of conditions such as the hereditary ataxias, ceroid lipofuscinosis (Batten’s disease), and various forms of leucodystrophy (De Meilier, Taylor, & Logan, 1988; Tobimatsu, Fukai, Kato, Kobayashi, & Kuroiwa, 1985). Multimodal evoked potentials, neuroradiography, metabolic testing, and genetic studies are often used together in these serious paediatric disorders (Taylor & McCulloch, 1992).

Cortical visual impairment

Cortical visual impairment is visual impairment associated with damage to the visual cortex. As dysfunction is rarely isolated to the cortex without associated damage to the posterior visual pathways, some prefer the term “cerebral visual impairment”. An operational definition is visual impairment in the absence of dysfunction of the eyes and anterior visual pathways with intact pupillary reflexes. For all aetiologies, pattern VEPs and VEP estimates of visual thresholds are useful indicators of visual function (Gottlob, Fendick, Guo, Zubcov, Odom, & Renecke, 1990; Odom & Green, 1984; Orel-Bixler, Haegerstrom-Portnoy, & Hall, 1989). An important caveat is that VEPs reflect visual function at the level of the visual cortex but affected individuals are at high risk for concurrent impairment of cognitive function. Thus, abnormal VEPs indicate limitations to visual function but normal VEPs do not ensure normal visual behaviour. When cortical damage is focal, such as in cerebral haemorrhage, congenital malformations or tumours, the utility of VEPs is limited. Variations in cortical topography and the large cortical areas that
respond to flash or pattern stimuli contribute to poor sensitivity and specificity of VEPs for assessing visual function (Bodis-Wollner, Atkin, Raab, & Wolkstein, 1977; Frank & Tores, 1979; Whiting, Jan, Wong, Floodmark, Farrell, & McCormick, 1985; Wong, 1991).

When cortical damage is widespread, in aetiologies such as asphyxia, intracranial infection, or toxic agents, not only do pattern VEPs provide an indication of visual function, but flash VEPs also have prognostic value for recovery (Barnet, Mason, & Wilner, 1970; Bodis-Wollner & Mylin, 1987; Duchowney, Weiss, Majlessi, & Barnet, 1974; McCulloch & Taylor, 1992; Regan, Regal, & Tribbles, 1982; Taylor & McCulloch, 1991). More specifically, a normal flash VEP is associated with recovery and abnormal or undetectable flash VEPs have good sensitivity for identifying those who may not recover. However, accuracy is limited—some infants with abnormal flash VEPs show visual recovery (Clarke, Mitchell, & Gibson, 1997).

**Other applications**

The visual pathways traverse the brain and VEPs are simple non-invasive measures of function. Thus, VEPs can be used to monitor general neurological function. In addition to the conditions described above, VEPs are used to assess neuro-toxic effects of medications with paediatric applications such as deferoxamine (Taylor, Keenan, Gallant, Skarf, Freedman, & Logan, 1987b), viagabatrin (Morong, Westall, Buncic, Snead, Logan, & Weiss, 2003), and chemotherapy drugs (Packer, Meadows, Roark, Goldwein, & D’Angio, 1987). Flash VEPs have prognostic value in childhood coma, although for this condition somatosensory evoked potentials have greater accuracy (De Meirlier & Taylor, 1987).

**CONCLUSIONS**

Since the 1970s, clinical scientists have used VEPs to understand visual maturation in human infants. These early VEP studies provided the basis for understanding that visual development is very rapid in the early months of life (Harris, Atkinson, & Braddick, 1976; Harter & Suitt, 1970; Marg et al., 1976; Sokol & Dobson 1976). The applications of VEPs in paediatrics are broad and limited only by our ability to design innovative strategies for testing visual functions within the attention span of infant subjects.

Standard VEP testing has a well-established role in paediatric neuroophthalmology practice. Innovations in areas such as signal detection have added to the accuracy of VEP testing in infants.

In the context of event-related potentials in infants, it is important to consider a VEP as a prerequisite for testing visual cognitive processes. VEPs to repetitive visual stimuli provide evidence of the function of the eyes and afferent visual pathways subserving vision.
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3 Development of face-sensitive event-related potentials during infancy

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A growing literature documents the existence and properties of components in adult event-related potentials related to the perception and recognition of faces. For example, the N170 has been related to the structural encoding of physical information in faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000a, 2000b), while later components, such as the N400 and P600, have been related to the recognition of facial identity (Eimer, 2000b). In contrast to the numerous studies of these components in adults, much less attention has been paid to their emergence during development. A developmental approach can provide unique insight into understanding the neural correlates of face processing in several ways. First, because different aspects of face processing may emerge at different ages, development provides the possibility of dissociating these aspects and studying them in isolation in a way not possible in adults. For example, in adults there is disagreement over whether the N170 reflects eye detection (Bentin et al., 1996) or encoding of the entire configuration of facial features (Eimer, 2000b). A recent study showing that the N170 response to eyes alone matures by 11 years of age, while that to the full face is not mature until adulthood (Taylor, Edmonds, McCarthy, & Allison, 2001), can be seen as supporting the view that there are separate eye-detection and face-detection generators of the N170 (e.g., Shibata et al., 2002).

Second, studying development of ERP components related to face processing can provide information that is important for putting constraints on debates about the degree of modularity and the role of expertise in face recognition. For example, recent studies showing that N170-like components observed in infants during the first year of life are less stimulus specific than the adult N170 (de Haan, Pascalis & Johnson, 2002; Halit, de Haan & Johnson, 2003) provide evidence against the view that face-specific cortical systems are present from birth. In this chapter we provide a brief and selective
review of models of the mature and developing face-processing system and of ERP components related to face processing in children and adults, together with a more detailed review of the development during infancy of ERP components related to face processing. We close by discussing the implications of the work with infants for understanding the mechanisms underlying face processing by adults.

THEORIES AND MODELS OF FACE PROCESSING

Face processing by adults

Evidence from a range of sources suggests that, in adults, face processing is mediated by neural and cognitive mechanisms that are to some extent different from those used to process most other classes of object. At the neural level, evidence showing that (1) certain neurons in monkeys’ temporal and frontal lobes fire more to faces than a variety of other stimuli (reviewed in Gauthier & Logothetis, 2000), (2) in human adults face or object processing can be selectively impaired following brain damage (de Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994), and (3) particular areas of ventral and lateral occipito-temporal cortex in human adults are more active during viewing of faces than a variety of comparison stimuli (Puce, Allison, Gore, & McCarthy, 1995), collectively suggests that there are cortical areas devoted preferentially to the processing of faces. The results of several studies also suggest that the face-related cortical areas of the right hemisphere are more extensive or are more critical for face processing than the homologous regions in the left hemisphere (De Renzi et al., 1994; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Kanwisher, McDermott, & Chun, 1997). At the cognitive level, it has been proposed that the type of information encoded and remembered for faces differs from that for objects. Although the difference in the nature of processing has been described in various ways (e.g., compare Diamond & Carey, 1986; Farah, 1990; Rhodes, Carey, Byatt, & Proffitt, 1998), the essence of all these approaches is that objects are represented mainly in terms of their isolated features or parts, whereas faces are represented in terms of global patterns or relations among parts. The main line of evidence in support of this view is the face inversion effect: stimulus inversion disproportionately impairs face compared to object processing. The most common explanation for this effect is that inversion disrupts the relational encoding used for faces more than parts-based encoding used to encode objects. The right hemisphere is believed to play a more prominent role than the left in relation encoding, providing a cognitive explanation for the right-hemisphere bias in face processing.

While these lines of evidence support the existence of a neurocognitive system dedicated to processing of human faces, this conclusion is challenged by investigations of visual expertise with other object categories. For example,
the same regions of the fusiform gyrus that are preferentially activated by faces can also be activated by other categories with which the perceiver has extensive experience (Gauthier, Skudlarski, Gore, & Anderson, 2000). These results have been used to argue that the mechanisms involved in the processing of faces are no different from those involved in any task that requires visual expertise for discriminating among exemplars of other categories with complex, visually similar members.

Development of face processing

Models of the development of face processing have largely focused on the question of how the differences in face and object processing observed in adults arise. There are currently several views that differ from one another on two main points (reviewed in de Haan & Halit, 2001): (a) whether the cortical face-processing system is domain specific, and (b) whether the degree of domain specificity changes with development. According to one account, the neural mechanisms underlying face processing are genetically determined and specific to faces, and thus a cortical module specifically dedicated to this process exists from birth (Farah, 2000; Farah, Rabinowitz, Quinn, & Liu, 2000). Evidence in support of this view comes from a patient who suffered brain damage at one day of age and subsequently, at age 16, showed disproportionate impairment in face recognition compared to object recognition (Farah et al., 2000). The authors interpret these results as evidence that the distinction between face and object recognition, and the anatomical localisation of face recognition, are genetically explicitly pre-specified.

In contrast to this view, two alternative accounts argue that the cortical face-processing system is initially not specific to faces, and both accounts emphasise the critical role of experience of viewing faces in development of the system. One such account argues that the neural specialisation for faces arises during development due to processes that parallel perceptual learning in adults (Diamond & Carey, 1986; Gauthier & Nelson, 2001). In this view, the mechanisms that are involved in the processing of faces are no different from those involved in tasks that require visual expertise for discriminating among exemplars of other categories with complex, visually similar members. These domain-general learning mechanisms appear to be specific to faces only because faces are a stimulus category for which all humans consistently develop a relatively high level of expertise. Evidence to support this view comes from studies showing that effects previously thought to be specific to faces can be obtained for other categories for which participants show expertise (Gauthier et al., 1999, 2000; Rossion, Gauthier, Goffaux, Tarr, & Crommelinck, 2002; Tarr & Gauthier, 2000).

A third perspective also argues that the cortical system used to process faces is initially not specific to faces, but postulates that there are developmental mechanisms that generate increasingly specialised processing within cortical areas (Johnson, 2000, 2001; Nelson, 2001). In this view, two distinct
brain systems are proposed to underlie development during infancy (Johnson & Morton, 1991): (a) “Conspec”, a system operating from birth that functions to bias the newborn to orient their visual attention towards faces, and (b) “Conlern”, a system sensitive to the effects of experience through passive exposure. In this model, Conspec is mediated by primitive, possibly largely subcortical, circuits, whereas Conlern is mediated by developing cortical circuits in the ventral visual pathway. The purpose of Conspec is to bias the input to the still-plastic cortical circuits underlying Conlern, providing the first step towards the eventual emergence of the specialised circuits for face processing observed in adults. From this perspective, early in life a given region of cortical tissue may be activated by a broad range of stimuli but over time its selectivity increases so that it responds only to certain kinds of inputs, e.g., upright human faces. In this way the face-processing system may develop from a broadly tuned, non-specific, complex figure recognition system into one tuned to the type of faces seen most frequently in the natural environment, i.e., upright human faces (Nelson, 1993, 2001). This view is supported by a recent study showing a decrease in discrimination abilities for non-human faces with age: 6-month-olds can discriminate between individual humans and individual monkeys, while 9-month-olds and adults tested with the same procedure discriminate only between members of their own species (Pascalis, de Haan, & Nelson, 2002).

EVENT-RELATED POTENTIAL STUDIES OF FACE PROCESSING

ERPs have provided a very useful tool in studying the face-processing system. Their excellent temporal resolution allows investigation of how the neurocognitive operations involved in face processing unfold over time, and they also provide one way of assessing the domain specificity of these processes. These studies have provided evidence relating the P1 and the N170 to encoding of faces, the N250r to the recognition of familiarity (Schweinberger, Pickering, Burton, & Kaufmann, 2002a), and longer-latency ERP components (> 400 ms after stimulus onset) to recognition of facial identity (e.g., Barrett & Rugg, 1989; Begleiter, Porjesz, & Wang, 1995; Eimer, 2000b; Itier & Taylor, 2002; et al., 2002a; Schweinberger, Pickering, Jentzsch, Burton, & Kaufmann 2002b; Uhl, Lang, Spieth, & Deecke, 1990) and/or retrieval of semantic information related to faces (Paller, Gonsalves, Grabowecky, Bozic, & Yamada, 2000).

Relatively few studies have examined the neural correlates of face recognition during infancy. ERPs provide an ideal tool for this type of study, as they are non-invasive and can be obtained passively, without a behavioural response being required from the participant. Among the questions that can be addressed are: (a) Can the precursors of components observed in children and adults be observed in infants? (b) To what degree are these responses
specific to faces? Answers to these questions can help to place constraints on theoretical debates about the degree of modularity and the role of expertise in face recognition. Below, components observed in infant ERPs during face processing are discussed in order of the temporal occurrence in the waveform, and possible links to similar components observed in adults and children are explored. Note that we focus on infant components for which responses to upright human faces have been compared to inverted faces, animal faces, or objects, and do not provide an exhaustive review of all components previously reported in the infant visual event-related potentials.

P1

The P1 is reliably elicited in response to visual stimuli in individuals of all ages, and has been shown to be influenced by manipulations of spatial (Hofp & Mangun, 2000) and other visual (Taylor, McCarthy, Saliba, & Degiovanni, 1999) information. Some investigators have argued for the existence of “global, holistic” stage of face processing in adults around 110 ms, reflected in the P1 (Itier & Taylor, 2002). The main lines of evidence in support of this view are that: (a) from 4 years of age the P1 is of shorter latency to faces than objects (flowers; Taylor et al., 2001a; but see Itier & Taylor, 2004a), (b) from age 4 years it is of shorter latency and in adults it is of smaller amplitude for upright than inverted faces (Taylor et al., 2001a; Itier & Taylor, 2002, 2004a), and (c) its amplitude is modulated by displacement of facial features, a manipulation that affects perception of facial configuration (Halit, de Haan & Johnson, 2000). However, an effect of inversion on the P1 has not been documented in all studies (Rossion et al., 1999), and the specificity of the inversion effect to faces is not well documented. Thus, the degree to which the processes reflected in the P1 are specific to faces remains somewhat unclear. Alternative explanations are that the modulations observed reflect top-down influences during the early encoding of faces (Taylor, 2002) and/or that they reflect more general visual attentional effects (e.g., differential allocation of attention within or between blocks of trials (Hillyard & Anllo-Vento, 1998).

The only relevant study in infants did find a difference in amplitude over the P1 at the midline occipital electrode for faces compared to objects (de Haan & Nelson, 1999). However, because the stimuli were not controlled for low-level physical differences that might influence the P1, the interpretation of this effect is unclear.

N290

The infant N290 is a negative-going deflection most prominent over midline and paramidline posterior electrodes whose peak latency decreases from approximately 350 ms to 290 ms between 3 and 12 months of age (Halit et al., 2003). The N290 may be a developmental precursor of the N170, a component observed in infants and adults that has been termed “face-sensitive”,
because the presence of a face causes systematic changes in its amplitude and/or latency compared to a wide range of other classes of object. Thus, while N170s of varying amplitudes can be elicited by non-face objects (Itier & Taylor, 2004a; Rossion et al., 2000), the response to human faces is consistently of larger amplitude and often shorter latency than that to any other object category tested (Bentin et al., 1996; Carmel & Bentin, 2002; Itier & Taylor, 2004a; Rossion et al., 2000; Taylor et al., 1999). The component is thought to be related to stages of structural encoding of the physical information in faces rather than to recognition of individual identity, as it is unaffected by the familiarity of individual faces (Bentin & Deouell, 2000; Eimer, 2000c; Rossion et al., 1999; Schweinberger et al., 2002a). Hemispheric differences in the amplitude of the component are not always present, but when they appear they tend to favour larger amplitudes over the right than left for faces (e.g., Itier & Taylor, 2002) but not for scrambled faces or objects (Taylor et al., 2001a). Further evidence that the N170 is a face-sensitive component comes from studies demonstrating that its amplitude and latency in response to faces are affected by manipulations thought to disrupt the encoding of configural information in faces. For example, several studies report that N170 amplitude is larger and/or latency is longer for inverted compared to upright faces (Bentin et al., 1996; de Haan et al., 2002; Eimer, 2000c; Itier, Latinus & Taylor, 2006; Itier & Taylor, 2002, 2004a; Rossion et al., 2000) or faces with features intact compared to scrambled (George, Evans, Fiori, Daviddof, & Renault, 1996). The N170 is not larger or slower for inverted compared to upright exemplars of non-face object categories (Bentin et al., 1996; Itier et al., 2006; Rebai, Poiroux, Bernard, & Lalonde, 2001; Rossion et al., 2000; but see Rossion, Joyce, Cottrell, & Tarr, 2003), even animal (monkey/ape) faces that share the basic eyes-nose-mouth arrangement with the human face (de Haan et al., 2002; Itier et al., 2006; but see Rousselet, Mace, & Fabre-Thorpe, 2004). The N170 is also observed in children as young as 4 years of age, although its amplitude is smaller and latency longer than in adults (Taylor et al., 1999, 2001a).

The N290 has been implicated as a possible precursor to the adult N170 in two types of studies: (1) comparing faces to noise, and (2) comparing upright and inverted faces. In one study comparing responses to faces with responses to noise composed of the same outer contour and amplitude and colour spectra, 3-month-olds showed a larger N290 to faces than noise (Halit, Csibra, Volein, & Johnson, 2004). These results paralleled those obtained for the N170 with adults under the same procedure (Halit et al., 2004). In other studies, infants’ and adults’ ERPs were recorded in response to upright and inverted human and monkey faces, in order to determine whether infants, like adults, show an ERP inversion effect that is specific to human faces. The results of these studies show that at 12 months of age the amplitude of the N290 is modulated by stimulus inversion in the same way as is the adult N170: inversion increases the amplitude of the N290 for human but not monkey faces (Halit et al., 2003; see Figure 3.1). However, at 3 and 6 months
Figure 3.1 Event-related potentials to upright and inverted human faces at 3, 6, and 12 months of age and adulthood. Adapted from de Haan et al. (2002) and Halit et al. (2003).
the N290 is unaffected by stimulus inversion (de Haan et al., 2002; Halit et al., 2003). This is not because younger infants cannot discriminate between upright and inverted faces, as at both ages inversion does influence the P400 (see below) that follows the N290. Thus, the N290 appears to become more sensitive to upright human faces with age (de Haan et al., 2002; Halit et al., 2003).

While some characteristics of the infant N290 are similar to the adult N170 by 12 months of age, there are also some differences between the two components in terms of their temporal and spatial characteristics. The N290 is of longer peak latency (290 ms vs 170 ms), and has a more medial distribution and a smaller peak amplitude to human faces than the adult N170. The differences in amplitude and latency are not unexpected, as studies of the N170 during childhood show an increase in amplitude and decrease in peak latency with age (Taylor et al., 1999). In fact, the latency of the N290 at 12 months of age is only 15–20 ms longer than the latency of the N170 in 4- to 5-year-olds (Taylor et al., 1999, 2001a). In terms of response properties, the 12-month-old’s N290 and adults’ N170 are also not identical. First, while the latency of the adult N170 is delayed by inversion, no effect of inversion is observed for the latency of the infant N290 at any age tested (de Haan et al., 2002; Halit et al., 2003). Second, while the amplitude of the adult N170 is larger for monkey faces than human faces, the infant N290 shows the opposite pattern at all ages tested (de Haan et al., 2002; Halit et al., 2003). Third, while the amplitude of the adult N170 is not affected by direction of gaze (Taylor, Itier, Allison, & Edmonds, 2001b), the amplitude of the infant N290 is larger for faces with direct than averted gaze (Farroni, Csibra, Simion, & Johnson, 2002). While these last two findings are consistent with a role for the N290 in face processing, they suggest that the information that is processed from the face may still differ for infants compared to adults. One possibility is that modulation of the N290 by eye gaze indicates that this component is primarily sensitive to eyes, an interpretation consistent with the view that eye detection develops more quickly than face detection (Taylor et al., 2001a) and with behavioural studies showing that the eyes are perhaps the most salient feature of the face, at least during the first months of life (Maurer, 1985). This interpretation could be consistent with the fact that the N290 differs for upright compared to inverted faces, even though both have eyes present with direct gaze, if the inversion effect is primarily driven by the eye region (see Itier et al., 2006).

With respect to latency, it is interesting to note that it appears the latency of the N290 at 12 months of age is only ~20 ms longer than the latency of the N170 observed at 4 to 5 years of age (Taylor et al., 1999, 2001a). This is especially striking since the N170 latency decreases more rapidly, by 35 ms, between 4 to 5 and 6 to 7 years of age (Taylor et al., 1999, 2001a). One possible explanation for the relatively slow change in latency between 1 and 4 years is that it is due to methodological differences between the studies that may affect peak amplitudes and latencies (e.g., filtering, reference, size of
stimuli). However, the fact that the latency of the N170 in adults was similar in the different studies (approx. 160 ms in de Haan et al., 2002; approx 160 ms in Taylor et al., 1999; approx 150 ms in Taylor et al., 2001a) is not consistent with this explanation. Another possibility is that the time between 1 to 4 years represents a period of relatively slow development of face processing and/or that the time between 4 to 7 years represents a period of relatively rapid development of face processing. The fact that the N170 in 4- to 5-year-olds, but not in infants or teenagers, appears to show a double peak (Taylor et al., 2001a), might make estimates of its latency less reliable at this age and/or support the idea that it is an important period of change in face processing. Given the absence of reports on the development of the N170 between 1 and 4 years of age and the relatively limited number of behavioural studies in the same age range, it is difficult to evaluate these possibilities.

P400

The P400 is a positive component most prominent over posterior lateral electrodes whose peak latency decreases from approximately 450 to 390 ms between 3 and 12 months of age. It has also been suggested as a precursor of the adult N170. Although the P400 differs in polarity from, and peaks at a later latency than, the N170, it is similar to the N170 in two ways: (a) like the N170, the P400 is more prominent at lateral than medial electrodes (de Haan et al., 2002; Halit et al., 2003), and (b) like the adult N170, the peak latency of the P400 is faster in response to faces compared to objects (de Haan & Nelson, 1999).

By 3 months of age the P400 differs for inverted compared to upright faces (Halit et al., 2003) as well as intact versus distorted faces and bodies (Gliga & Dehaene-Lambertz, 2005; but see Macchi Cassia, Kuefner, Westerlund, & Nelson, 2006). However, the response to inversion is not adult-like even by 6 months of age, as it is not specific to human faces (see Figure 3.1; de Haan et al., 2002). In contrast, by 12 months of age the latency of the P400 is influenced by inversion in a manner similar to the adult N170: latency is longer for inverted than upright human faces, but does not differ for inverted compared to upright monkey faces (Halit et al., 2003). Thus, like the N290, the P400 appears to become more finely tuned to human faces with age.

Negative central (Nc)

The negative central (Nc) component is one of the most well-studied components of the infant cognitive visual ERP (see Chapter 4, this volume, for further discussion of the Nc). It is a negative deflection occurring between 400–800 ms after stimulus onset in 6-month-olds, most prominent over fronto-central electrodes. It is sensitive to stimulus probability, and tends to be of larger amplitude for infrequent compared to frequent events in oddball paradigms (Courchesne, Ganz, & Norcia, 1981; Karrer & Ackles, 1987;
Karrer & Monti, 1995; Richards, 2002). In this context, the Nc has been interpreted as reflecting either the infant’s allocation of attention, with the greater negativity to the infrequently presented face reflecting greater allocation of attention to the novel or more unexpected face (Courchesne et al., 1981; Nelson, 1994), or a more generalised arousal elicited by novel stimuli (Richards, 2002).

The Nc also appears to reflect aspects of recognition, as its amplitude is affected by stimulus familiarity even when items are present with equal probability. At 6 months of age, the Nc is larger for the mother’s face than a stranger’s face, and for familiar toys than novel ones (see Figure 4.1 in Chapter 4, this volume; de Haan & Nelson, 1997, 1999; Nelson, Wewerka, Thomas, Tribby-Walbridge, deRegnier, & Georgieff, 2000; but see Webb, Long, & Nelson, 2005). The spatial distribution of this recognition effect differs for faces compared to toys: for faces it is observed over midline and right anterior temporal sites (T4), while for objects it is observed for midline and bilateral anterior temporal sites (T3, T4). The right lateralisation of the response for recognition of faces is consistent with split visual field investigations of infants in this age range, demonstrating a left visual field (right hemisphere) advantage for recognition of the mother’s face (de Schonen & Mathivet, 1990).

The difference in Nc amplitude to familiar compared to novel items may reflect greater allocation of attention to the familiar items, although in tests of visual attention infants of this age do not look longer at the mother’s face than a stranger’s face (de Haan & Nelson, 1997; Robinson, 2002). It may also reflect processing of semantic and/or emotional information related to the mother’s face, as Nc amplitude is also known to be modulated by the emotional content of the face in infants of a similar age (de Haan, Belsky, Reid, Volein, & Johnson, 2004; de Haan & Nelson, 1999; Nelson & de Haan, 1996). In support of the view that the response is related to the relative salience of the face, the direction of the differences in amplitude between mother’s and stranger’s faces, but not between familiar and unfamiliar objects, changes with age. Children younger than 24 months show a larger Nc to mother’s face compared to stranger’s face, but children older than 45 months show a larger Nc to stranger’s face compared to mother’s face (Carver et al., 2003). The authors interpret this result as indicating that the caregiver’s face is particularly salient in the first years of life, as children are forming their relationship with and mental representation of the caregiver, but these are well established enough by 4 years that children begin to devote more resources to processing strangers’ faces.

Interestingly, modulation of the midline Nc by familiarity of a face is observed only when mother’s and stranger’s faces are perceptually quite distinct. When the faces are similar looking, the midline Nc amplitude is not affected by familiarity and instead a positive slow wave over bilateral posterior temporal electrodes is larger for stranger’s than mother’s faces (de Haan & Nelson, 1997). Positive slow wave activity has been linked to updating
information in memory representations (see below). It is possible that, for similar-looking face pairs, no difference is observed in the Nc because both faces are “recognised” as mother, but that, because of the stranger’s greater perceptual difference from the stored representation of mother, it elicits a positive slow wave.

Further evidence linking the Nc to recognition comes from a study investigating 2- to 5-year-old children with autism and typically developing children (Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2001). Typically developing children showed the expected pattern with different amplitude of the Nc for familiar compared to unfamiliar items, and a more widespread distribution of this response for objects than for faces. In contrast, children with autism, a developmental disorder characterised by impairments in face perception and social skills, showed evidence of recognition of objects, but not of faces.

How the Nc relates to components elicited during adults’ recognition of faces is unclear, since adults have not been tested under the same conditions. However, several studies have compared responses to briefly familiarised or famous faces with responses to unfamiliar faces. While some studies have found no difference (e.g., Schweinberger, Sommer, & Stillier, 1993), others have shown three time windows in which components are larger for familiar than unfamiliar faces: (a) a negative component occurring 250–600 ms (Eimer 2000b; Smith & Halgren, 1987; Uhl et al., 1990) (b) a positive component peaking at approximately 520 ms (Eimer, 2000b; Smith & Halgren, 1987), and (c) a negative slow wave following the positive component, that also tends to be larger over the right than the left hemisphere (Smith & Halgren, 1987; Uhl et al. 1990; but see Barrett, Rugg, & Perrett, 1988).

The specificity of the memory-related components elicited during recognition of facial identity in adults has not been a frequent focus of investigation. Some investigators have addressed this question indirectly by comparison to language processing. These studies have focused on the N400, a component that in studies of language is larger for words appearing in an unexpected context than words appearing in an expected context (e.g., Kutas & Van Petten, 1988). Investigators have been interested in determining whether this effect is specific to language or also occurs for non-verbal stimuli such as faces. For faces, the N400 is elicited in tasks where participants are asked to decide if two sequentially presented face match or mismatch. Some studies have concluded that, for both faces and words, the N400 response to mismatch is usually bilaterally symmetric and without a distinctive topography (Barret & Rugg, 1989; Barrett et al., 1988; the exact topography appears to depend on factors such as the reference used), suggesting it reflects processing common in linguistic and non-linguistic domains (Barrett & Rugg, 1989). However, in a study in which the amount of verbal information associated with faces was systematically varied, the timing and topography of the N400 varied with verbal loading. There was a predominant right posterior temporal localisation in the condition involving “pure” face processing that
differed from the pattern observed in the various verbal loading conditions (Olivares, Iglesias, & Rodriguez-Holquin 2003). These results suggest that there may be a non-linguistic N400 related to purely visual information. Whether there is a response specific to faces within the visual domain is unknown, but another study that also found a right-lateralised mismatch effect for upright faces did find that the mismatch effect for inverted faces was of longer latency and bilaterally distributed (Mills, Alvarez, St. George, Appelbaum, Bellugi, & Neville, 2000).

Whether the Nc reflects the developmental precursor of any of these components remains an open question. Future studies in which infants and adults are tested under the same conditions with familiar and unfamiliar faces may provide some answers.

**Positive slow wave**

Positive slow wave activity beginning approximately 800 ms after stimulus onset has been linked to the updating of memory representations in infants (Nelson, 1994, 1997) and is detectable by 3 months of age in visual studies (Pascalis, de Haan, Nelson & de Schonen, 1998). Thus, in the context of face recognition, it might reflect encoding processes related to creating new and/or modifying perceptual representations of known faces (de Haan & Nelson, 1999). The observation that the slow wave diminishes in amplitude and returns to baseline across repeated presentations is consistent with this view (Webb, Snyder, & Nelson, 2001).

In order to investigate further the influence of stimulus type on expression of the positive slow wave, we conducted an experiment aimed at determining whether the positive slow wave differed during encoding of different stimulus categories. Because these results are previously unpublished, we will describe the methods and results in some detail here (full details of the methods can be obtained from Johnson, 2000, in which the results from the Oz electrode in this experiment are also described).

We presented 6-month-old infants ($n = 22; M$ age = 185 days, $SD = 5$ days; 14 boys) with a series of coloured images of upright faces, inverted faces, and objects (infant toys) while recording ERPs (Cz, Pz, Fz,T3, T3, T5, T6, referenced to averaged ears; sampling rate 100 Hz, bandpass 0.1–30 Hz with a 60-Hz notch filter; further details of recording can be found in Johnson et al., 2001). Each category was presented with equal probability so that any category-related effects were not due to stimulus probability. Within each category, there were five different exemplars that were presented repeatedly (six times each), to allow opportunity for encoding of face/object identity.

Mean amplitude of the slow wave between 800 to 1500 ms was analysed in separate repeated measures ANOVAs for midline (Electrode [Pz, Cz, Fz] by Stimulus Type [Upright Face, Inverted Face, Object]) and lateral (Hemisphere [Right, Left] by Anterior-Posterior [Anterior Temporal, Poster Temporal] by Stimulus Type [Upright Face, Inverted Face, Object] electrode groupings.
At midline electrodes, the component did not differ between upright and inverted faces or toys, $F(2, 42) = 0.03, p > .1$. At temporal electrodes there was a Stimulus Type by Hemisphere interaction, $F(2, 42) = 3.41, p < 0.05$, illustrated in Figure 3.2. For upright faces, there was a positive slow wave over the right hemisphere electrodes ($M = 5.23 \mu V$) but a return to baseline over left hemisphere electrodes ($−0.91 \mu V$). For inverted faces there was a bilateral negative slow wave more prominent over left ($−7.5 \mu V$) than right ($−3.5 \mu V$) hemisphere electrodes, while for toys there was a bilateral positive slow wave more prominent over left ($10.23 \mu V$) than right ($4.45 \mu V$) hemisphere electrodes.

Since positive slow wave activity is thought to reflect updating of memory for a partially encoded stimulus, neural activity underlying memory representations of the faces and toys may occur bilaterally for upright toys but more unilaterally on the right for upright faces. This spatial pattern is qualitatively similar to that pattern of lateralisation observed for the Nc during recognition of familiar faces and toys. It has been suggested that the positive slow wave may reflect activity of the hippocampus (Nelson, 1994; see also Reynolds & Richards, 2005). This interpretation is consistent with studies showing that the right hippocampal-parahippocampal region is involved in encoding of faces in adults (Grady et al., 1994; Haxby, Ungerleider, Horwitz, Maisog, & Grady, 1994).

In contrast to the upright faces and toys, inverted faces elicited a negative slow wave bilaterally. The negative slow wave is thought to reflect detection of novelty (Nelson, 1994). It is possible that this activity reflects infants’ perception of inverted faces as unusual or unfamiliar. The greater similarity for infants’ responses to faces and toys than to inverted faces suggests that

![Figure 3.2](image-url)  
Figure 3.2 Amplitude of slow waves recorded during viewing of upright human faces, inverted human faces, and objects (toys without faces) in 6-month-old infants.
infants’ familiarity with a category may influence how they encode new exemplars. They may have mental schemas for upright face and toys which allow them to more easily begin to form mental representations of individual items within these categories, while they may not have a similar schema for inverted faces and therefore respond to them as novel.

The relation of these slow wave responses to those observed during adults’ face processing is not entirely clear. In general, investigations of the effects of repeating visual stimuli on adults’ ERPs tend to find greater positivity for repeated face and nonface stimuli (e.g., Doyle & Rugg, 1998; Eimer, 2000b; Smith & Halgren, 1987; Uhl et al., 1990). One study that compared infants’ and adults’ ERPs to a single familiar face and a single novel face found that adults showed a larger positive slow wave to the novel face while infants showed a larger positive slow wave to the familiar face (Nelson, Thomas, de Haan, & Wewerka, 1998). However it is not clear whether the difference in pattern of responding was due to developmental differences in the function/response properties of the slow wave or to the different familiarisation procedures used for infants compared to adults. Future studies, in which adults and infants are tested under the same conditions, will provide a clearer picture of the relations among these components.

GENERAL DISCUSSION

ERP studies in adults have been very useful in addressing questions as to the timing and domain specificity of the perceptual-cognitive processes involved in face recognition. Although there are relatively few studies to date, investigating the development of the ERP correlates of face processing during infancy not only can provide insight into the nature of specific ERP components identified in adults, but also has broader implications for theories of the development of face processing.

In studies of adults, ERP components can be identified by examining their peak latencies, morphology, and spatial distribution. For example, a target-elicited P300 might be described as a positive component peaking between 300–500 ms with a parietal maximum. Identifying the infant equivalents of such components is not simply a matter of applying the same criteria to the younger age group, as investigations of ERPs during childhood and old age have clearly shown that timing and topography of components can change across the lifespan (e.g., Taylor & Pang, 1999). This problem is not unique to the study of face processing, and has been tackled in other studies questioning, for example, whether there is an infant equivalent of the adult P300 (e.g., McIsaac & Polich, 1992; Nelson et al., 1998). One basic approach to identifying the infant and child equivalents of adult ERP components has been a functional one: test younger and older participants under the same conditions and look for ERP components that show similar stimulus- or task-related modulations across age. While this approach has proved useful in
practice, it is important to keep in mind that it makes the assumption that there will be no change in functionality with age.

In the field of face processing this functional approach has been used most extensively to study the developmental trajectory of the N170. As discussed earlier, developmental studies through childhood have identified the N170 as a negative deflection over posterior temporal scalp regions that, like the adult N170, is larger in amplitude and often shorter in latency for faces compared to other objects (Taylor et al., 1999). These studies show that the peak latency of the N170 decreases with age into adolescence, and that the peak amplitude over the right hemisphere increases over this time (Taylor et al., 1999; Taylor et al., 2001a).

With respect to the components described in infants as potential precursors of the N170, two components have been identified based on their response properties. The N290 component is similar to the N170 in that it shows an adult-like effect of face inversion on amplitude, and a relatively similar timing and polarity. However, the basic question of whether the N290 differs for faces versus objects (a defining characteristic of the adult N170) remains to be tested. The P400 is like the N170 in that it is of shorter latency for faces than objects (de Haan & Nelson, 1999), and shows an adult-like effect of face inversion on peak latency by 12 months of age (Halit et al., 2003). With respect to spatial distribution the P400, like the N170, shows a more lateral distribution. However, the P400 differs in latency and polarity from the N170. Overall, these findings suggest that both the N290 and P400 reflect processes that in the adult may become integrated in time in the N170 component. In other words, the structural encoding of faces may be spread out over a longer time of processing in infants than adults. It is possible that, as they become more automated, the processes involved in face processing are carried out more quickly and/or in a parallel rather than serial fashion.

Currently, there is a gap between those studies that have examined face-related ERPs up to 12 months, and studies of older children that begin at 60 months, which prevents a firm conclusion.

Both the N290 and P400 show changes in their spatial-temporal distribution over the first year of life. Their latencies decrease from 3 to 12 months, a change likely in part to reflect general changes in information processing rather than changes specific to face processing. Decreases in latency of ERP components with age are commonly reported (e.g., Karrer & Ackles, 1987; Nelson, 1997) and are often interpreted as reflecting the increased speed of neural processing with myelination. Whether there are changes in amplitude and latency with age for the N290 and P400 that are specific to faces remains to be carefully investigated by directly contrasting the responses to a wider variety of stimuli over different ages. The spatial distribution of both the N290 and P400 also changes from 3 to 12 months, with the location of peak amplitude shifting laterally for both. In addition, the maxima of these components appear more superior than in adults, a result consistent with studies of children finding a shift from superior to inferior maximum of the N170.
with age (Taylor et al., 2001a). In this way, both become more like the adult N170 with age, as the N170 peaks maximally over lateral (T5/T6) electrodes. One possibility is that this reflects a change in the configuration of generators underlying these components with age. Several areas, including regions of the fusiform gyrus (Shibata et al., 2002), the posterior inferior temporal gyrus (Bentin et al., 1996; Shibata et al., 2002), superior temporal sulcus (Henson, Goshen-Gottstein, Ganel, Otten, Quayle & Rugg, 2003; Itier & Taylor, 2004b) and lateral occipito-temporal Cortex (Bentin et al., 1996; Schweiberger et al., 2002b) have been proposed as underlying the adult N170. It is possible that several or all of these regions do contribute to the N170, but that different generators develop at different rates and lead to a change in the spatial distribution of the component with age. Another possible explanation for the shift and spatial distribution with age is that it occurs incidentally as a consequence of brain growth, which may cause the generators of the components to shift in location or orientation. Results of one source analysis study suggests that areas including the lateral occipital area, right fusiform gyrus and right superior temporal sulcus contribute to the infant N290, suggesting similarity in the generators involved in the infant N290 and adult N170 (Johnson et al., 2005). Future studies modelling and comparing the generators of the infant, child, and adult component can help to further detail the degree of stability or change in the configuration of generators underlying the N170 over development.

While existing studies allow a potential link between the N290/P400 and the adult N170, the correspondence between other infant and adult components is less clear. The two components that have been linked most strongly to infants’ recognition of familiar faces, the Nc and the positive slow wave, may relate to the N400 and P600 identified in adults during identity recognition tasks (Eimer, 2000b). However, because there are no studies of recognition of facial identity that have tested infants and adults under the same conditions, such interpretations remain very speculative. The studies with infants and adults differ in factors such as the response demands (passive tasks with infants but active behavioural responses in adults) and definitions of familiarity, and thus are difficult to compare directly.

It is also more difficult to draw conclusions regarding the stimulus specificity of the later-latency ERP components. There is evidence of right lateralisation of the Nc and positive slow wave for faces but not objects in infants (de Haan & Nelson, 1997, 1999), a result consistent with the hypothesis that the right hemisphere is more involved than the left in processing of faces. However, studies of recognition of identity in adults have tended not to compare faces directly with other categories. Those that do have tended to compare faces with verbal stimuli in order to contrast verbal and nonverbal processing, an approach that does not address the question of whether there are differences in processing for different categories within the visual domain.

The results of infant ERP studies of face processing have implications for theories of the development of the mechanisms underlying face processing in
adults. Young infants, who are not considered experts in face recognition, show many of the characteristics of adult face processing (e.g., right hemisphere bias, inversion effects). These are results are consistent with the view that regions involved in face processing in adults are also active during infancy. However, these regions may be competitively selected from an initially larger set of activated areas (Johnson, 2001), and may initially respond to a wider range of stimuli. In terms of the three perspectives on the development of face processing discussed earlier, we suggest that the current ERP evidence is most consistent with the third perspective in which a series of biases combine during development to ensure that some cortical regions become specialised for face processing. The early appearance of characteristics of face processing may be one difference (or be indicative of differences) between the process of development and process of adult learning.

The results of infant ERP studies also clearly show that components elicited during face processing in infants are less specific to upright human faces than is the adult N170 component. These results show a gradual increase in the specificity of two components, the N290 and P400 over the first year of life. However, even by 12 months of age the components and their response properties are not adult-like. The gradual emergence of the specificity of response is consistent with the view that experience in viewing faces plays an important role in the ultimate emergence of the adult face-processing system. Results from a recent behavioural study support this view. In this study, individuals who were deprived of pattern visual input in the first months of life later showed impairments in encoding configural information from faces, in spite of normal encoding of featural information in faces and configural information in geometric patterns (Le Grand, Mondloch, Maurer, & Brent, 2001).

In summary, the P1, N290, P400, Nc, and positive slow wave are all elicited during infants’ processing of faces. The relation of these components to those elicited in children and adults remains an open question for study, although there is convincing evidence relating both the N290 and P400 to the adult N170. Further investigations that document changes across a number of time points in development, particularly from 12–60 months, and using the same procedure across ages, are needed. Use of high-density recordings in these studies will help to clarify questions regarding changes in the generators underlying particular components with age.

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4 Visual attention and recognition memory in infancy

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The simple observation that infants look longer at familiar than novel stimuli has had a major impact on the study of infant memory (Fantz, 1961). Many investigators have exploited this preference using the “visual paired comparison” procedure to investigate at what age and for how long infants can remember what they see (reviewed in de Haan, 2003). Measurement of infant visual recognition memory has thus been closely tied to visual attention, as the contents of infants’ memories are inferred on the basis of their allocation of visual attention (looking time). More recently, event-related potentials (ERPs) have been used to investigate infant recognition memory. ERPs can potentially provide information that behavioural measures cannot, in terms of the precise timing and general spatial pattern of brain activation that occurs when infants see familiar and novel items. The aims of this chapter are to provide an overview of the main ERP components elicited in infant visual recognition memory tasks, a discussion of how these results have influenced theories of infant memory development, and illustrations of the application of ERPs to the study of atypical memory development.

INFANT ERP COMPONENTS RELATED TO RECOGNITION MEMORY

Nc

The Nc (negative central component see Figure 4.1) is perhaps the most well-studied endogenous component in the infant visual event-related potential. It is a negative deflection that tends to be most prominent over fronto-central electrodes (Ackles & Cook, 1998; Goldman, Shapiro, & Nelson, 2004; Karrer & Monti, 1995; Snyder, Webb, & Nelson, 2002; Webb, Long, & Nelson, 2005; Webb & Nelson, 2001; Wiebe, Cheatham, Lukowski, Haight, Muehleck, & Bauer, 2006). It is believed to be the first endogenous ERP to emerge in development, being present at birth, with peak latency decreasing from 1000–1200 ms in newborns (Nelson, 1996) to about 800 ms in 1-month-olds (Karrer & Monti, 1995), 600 ms in 6-month-olds (Ackles & Cook 1998) and
400–500 ms in 1- to 3-year-olds (Goldman et al., 2004; Nelson & deRegnier, 1992; Parker & Nelson, 2005). Its peak amplitude increases with age over the first year of life (at least between 3 and 12 months in studies that have tested more than one age with the same procedure; Davis, Karrer, & Walker, 1998; Richards, 2003; see Webb et al., 2005 for longitudinal results), and then decreases in third year of life (Parker & Nelson, 2005). In spite of the fact that

Figure 4.1 Nc elicited by mother’s face compared to stranger’s face (left side) and two strangers’ faces (right side) in 6-month-old infants. The Nc is indicated by the arrow. Data are from de Haan and Nelson (1997).
a component of roughly this description has been observed in virtually every visual cognitive ERP study of infants (see Appendix), its functional significance is still a matter of debate. Most investigators would agree that the Nc reflects some aspect of attention, but opinions differ as to whether it reflects an automatic orienting response (e.g., Nelson, 1994; Richards, 2003; Vaughan & Kurtzberg, 1992) or a more controlled deployment of attentional resources (e.g., Ackles & Cook, 1998), and as to whether it reflects primarily attentional processing (e.g., Nelson, 1994; Richards, 2003) or also reflects aspects of memory (e.g., Ackles & Cook, 1998; Courchesne, Ganz, & Norcia, 1981; de Haan & Nelson, 1997).

The Nc has been most often studied using the oddball paradigm, in which one “standard” stimulus is presented frequently and the other “oddball” stimulus is presented infrequently. The results of these studies are quite consistent: by 3 months of age the amplitude of the Nc is larger to the oddball than the standard (Courchesne et al., 1981; Davis et al., 1998; Hill-Karrer, Karrer, Bloom, Chaney, & Davis, 1998; Hunter & Karrer, 1993), and the latency is often longer for the oddball than the standard (Courchesne et al., 1981; Hill-Karrer et al., 1998). The size of the oddball effect does not appear to be influenced by how infrequently the oddball is presented (Ackles & Cook, 1998), so long as the probability is less than 50% (Ackles & Cook, 1998; de Haan & Nelson, 1997; Nelson & Collins, 1991, 1992; Nelson & Salapatek, 1986). Sensitivity to stimulus probability is also observed in infants as young as 1 month, although at this age there is only a latency difference which is in the opposite direction (longer latency Nc to standard than oddball) from that observed in older infants (Karrer & Monti, 1995).

In contrast to the relatively consistent findings of studies using the two-stimulus oddball paradigm, those using the three-stimulus oddball are somewhat conflicting. In the three-stimulus oddball, a standard and oddball are presented, along with an additional low-frequency category of novel, trial-unique stimuli. In a series of experiments, Nelson (Nelson & Collins, 1991, 1992; see also Richards, 2003) first familiarised infants to two female faces by presenting them in alternation over 20 500-ms trials; then infants were tested in a three-stimulus oddball in which one of the two faces was presented frequently (60%), one infrequently (20%), and a unique novel face shown for each of the remaining trials. Neither 4-, 6-, nor 8-month-olds showed any difference in the amplitude or latency of the Nc among the three classes of stimuli. One possible explanation for the null findings is that the familiarisation infants received prior to the three-stimulus oddball prevented the typical pattern of response to the infrequent categories seen in the two-stimulus oddball. To test this hypothesis, Reynolds and Richards (2005) compared 4.5-, 6-, and 7.5-month-old infants’ ERPs in the three-stimulus oddball with and without prior familiarisation. Their procedure was somewhat different from that of Nelson and Collins (1991, 1992) in that their stimuli were geometric patterns rather than faces, their familiarisation period was longer (20 seconds cumulated looking to each of the two familiar stimuli), and they
presented the stimuli in alternation with a Sesame Street video. Reynolds and Richards found that the Nc was larger to trial-unique novel stimuli compared to other stimuli in the group with prior familiarisation, while Nc amplitude did not differ among the stimuli without prior familiarisation (see Figure 4.2). These findings conflict with those of Nelson and colleagues, but do indicate that the mere presence or absence of a familiarisation period may not be the only factor contributing to the differing results of studies using two- versus three-stimulus oddball paradigms. Another possible explanation for the conflicting results is that the larger number of different stimuli presented to infants in the three- compared to two-stimulus oddball task makes it a more difficult task. In support of this view, infants as young as 3 months show a larger amplitude Nc to the oddball in the two-stimulus task (Davis et al., 1998), while infants do not show a differential response at any latency in the three-stimulus task without familiarisation until 4.5–6 months of age, when they show differential slow-wave activity to the three types of stimuli following the Nc (including a negative slow wave to the trial-unique novel stimuli; Nelson & Collins, 1991, 1992). However, with adequate familiarisation, and as they are older, infants are able to demonstrate a larger Nc to trial-unique novel stimuli. They do so: (a) at 4.5 to 7.5 months when they receive a more extensive exposure during familiarisation (Reynolds & Richards, 2005), (b) at 9 months when they receive repeated real-life exposure (Wiebe et al., 2006), and (c) by 24 months of age even with no familiarisation (Goldman et al., 2004).

The Nc and attention

Looking time

Perhaps the most common interpretation of the Nc is that it reflects allocation of attention to interesting or salient stimuli (Courchesne et al., 1981). This could explain why the Nc is larger for the oddball than standard (reviewed above) and larger for salient faces (e.g., the mother’s face; a fearful emotional expression) than comparison faces (de Haan, Belsky, Reid, Volein, & Johnson, 2004; de Haan & Nelson, 1997, 1998, 1999; Nelson, Wewerka, Thomas, Tribby-Wallbridge, de Regnier, & Georgieff, 2000). Researchers have attempted to test this hypothesis by looking for links between the size of the Nc and the length of infants’ visual fixations. One approach has been to examine whether oddball stimuli elicit not only larger Ncs but also longer fixations. Infants’ fixations during the ERP experiment are measured and then divided according to whether they included only standard stimuli (“standard looks”) or at least one oddball (“oddball looks”). Several studies have reported that oddball looks are longer than standard looks (Ackles & Cook, 1998: Hill-Karrer et al., 1998; Karrer & Ackles, 1987), and this holds even when various control analyses are computed (e.g., to disentangle whether oddball looks are in fact longer, or whether the association occurs
Figure 4.2 Event-related potentials elicited for frequent familiar, infrequent familiar, and infrequent novel stimuli are shown on the left for infants who did (upper two graphs) or did not (lower two graphs) receive prior familiarisation with the two familiar stimuli. To the right of the graphs are shown the corresponding amplitude distributions averaged over an 80-ms period at the peak amplitude of the Nc. Reprinted from Reynolds, G.D., & Richards, J.E. (2005). Familiarization, attention and recognition memory in infancy: An ERP and cortical source localisation study. Developmental Psychology, 41, 598–615. Copyright © 2005 by the American Psychological Association. Reprinted with permission.
merely because the likelihood of an oddball occurring increases with increasing look length; Ackles & Cook, 1998). While these results suggest that larger Ncs may be related to longer looking times, studies that have related Nc amplitude to looking times recorded in a separate session after the ERP experiment have yielded less positive results. For example: (a) while at 6 months of age the Nc is larger for the mother’s face than an unfamiliar face, infants do not look longer at the mother’s face (de Haan & Nelson, 1997); (b) while infants show a larger Nc and longer looking times to fearful compared to happy faces (de Haan et al., 2004; de Haan & Nelson, 1998), there is no correlation between the amplitude of the Nc and the length of looking (de Haan et al., 2004); (c) in visual paired comparison tests of novel and standard stimuli given after two-stimulus or three-stimulus oddball tests, there is no consistent evidence that infants look longer at the novel stimuli (Karrer & Monti, 1995; Nelson & Collins, 1991, 1992; but see Quinn, Westerlund, & Nelson, 2006) and no correlation between the Nc and the duration of looking to novelty (Karrer & Monti, 1995); and lastly (d) while both Nc amplitude and the duration of infants’ fixations decrease over a study session, the decrease in fixation appears to happen more rapidly (Nikkel & Karrer, 1994).

Together these findings suggest that there is not a close relation between Nc amplitude and length of looking to novel/salient stimuli (Nikkel & Karrer, 1994), at least across individuals. One possible reason for the negative result is that there can be quite large individual differences in the overall amplitude of ERP components; it may be that these more general amplitude differences overwhelm any more subtle modulations related to attentional processes reflected in the Nc, and obscure relations with looking time. A second possible explanation is that a negative slow wave (see below) may often be superimposed on the Nc and confound correlations between Nc amplitude and behavioural measures of attention. A third possible reason is that the Nc reflects a process of orienting or attention allocation, but does not reflect the processes involved in sustaining attention or determining duration of looking. However, this third possibility conflicts with a study showing a correlation between Nc amplitude to oddballs at right frontal (F4, F8) electrodes and performance on the Early Childhood Vigilance Test (essentially a looking-time measure of “time on task” to a 7-minute audio-visual display; Goldman et al., 2004). These authors conclude that the Nc may reflect activation of right frontal brain areas believed to be involved in vigilance/sustained attention (Posner & Petersen, 1990). This latter study may have had more success in finding correlations in part because of the similarity between the Early Childhood Vigilance Task and the stimulus presentation procedure for visual ERPs. Success on both tasks involves being able to maintain attention to a visual display in which interesting visual stimuli are alternated with periods during which the screen is blank. This contrasts with paired comparison measures of novelty preference where stimuli are always present and the measures reflect a choice, switching attention from one to the other.
Heart rate

A link between the Nc and sustained attention has also been observed in studies that have concurrently measured heart rate and ERPs. Infants’ heart rates can be used to define different periods of attention, including sustained attention, stimulus orienting, and inattention (Richards, 1997; Richards & Casey, 1991). The results of this research are somewhat mixed. While one study reported that the Nc is larger during periods of sustained attention (as measured by heart rate deceleration) than during periods of inattention, and that age-related increases in Nc amplitude occur only during periods of sustained attention (Richards, 2003), these same findings were not replicated in a subsequent study (Reynolds & Richards, 2005).

Nc and memory

Another hypothesis that has been put forward is that the Nc is related to memory trace strength, such that stimuli with lower trace strengths elicit a larger Nc (Courchesne et al., 1981). This could explain why the Nc is larger for oddball stimuli, as presumably they have a lower trace strength as a consequence of the low frequency with which they occur. However, this hypothesis is difficult to reconcile with findings showing, for example, that for children younger than 24 months the Nc is larger for the mother’s face than a stranger’s face when the two are present with equal probability (Carver et al., 2003; de Haan & Nelson, 1997, 1999; Nelson et al., 2000; but see Webb et al., 2005). If the memory trace hypothesis were true, a larger Nc for the stranger’s face would be expected. At the same time, the fact that the Nc does differ for familiar vs novel stimuli presented with equal probability suggests that at least some aspect of recognition memory must occur at the time of the Nc or preceding it, in order for this differential response to be seen.

Correlational evidence also indirectly supports a link between the Nc, particularly its latency, and infants’ memories for familiar items. In these investigations (Bauer et al., 2006; Bauer, Wiebe, Carver, Waters, & Nelson, 2003; Carver, Bauer, & Nelson, 2000), 9- to 10-month-old infants were first familiarised with a series of two-step event sequences by observing experimenters modelling actions leading to an interesting outcome (e.g., “pop up book”: 1. open book, 2. pull handle, result is photo of duck popping up); after several exposures over two to three visits, infants were either immediately or after a 1-week delay given an ERP test (in which still photos of the actions from a familiar sequence and of a novel sequence were presented with equal probability) and after 1 month were tested for their recall of the action sequences. These studies report that the latency of the Nc for familiar items is longer than that for novel ones (Bauer et al., in press, 2006, 2003), and that the magnitude of the latency difference predicts the number of items recalled in memory tests 1 month later (Bauer et al., 2006). The authors interpret the longer latency to familiar items as indexing the reintegration of these items.
into the existing memory trace, a process that presumably facilitates later recall.

Finally, one study has suggested that the Nc is sensitive to repetition priming (Webb & Nelson, 2001). In this study, 6-month-old infants were presented with four blocks of trials, in each of which they first saw 12 unique novel faces and then saw 8 of these repeated intermixed with 4 novel faces. The lag between repetitions varied between 6–12 images (15–30 seconds). The results showed that over lateral, but not midline, leads, the Nc was larger in amplitude to primed than novel faces. It is important to note that other studies have observed that Nc amplitude diminishes in response to multiple repeated presentations of a stimulus (Hill-Karrer et al., 1998; Nikkel & Karrer, 1994; Wiebe et al., 2006). It is possible that these findings reflect generalised habituation or fatigue effects rather than responses to repetition of specific stimuli, and/or that there are non-linear changes in Nc amplitude over repeated presentations of the same stimulus. One argument against the general habituation or fatigue interpretation is that the decrease in amplitude from earlier to later blocks of trials occurs only for stimuli that are repeated and not for trial-unique novel stimuli (Wiebe et al., 2006).

Any account of the functional significance of the Nc must be able to explain why the same stimuli elicit different patterns of response at different ages. For example, while several studies have shown that the Nc is larger to the mother’s face than a stranger’s face in infants of 6 months of age (de Haan & Nelson, 1997, 1999; Nelson et al., 2000), a cross-sectional study of children aged 18–54 months observed that infants aged 18–24 months showed the same effect as the 6-month-olds, while children aged 24–45 months showed no difference between the two faces and children aged 45–54 months showed the opposite pattern with a larger Nc to the stranger’s face than the mother’s face (Carver et al., 2003). Similarly, in their study examining ERP responses to pictures of toys that were either novel or that infants had previously seen used in demonstrations of action sequences, Bauer et al., (2006) observed that 9-month-olds showed a larger Nc to novel than familiar toys (see also Carver et al., 2000), while 10-month-olds showed a larger Nc to familiar compared to novel toys. This pattern of results is consistent with the view that, while the Nc is clearly influenced by item familiarity, it does not necessarily directly reflect memory trace strength. The results could be seen as consistent with the view that the Nc reflects attention to salient events, but which event is more salient changes with age. The difficulty in this argument is to determine a priori which items are most salient and why, rather than simply using this idea as a post-hoc interpretation. This difficulty in determining why infants sometimes seem to allocate more attention to familiar events and sometimes to novel ones echoes a parallel issue in behavioural studies of infants’ novelty preferences in visual paired comparison tests (discussed in Pascalis & de Haan, 2003).

With respect to the Carver et al. (2003) study, it is interesting to note that the response to strangers’ faces (novelty) did not change with age, only the
response to the mother. This suggests that infants are equally interested in new faces across the age range tested, but that they devote particular resources to the mother’s face in the first year and half of life compared to when they are older. The authors argue that these results reflect the fact that infants are forming their attachment to the mother and creating a long-lasting mental representation of her over this period. This interpretation could be seen as consistent with the results of Bauer et al. (2006). In that study, infants at 9 months showed a larger Nc to new than familiar items but showed no evidence of recall 1 month later, while infants at 10 months showed a larger Nc to familiar compared to novel items and did show evidence of recall later. Thus, the 10-month-olds’ larger Nc to familiar items could also have reflected their allocation of resources towards forming a lasting mental representation of the action sequences, while the 9-month-olds’ greater response to the novel items may have reflected recognition without this further processing.

[It should be noted that the authors themselves reject the notion that the infants were encoding different aspects of the events at different ages, e.g., encoding the actions at 10 months but only perceptual object features at 9 months. They draw an analogy instead to a different study of recognition of the mother’s face in which 6-month-olds showed a larger Nc at midline leads to the mother’s than a stranger’s face only when the two faces were dissimilar (easier task) but showed a larger Nc at lateral leads to a stranger’s face than the mother’s face when the two faces were similar (harder task; de Haan & Nelson, 1997). They argue that the 10-month-olds found the task easier and thus showed a larger Nc to the familiar item (as the 6-month-olds did to the mother’s face in the easy task) while the 9-month-olds showed a larger Nc to the novel item because they found the task harder.]

**Is there more than one Nc?**

Some authors have noticed a double peak in the Nc component and proposed that it may represent two processes, labelled Nc1 and Nc2 (Hill-Karrer et al., 1998). In infant visual studies, the Nc1 and Nc2 show similar effects in the two-stimulus oddball task, but the Nc2 appears to habituate more quickly as it is more prominent in earlier blocks and disappears in later blocks (Hill-Karrer et al., 1998). This might be why some investigators have not observed the double peak, if they are averaging over a longer session and/or happen to have more “good” trials from later in the recording session. Further support for the suggestion that there are two Ncs comes from a studying in which source analysis of the Nc indicated two separate frontal sources with different time courses: a prefrontal activation beginning 250 ms after stimulus onset and a frontal pole activation beginning 500 ms after stimulus onset (Reynolds & Richards, 2005).

The functional distinction between the Nc1 and Nc2 is not clear from visual studies with infants, other than the proposal that the Nc2 reflects
“further processing” (Hill-Karrer et al., 1998). However, auditory studies with older children (9–13 years) have also observed a double-peaked Nc in a three-stimulus oddball task using sounds, which is larger in amplitude to oddball or novel sounds (Ceponiene, Lepisto, Soininen, Aronen, Alku, & Naatanen, 2004). The Nc1 occurred between 450–800 ms, was largest frontally in mastoid-referenced data, diminished in size with nose-referenced data, and also inverted polarity from anterior to posterior electrodes with nose-referenced data. The Nc2 (800–1000 ms) was also diminished in size in nose- compared to mastoid-referenced data but showed no anterior to posterior polarity inversion. The authors suggested that the Nc1 reflects the cognitive processing of salient stimuli, while the Nc2 might reflect reorienting after distraction (similar to the “reorienting negativity” that has been reported in adults and children; Schroger, Giard, & Wolff, 2000; Schroger & Wolff, 1998; Wetzel, Berti, Widmann, & Schroger, 2004).

If the Nc does reflect a composite component of two peaks, this has implications for prior infant studies which have tended to focus on a single peak within the Nc time window. If two functionally distinct peaks are present even in infants, then this could possibly contribute to variability between subjects within a study and between studies, if sometimes a peak extraction identified the Nc1 and other times the Nc2 as being the most extreme point in the time window, or if average amplitude measures averaged the two peaks. Future studies in which higher-density electrode arrays are employed may also help to determine whether the Nc1 and Nc2 in infant visual recognition tasks show different topographies.

What are the underlying generators of the Nc?

Although there is some variation across studies, a fairly consistent finding is that the Nc is larger at anterior (Fz, Cz) than posterior (Pz, Oz) electrodes (Davis et al., 1998; Karrer & Monti, 1995; Nelson et al., 2000; Snyder et al., 2002; Webb et al., 2005; Wiebe et al., 2006) and larger at electrodes closer to midline than more lateral electrodes (Webb & Nelson, 2001). Hemispheric differences are not always observed, but when reported tend to favour the right (Carver et al., 2003; Davis et al., 1995; Goldman et al., 2004; Parker & Nelson, 2005; Wiebe et al., 2006). This topographical pattern has led to speculation that the Nc is generated by frontal/anterior brain regions.

A recent study using source analysis (Reynolds & Richards, 2005) is consistent with this speculation. These authors first performed an Independent Component Analysis (ICA; see Chapter 1 for brief description, or Johnson et al., 2001, for more detailed description) on data obtained from 4.5- to 7.5-month-old infants in a three-stimulus oddball paradigm, and then estimated the cortical sources of the ICA weights using an equivalent current dipole procedure. The results of their analyses were interpreted as indicating that the Nc may be generated by areas within the prefrontal and frontal pole regions (see Figure 4.3). The authors noted that the prefrontal source was
Figure 4.3 ICA component cluster for the prefrontal component. The topographical map average of the ICA loadings is similar to the topographical map of the grand average ERP of the Nc component. The equivalent current dipole locations are displayed on MRI slices, with each location representing an ICA from one individual. Reprinted from Reynolds, G.D., & Richards, J.E. (2005). Developmental Psychology, 41, 598–615. Copyright © 2005 by the American Psychological Association. Reprinted with permission.
active earlier (by 250 ms) and influenced by familiarisation prior to the oddball procedure, while the frontal polar source was active later (by 500 ms) and was not influenced by familiarisation. They argue that differences across prior studies in the effects of familiarisation on Nc amplitude might be due to differences in activation and/or sensitivity of the ERP procedure to recording activity from the two regions.

Further indirect evidence that can be seen as supporting a link between the Nc and frontal cortex is that the developmental course of changes in Nc amplitude during childhood closely parallels that of cortical synaptogenesis, particularly in the frontal cortex (Courchesne, 1990; Shibasaki & Miyazaki, 1992).

Finally, developmental decreases in the latency of the Nc have also been linked to neuroanatomical development. For example, Courchesne (1990) has argued that these decreases in latency are related to the myelination of the non-specific thalamic radiation that occurs during the first 7 years of life.

**Nc: Summary**

The Nc is a negative deflection most prominent over midline fronto-central electrodes that peaks about 600 ms in 6-month-olds, and may reflect activation of frontal polar and/or prefrontal cortical sources. The Nc decreases in latency and increases in amplitude over the first year of life. The extent to which this reflects changes in the underlying neural generators and their strength of activation, and/or to which it reflects an increased consistency in the timing of the response over ERP trials, is not clear.

The Nc appears to reflect both aspects of sustained attention and orienting of attention to salient stimuli (which may be salient due to their novelty, or to some other factor, e.g., salience of mother’s face to young infants). While some authors have argued that the Nc reflects attentional processes with recognition occurring afterwards (e.g., Nelson, 1994), it seems clear that stimulus recognition must occur on at least some level by the time of the Nc, since its amplitude can differ for stimuli presented with equal probability that differ only in prior familiarity (e.g., de Haan & Nelson, 1997). There is some indication that the latency at which differences between novel and familiar stimuli are observed might decrease with increasing age and/or decreasing task complexity, although this remains to be directly tested.

The Nc may to some extent reflect “automatic” orienting of attention, as it is elicited for virtually all types of visual stimuli. Modulations of its amplitude may reflect more controlled allocation of attentional resources based on memory or other factors. However, it is important to keep in mind that by their design infant visual ERP tasks are essentially tasks of sustained attention (i.e., to obtain sufficient good data infants must show periods of sustained attention to the visual display). This may instead, or in addition, be a factor contributing to its consistent appearance across studies.

Future investigations of the Nc should be aware that it may actually consist
of two components, Nc1 and Nc2, and may find it informative to use higher-density arrays to provide a better characterisation of topographies of the Nc in different tasks.

**LATE COMPONENTS AND SLOW WAVE ACTIVITY**

Various types of ERP activity have been observed following the Nc that are thought to reflect aspects of recognition memory, including positive and negative slow waves and the Pc (see Figure 4.1).

**Late slow waves**

A pair of late slow waves following the Nc were described by Nelson and colleagues (Nelson & Collins, 1991, 1992; Nelson & deRegnier, 1992): a positive slow wave that was interpreted as reflecting updating of memory representations of partially encoded stimuli, and a negative slow wave that they interpreted as reflecting detection of novelty. A return to baseline was thought to reflect either a response to a fully encoded familiar stimulus or a response to a stimulus that was not encoded at all (for fuller discussion, see Nelson, 1994, 1996). In the three-stimulus oddball, Nelson and colleagues observed no differential activity among the three stimuli at 4 months (Nelson & Collins, 1992); a negative slow wave to novel stimuli, a positive slow wave to the oddball, and a return to baseline for the standard at 6 months (Nelson & Collins, 1991); a negative slow wave to novel stimuli and a return to baseline for oddball and standard at 8 months (Nelson & Collins, 1992). At 12 months of age, the oddball again elicited a positive slow wave, while the novels and standard showed a return to baseline (Nelson & de Regnier, 1992). These results were interpreted as reflecting the increasing memory abilities of infants across the first year of life—by 6 months infants are able to encode even low-frequency stimuli but these require more updating (positive slow wave) than high-frequency stimuli; by 8 months repeated stimuli are well encoded regardless of frequency (return to baseline for both). With respect to response to novelty, at 6 and 8 months infants were able to detect novelty (negative slow wave) but were not yet able to group the novel stimuli into a category of “novelty”. By 12 months of age, however, the return to baseline for the novel stimuli suggests that infants are able to form such a category. This pattern has been generally replicated in other studies using the three-stimulus oddball with infants 4.5–7.5 months of age (Richards, 2003; Reynolds & Richards, 2005).

While this functional interpretation of infant slow wave activity is very useful, one problem is that it can be difficult to predict a priori which stimuli will show positive vs negative slow waves. For example, in one study 3-month-olds were habituated to criterion to one face, and then 2 minutes later ERPs were recorded while they were shown the familiar face and a novel face with
equal probabilities (Pascalis, de Haan, Nelson & de Schonen, 1998). In making predictions with respect to the above model, one might expect several outcomes: (a) no differentiation if the task is too hard; (b) a negative slow wave to novelty; (c) a return to baseline for the familiar since it was encoded to criterion, or a positive slow wave if the memory representation decayed over the 2-minute delay. In fact, the results show a positive slow wave to novel stimuli and a return to baseline for familiar stimuli. While the result for the novel stimuli might not be the most obvious, it is still interpretable in the model—it can be seen as infants’ attempts to encode the “novel” stimulus during the course of the experiment.

It is not entirely clear whether the slow waves described above are the same as or independent from two other types of ERP activity that have been reported, an early negative slow wave and the Pc.

**Early negative slow wave**

The early negative slow wave (eNSW), like the Nc, has a fronto-central maximum and typically begins 100 ms or even earlier after stimulus onset. The time window used to define this slow wave varies across studies and sometimes (e.g., 100–900 ms in Ackles & Cook, 1998) though not always (10–400 ms in Hill-Karrer et al., 1998; 100–500 ms in Davis et al., 1998) overlaps with the start of the typical time window for the negative slow wave described above. Like the Nc, the eNSW is larger to oddball than frequent stimuli (Davis et al., 1998; Hill-Karrer et al., 1998; Karrer & Ackles, 1987; Karrer & Monti, 1995; one exception is Ackles & Cook, 1998 who found no effects, but this may be because they used a much longer time window than the other studies). Unlike the Nc (Courchesne et al., 1981; Nikkel & Karrer, 1994; but see Snyder et al., 2002) the eNSW does not decrease in amplitude over trials (Nikel & Karrer, 1994). The eNSW is believed to represent aspects of attention, such as expectancy regarding when the next stimulus will occur (Karrer & Ackles, 1990) or a processing negativity as has been described in older children and adults (Karrer & Monti, 1995). However, the degree to which this component is separable from the late negative slow wave described above is unclear, as both appear to be larger for novel stimuli. Part of the difficulty is in defining the time window of a slow wave. As illustrated above, time windows for slow waves can vary considerably, and the start of the late NSW is often defined as the end of the Nc time window, even when grand averages suggest that a sustained slow wave has begun before this time (e.g., Nelson & Collins, 1991; Pascalis et al., 1998). In one study the late negative slow wave is described as the result that occurs when the Nc fails to resolve (Nelson et al., 2000), suggesting that the late negative slow wave may be a continuation of processing negativities that have begun at earlier latencies such as the eNSW.
Instead of a sustained positive slow wave following the Nc, some authors have reported a broader positive peak labelled the Pc. Like the positive slow wave, the Pc is maximal over frontal areas (Courchesne et al., 1981) but unlike the positive slow wave it is not affected by stimulus probability (Ackles & Cook, 1998; Courchesne et al., 1981; Hunter & Karrer, 1993; but see Nelson & Salapatek, 1986). Again, whether the Pc is different from the late positive slow wave described above is unclear. In some prior studies (e.g., de Haan & Nelson, 1997) a broad peak that might be the Pc is observable in the “slow wave” time window, whereas in others this is less obvious (e.g., Pascalis et al., 1998).

An important issue for further studies is the proper definition and interpretation of slow wave activity, as this activity is commonly observed in infants’ ERPs. Variations in the definition of slow wave activity, and how such activity might be superimposed on, and influence the analysis and interpretation of, components such as the Nc has received little attention.

What are the generators of the slow waves?

The slow wave responses can be somewhat variable, but topographical analysis shows they tend to be larger over temporal than midline electrodes (Snyder et al., 2002) and larger over anterior than posterior electrodes (Nelson et al., 2000; Snyder et al., 2003; Webb et al., 2005).

Nelson (1996) has speculated that the positive slow wave may be generated in temporal lobe memory regions. This view is supported by a recent report using source localisation linking the positive slow wave to right temporal regions (Reynolds & Richards, 2005). By contrast the late negative slow wave elicited by novel stimuli may be generated by frontal brain regions (Reynolds & Richards, 2005).

HOW DO INFANT COMPONENTS RELATE TO ADULT COMPONENTS?

The relation of the infant ERP components described above to adult ERP components is not entirely clear. For the Nc, some investigators have argued that it is a developmentally unique component that disappears by adulthood (Courchesne, 1978), while other investigators have suggested that it may be analogous to adult components such as the N2 (Karrer & Monti, 1995; Nelson & Dukette, 1998; Vaughan & Kurtzberg, 1992) or N400 (Friedman, 1991). The same diversity in views applies to the positivities following the Nc. Some investigators have argued that they are independent of the adult P300 (Courchesne et al., 1981), while other authors have suggested that late positive activity may be a precursor to the adult P300 (Nelson, Thomas, de
Haan, & Wewerka, 1998; note that in the auditory domain it has been reported that a P300 may in fact already be evident in infants; McIsaac & Polich, 1992). It is unlikely that these debates can be resolved until there are more studies allowing a direct comparison of ERPs in infants, children, and adults using similar procedures. As can be seen in the Appendix, while some studies have tested infants and adults and used similar procedures, none has used the identical stimuli and task and tested both infants and adults or older children.

INFANT ERP STUDIES AND THEORIES OF MEMORY DEVELOPMENT

In order to appreciate how ERP studies in infants have informed theories of infant memory development, it is necessary to first provide a brief overview of the basic neuroanatomy of visual recognition memory.

Brief neuroanatomy of adult visual recognition memory

The pathway for visual object recognition begins at the retina, where visual input is first received. This information then proceeds to the striate (visual) cortex and on to a ventral/medial-directed chain of cortical visual areas in the temporal lobe that extract information about stimulus quality (e.g., size, colour, and shape) and ultimately synthesise a complete representation of the object (Mishkin & Murray, 1994). Storage occurs each time a representation formed in this way activates relevant memory areas in the medial temporal lobe.

In adults, memory is not a unitary function and can be divided into different components. One such distinction is between explicit and implicit memory (similar distinctions are also meant by declarative versus non-declarative memory and by incidental versus intentional memory). Explicit memory depends on the hippocampus and anatomically related structures in the medial temporal lobe and diencephalons, and is characterised by relatively rapid learning and (at least in adult humans) conscious recollection of previous experiences. Recognition memory is typically considered a test of explicit memory. Implicit memory, by contrast, involves a number of abilities that are independent of the medial temporal lobe and are expressed as skills or habits, some of which are characterised by relatively slow learning over repeated experiences. Implicit memory is typically measured by changes in performance (e.g., decreased reaction time or increased perceptual fluency).

The distinction between explicit and implicit memory arose from studies of patients with damage to the medial temporal region of the brain (Squire, 1992). The first of these patients whose memory was studied quantitatively was the famous case HM, who showed a profound anterograde amnesia (difficulty in remembering things that occurred after the brain injury)
following bilateral removal of the medial temporal regions for treatment of epilepsy (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). HM and other patients with similar or more circumscribed medial temporal damage show deficits in explicit memory. For example, HM could neither remember his new address nor be trusted to find his way home alone even 1 year after moving house (Milner, 1966). However, such patients retain some other learning abilities, collectively called implicit memory, such as priming, simple conditioning, and motor learning (Squire & Knowlton, 1995). For example, HM was able to learn to trace a drawing when looking in a mirror, and retained this learning over days (Milner, 1965).

Explicit memory has also been further divided into episodic and semantic memory. Recall of items from episodic memory is by definition associated with retrieval of contextual details related to the encoding, whereas recall of items from semantic memory is not (Tulving, 1972). A similar distinction applies to recognition, whereby it can occur with retrieval of contextual details related to encoding (“recollection-based recognition”) or without these additional details (“familiarity-based recognition”; Tulving, 1985; Yonelinas, 1994). There is consensus that the medial temporal lobe-cortical (MTL) circuit, involving the hippocampus and the perirhinal, entorhinal, and parahippocampal cortices, supports cognitive memory in human adults. According to one view (Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997), structures within the medial temporal lobe function in a hierarchy, wherein perceptual information first enters the parahippocampal regions mediating semantic memory (and familiarity-based recognition), and only then passes to hippocampal regions necessary for episodic memory (and recollection-based recognition).

Theories of infant memory

Theories of infant memory differ as to whether they emphasise continuities or differences in memory processes across the lifespan. Results from behavioural studies of the development of recognition memory demonstrate many similarities in the characteristics of infant and adult recognition memory, suggesting that there is a remarkable continuity in this ability (reviewed in de Haan, 2003). For example, the fact that recognition memory is present from birth and that infants’ recognition abilities are related to measures of their intellectual function later in life (Rose & Feldman, 1997) suggests that it may present a basic aspect of cognition that is continuous from infancy and adulthood. This has led some investigators to conclude that “. . . there seems to be considerable invariance in memory development, at least at the level of basic processes and mechanisms. That is, whatever these ‘basics’ necessary for storage and retrieval of information are, they are clearly present and operating in the first year of life” (Howe & Courage, 1997, p. 157).

By contrast, theories of the neural bases of development of recognition memory have tended to focus on differences between infants and older
children and adults, and on seeming discontinuities in memory such as infantile amnesia (e.g., Nelson, 1995). For example, some authors have suggested that, while implicit memory is present from early in infancy, explicit memory does not begin to emerge until approximately 8–12 months of age (Schacter & Moscovitch, 1984). In other words, recognition memory is fundamentally different in the first months of life compared to the end of the first year. Other investigators suggest that an immature form of explicit memory, labelled “pre-explicit” is operational from birth (Nelson, 1995; Nelson & Webb, 2003). This form differs from true explicit memory in that it relies primarily on the hippocampus and is driven by response to novelty. According to this view, true explicit recognition memory does not emerge until other structures in the memory circuit (e.g., temporal cortical areas surrounding the hippocampus, frontal cortex) and their connections with the hippocampus mature. Still others have suggested the opposite view, that early memory is primarily mediated by cortical regions surrounding the hippocampus (perirhinal cortex) that in adults are important for familiarity-based recognition, whereas the hippocampus itself only becomes involved in recognition more slowly as it progressively develops (Bachevalier & Vargha-Khadem, 2005).

**ERPs and theories of infant memory**

ERPs can potentially provide an important source of evidence regarding the nature of early memory development, as any major change in the brain areas supporting memory would be expected to be reflected in the ERPs. For example, if in the first half-year of life recognition relies mainly on the hippocampus and later comes to rely on a more complex brain circuit involving additional cortical areas, one would predict changes in the type and/or topography of ERP components elicited in recognition tasks over this time.

Some authors have argued that ERP studies do provide evidence that there is a transition in the developing memory system at about 8–10 months of age. One piece of evidence comes from the studies using the three-stimulus oddball (Nelson & Collins, 1991, 1992). In those studies, it was reported that only at 8 months of age are infants able to process a familiar stimulus in the same way regardless of its frequency of occurrence during the memory test (Nelson & Collins, 1992). This was evident in the return-to-baseline for both the frequently occurring and infrequently occurring familiar faces. Before 8 months, infants either do not show evidence of recognition at all (4 months; Nelson & Collins, 1992), or treat the infrequently presented familiar faces differently from the frequently presented familiar ones (6 months; Nelson & Collins, 1991). These results were interpreted as evidence that infants are capable of “true” recognition only at 8 months; prior to this time, infants’ responses are driven more by the frequency of occurrence or novelty of stimuli, and thus reflect the pre-explicit form of recognition.

There are some difficulties with this interpretation of the results. For example, it is not clear how the results reported for 12-month-olds fit with
this explanation. Why should 12-month-olds show a positive slow wave for the infrequently presented familiar faces, as the 6-month-olds did? In addition, it is not clear that the pattern of results could only be explained by a qualitative change in the neural circuits underlying recognition. For example, the results for 4- to 8-month-olds might also be expected if younger babies simply forget more quickly than older babies. In this interpretation, the 6-month-olds treat the infrequently occurring familiar face differently from the frequently occurring one because their memories for the infrequently occurring face decay more quickly, as they see it less often during the test. If 4-month-olds have more rapidly decaying memories they may not be able to remember the stimuli at all, and if 8-month-olds have less rapid forgetting then they will be able to remember both stimuli equally well. Thus, the same pattern could be accounted for by a more continuous change in rate of forgetting.

Another series of studies involving ERPs has also implicated the period around 9 months of age as a time of potential change in the developing memory system. For example, one study found that only infants who showed ERP evidence of recognising the props they had seen used to model events 1 week earlier were able to recall the order of the steps in the events 1 month later (Carver et al., 2000; see also Bauer et al., 2006; 2003). Specifically, about half of the 9-month-olds were able to recall the order, and these infants showed a larger Nc to novel than familiar items, as well as a positive slow wave to familiar items and a negative slow wave to novel items, during the ERP test. Importantly, a subsequent study demonstrated that this was not simply because the other half of the infants failed to encode the events at all (Bauer et al., 2003). The authors argue that the results indicate that ‘...the memory system that is involved in recognition and recall memory undergoes significant developmental change near the end of the first year of life’ (p. 244).

There is thus some indication from ERP studies which might support the view that there is a developmental transition in memory during the second half of the first year of life. However, these data are by no means conclusive and at present do not differentiate among the theories proposing different neuroanatomical bases for the transition. Further investigations using higher-density recording montages will be useful in better characterising the nature of the changes in the neural systems underlying memory during the first year.

USING ERP TO ASSESS INFANT MEMORY IN SPECIAL POPULATIONS

ERPs during infant visual recognition tasks have been used to examine development in infants with global developmental delay (e.g. Downs syndrome; Hill-Karrer et al., 1998) as well as those believed to be generally at
risk for cognitive impairment (de Regnier, Georgieff, & Nelson, 1997) or at particular risk for memory disorders (Nelson et al., 2000; see deRegnier, 2005, for a general review of neurophysiologic investigations of cognitive development in high-risk infants). There are many important factors to consider when using ERPs to compare typically developing and at-risk or atypical groups. As discussed above for the Nc, various aspects of the ERP procedure and data processing can affect the amplitude or latency of components other than true differences in cognitive processing between groups. For example, one study showed that the amplitude of the Nc differed for infants who saw a different total number of trials in the recording procedure (even when there were no differences in number of trials used to create averages; Snyder et al., 2002). Thus, if typical and atypical groups see different total numbers of trials (which can happen as the length of sessions is often determined by the extent of infants’ cooperation), differences may be detected that are related to this procedural difference but might be interpreted as reflecting delayed or deviant development in the atypical group.

In spite of these difficulties ERPs, if used carefully, can potentially provide a very useful tool for assessing early cognitive processing. For example, one study examined infants of diabetic mothers, as they may be at risk for memory disorders due to the adverse foetal environment that occurs in this condition, including chronic hypoxia, reactive hypoglycaemia, and iron deficiency. All of these factors may particularly affect a structure known to be critical for normal memory, the hippocampus (see discussion in Nelson et al., 2000, or de Regnier, Chapter 5, this volume, for further discussion). In this study, 6-month-old infants who had been born to diabetic mothers, as well as control infants, were tested with the mother’s face and a stranger’s face. The results with the control infants largely replicated prior findings showing a larger Nc to the mother’s face over right hemisphere electrodes and a larger positive slow wave to the stranger’s face (Nelson et al., 2000). By contrast, the infants of diabetic mothers did show an Nc and positive slow wave but did not show differentiation between the two faces. In spite of these differences detected with ERPs, the two groups did not differ on a test of general ability level (Bayley Scales of Infant Development) or in a behavioural test of memory using the visual paired comparison procedure. These results illustrate the potential sensitivity of ERPs in detecting atypical development at the group level. The findings that the slow wave response was atypical is consistent with the idea that hippocampal development was affected in the infants of diabetic mothers, as there is evidence that this response is generated in the temporal lobe (Reynolds & Richards, 2005). However, the extent to which the results can be interpreted as reflecting specifically hippocampal abnormality in this

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1 Nelson et al. (2000) state that the positive slow wave was “absent or diminished” in the infants of diabetic mothers, but there was no main effect of Group on amplitude and they report no other direct statistical comparison of amplitude between groups.
population is unclear. For example, infants of diabetic mothers performed normally on the visual paired comparison test, which is also believed to assess hippocampal function (reviewed in Nelson, 1995; Pascalis & de Haan, 2003; but see Bachevalier & Vargha-Khadem, 2005) and these infants also showed an abnormal Nc, a response thought to be generated in the frontal lobes (Reynolds & Richards, 2005).

While this and a few other studies cited above indicate that ERPs in visual cognitive tasks are potentially sensitive to atypical cognitive processing in young infants at risk, many questions and issues remain regarding their clinical utility, and this area is less developed in the visual compared to the auditory domain (see Molfese et al., Chapter 7 this volume for predictive studies using auditory ERPs). For example, none of these visual studies has as yet provided follow-up information to determine whether and how these early differences relate to later cognitive impairments—thus the specificity and sensitivity of these early measures for predicting later difficulties remains unknown.

SUMMARY AND FUTURE DIRECTIONS

Studies of infant visual recognition memory using ERPs have found that infants show differential brain wave activity to novel compared to familiar visual stimuli as young as 1 month of age (Karrer & Monti, 1995). Generally, novel stimuli elicit more negative-going waveforms while familiar stimuli elicit more positive-going waveforms, although the latency at which these effects are observed can vary across studies. There are important exceptions to this general statement, in that familiar stimuli that are particular salient to infants of a given age (e.g., their mother’s faces) can elicit a more negative-going waveform than novel stimuli. Generally speaking, while visual stimuli typically elicited a robust perceptual response over occipital areas (see McCulloch, Chapter 2 this volume), the components and slow waves that are affected by familiarity are often described as having a more anterior distribution.

Although there is an increasing body of literature describing the development of ERP components related to infant visual recognition and memory (see Appendix), and application of ERP methods to address questions regarding theories of memory development and the nature of atypical early memory development, in many ways this area is still in its beginnings. Further investigations using high-density electrode arrays to study developmental changes at frequent intervals over infancy are needed in order to better characterise normative development. Such data will help to address debates regarding the degree of continuity of memory processes from infancy to childhood. They will also likely prove very useful in understanding results obtained in at-risk populations, such as in evaluating whether development is deviant, or typical but delayed.
ACKNOWLEDGEMENTS

Many thanks to Dr J. E. Richards and Dr G. Reynolds for kindly providing Figures 4.2 and 4.3.
## APPENDIX

<table>
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<th>Montage (reference)</th>
<th>Time window of Nc</th>
<th>Results</th>
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<tbody>
<tr>
<td>Schulman-Galambos &amp; Galambos, 1978</td>
<td>Adults 18–25 years, n = 20</td>
<td>Adults: 20%</td>
<td>Photos of real world scenes, Disneyland, children’s drawings, etc. (2000 ms; stimulus set differed for different ages/subjects)</td>
<td>C3, C4, Lower EOG (linked ears)</td>
<td>All recordings “dominated by a large negative deflection peaking between 500–650 ms for most subjects”</td>
<td>No statistical analyses reported</td>
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<tr>
<td></td>
<td>Infants aged 7 weeks–12 months, n = 10 to 21 depending on stimulus condition</td>
<td>Infants: 34–68%</td>
<td>A variety of images presented in or out of focus</td>
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<tr>
<td>Courchesne et al., 1981</td>
<td>4 to 7.2 month olds, n = 10</td>
<td>62%</td>
<td>2 female faces (100 ms)</td>
<td>Fz, Pz EOG (Right Mastoid)</td>
<td>300–1200</td>
<td>Amplitude is larger to oddball than standard at all electrodes, and latency is 200 ms slower to oddball.</td>
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<tr>
<td>Nelson &amp; Salapatek, 1986</td>
<td>6 months, n = 15 to 16 in each of 3 experiments</td>
<td>54%</td>
<td>male and female faces (100 ms)</td>
<td>Oz, Pz, Fz, EOG (Right Mastoid)</td>
<td>300–700</td>
<td>Expt 1: Area larger to frequent then oddball at Cz in the 551–700 ms window Expt 2: Area larger to during the familiarisation trials than to the novel during test at Cz in the 551–700 ms window Expt 3: No differences</td>
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<tr>
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<tr>
<td>Nelson &amp; Collins, 1991</td>
<td>6 months, n = 12</td>
<td>84%</td>
<td>female faces (500)</td>
<td>Familiarisation with two faces shown in alternation for 20 trials, then immediately a test with one familiar face shown 60%, the other 20%, and trial unique faces for 20%</td>
<td>Oz, Pz, Cz, Fz (linked ears)</td>
<td>400–800</td>
<td>No differences</td>
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<tr>
<td>Nelson &amp; Collins, 1992</td>
<td>4 months, n = 14 and</td>
<td>4 months: 54%</td>
<td>female faces (500)</td>
<td>Same as Nelson &amp; Collins (1991)</td>
<td>Oz, Pz, Cz, Fz (linked ears)</td>
<td>Not reported (appears ~400–800 ms in graphs)</td>
<td>Not analysed</td>
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<td></td>
<td>8 months, n = 17</td>
<td>8 months: 58%</td>
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<tr>
<td>Hunter &amp; Karrer, 1993</td>
<td>6 months, n = 36</td>
<td>n/a</td>
<td>n/a</td>
<td>Oddball with 80/20 probability, varying stimulus duration (100, 500 or 1000)</td>
<td>Oz, midline and hemispheric</td>
<td>n/a</td>
<td>Amplitude larger for oddballs</td>
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<td>Stimulus duration affects latency, with longer latency for 500 ms duration then for shorter or longer presentations</td>
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<tr>
<td>Nikkel &amp; Karrer, 1994</td>
<td>6 months, n = 28</td>
<td></td>
<td>2 female faces</td>
<td>Oddball with 80/20, but here examine only response to frequent and how it changes over the first, second and last third of the session</td>
<td>Fz Cz Pz Oz C3/4 EOG (linked ears)</td>
<td>400–900</td>
<td>Amplitude decreases from second to third blocks at Cz</td>
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<tr>
<td>Study</td>
<td>Age</td>
<td>Sample Size</td>
<td>Task Description</td>
<td>Condition Details</td>
<td>Results</td>
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<td>Karrer &amp; Monti, 1995</td>
<td>4-7 weeks, n = 20 in total but 11–18 included depending on analysis</td>
<td>43% geometric shapes</td>
<td>Oddball with 80/20 probability Cz, Fz, Pz, Oz, C3/4 EOG 500–1000</td>
<td>Area is larger at Cz than Fz Latency is longer to frequent than oddball at Fz, Cz, C3/4</td>
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<tr>
<td>Nelson &amp; de Haan, 1996</td>
<td>7 months, n = 19 per experiment</td>
<td>Expt 1: 55% Expt 2: 64% Happy, fearful and angry faces (500 ms)</td>
<td>Expt 1: Happy and fearful face presented 50/50 Expt 2: Fearful and angry face presented 50/50</td>
<td>Oz, Pz, Cz, Fz, T3/4 (Linked ears) 370–680</td>
<td>Expt 1 Amplitude larger for fearful than happy faces Expt 2 No difference in amplitude or latency for fearful compared to angry faces</td>
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<tr>
<td>de Haan &amp; Nelson, 1997</td>
<td>6 months, n = 22 per experiment</td>
<td>Expt 1: 64% Expt 2: 65% Expt 3: 64% Expt 4: 61% Two faces presented with equal probability</td>
<td>Expt 1: Mother’s and dissimilar stranger’s face Expt 2: Two dissimilar strangers’ faces Expt 3: Mother’s and similar stranger’s face Expt 4: Two similar strangers’ faces</td>
<td>Oz, Pz, Cz, Fz, T3/4, T5/6, EOG (linked ears) Midlines: 400–800 Lateral: 250–700</td>
<td>Across all experiments amplitude was negative at T3/4 and positive at T5/6 In experiments 2 and 4 latency was increased from anterior to posterior midline leads Larger amplitude for mother’s face compared to dissimilar stranger at Pz, Cz, Fz and T4 Larger amplitude for similar stranger than mother’s face at T6 and T5 (with strongest effect at T5) No difference in Nc amplitude or latency between two strangers’ faces 1 (Continued Overleaf)</td>
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<td>de Regnier et al., 1997</td>
<td>4 months, n = 16</td>
<td>Not reported</td>
<td>Red cross and red corkscrew shapes (500 ms)</td>
<td>Familiarisation to red cross, then familiar red cross shown 80% and novel red corkscrew shown 20%</td>
<td>Oz, Cz, Pz, Fz, EOG (linked ears)</td>
<td>500–1000</td>
<td>No effects</td>
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<td>Ackles &amp; Cook, 1998</td>
<td>6 months, n = 96</td>
<td>36%</td>
<td>female faces</td>
<td>Oddball with 90/10, 80/20, 70/30, or 60/40 probabilities, or 50/50 with random or alternating sequence</td>
<td>Oz, Pz, Cz, Fz, EOG (Right ear)</td>
<td>350–900</td>
<td>Amplitude biggest centrally and latency decreases from anterior to posterior. Amplitude significantly bigger to oddball for 90/10 and 60/40 conditions and similar trend for 70/30, but not significant for 80/20 or 50/50 conditions. No effect of probability on Nc latency. Local probability effects also reported (e.g., No bigger for oddball and standard preceding oddball then standard after oddball)</td>
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<td>Hill-Karrer et al., 1998</td>
<td>6 months, n = 10</td>
<td>19%</td>
<td>2 female faces</td>
<td>Oddball with 2 female faces 80/20</td>
<td>Oz, Cz, Pz, Fz, C3/4 EOG (Left Ear)</td>
<td>Nc1:400–800, Nc2:800–1200</td>
<td>Nc1 peak is larger to oddball at all electrodes and area larger to oddball at all but C4</td>
</tr>
</tbody>
</table>
Nelson et al., 1998 Adults 17–40 yrs, 
7 adults, 48 
8 months, n = 20

Adults: 39% 
Babies: 73% (500 ms)

Female faces

Babies: Habituation-to-criterion to one face, 
then either 1 or 5 
min delay and ERP 
test with familiar 
and novel faces 
presented 50/50 
condition. 
Adults tested under 
similar but not 
identical 
conditions. 

Oz, Pz, Cz, Fz, 
C3/4, T3/4, T5/ 
6, EOG (linked 
mastoids)

300–703 Amplitude larger 
over anterior 
compared to 
posterior leads 
Amplitude to 
familiar stimuli larger 
over left than right 
hemisphere 
Over right 
hemisphere only, 
amplitude larger to 
familiar than novel 
stimuli 
For 5-min delay only, 
latency longer to 
familiar than novel. 

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<th>Attrition</th>
<th>Stimuli (duration)</th>
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<th>Montage (reference)</th>
<th>Time window of Nc</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Pascalis et al., 1998</td>
<td>3 months, $n = 15$</td>
<td>75%</td>
<td>Female faces (500 ms)</td>
<td>Habituation to criterion to one face shown in different poses, then ERP test with familiar and novel face shown 50/50</td>
<td>Oz, Pz, Cz, Fz, C3/4, T3/4, T5/6, EOG (linked mastoids)</td>
<td>750–1200</td>
<td>Amplitude larger to familiar face at lateral and midline leads.</td>
</tr>
<tr>
<td>de Haan &amp; Nelson, 1999</td>
<td>6 months, $n = 44$</td>
<td>50%</td>
<td>Mothers’ and strangers’ faces and familiar and unfamiliar toys (500 ms)</td>
<td>Mother’s and dissimilar stranger’s face presented 50/50 or familiar and unfamiliar toy presented 50/50</td>
<td>Oz, Pz, Cz, Fz, T3/4, T5/6, EOG</td>
<td>250–800</td>
<td>Amplitude larger to mother’s face than stranger’s face at Pz, Cz, Fz and T4 Amplitude larger to familiar toy than novel toy at Pz, Cz, Fz and lateral leads</td>
</tr>
<tr>
<td>Carver, Bauer &amp; Nelson 2000</td>
<td>9 months, $n = 20$</td>
<td>57%</td>
<td>Slides of 2-step action sequences plus end state, one of a new event and one of a familiar sequence observed over 3 real-life exposure sessions (500 ms)</td>
<td>Familiarisation to action sequence in 3 distributed, real life demonstrations of the sequence, then one week after last exposure ERP test with still images of familiar and novel sequences presented 50/50</td>
<td>Pz Cz Fz T3/4, T5/6 (linked ears)</td>
<td>260–870</td>
<td>Amplitude larger to novel than familiar images at midline but not lateral leads Planned comparisons show this effect is significant only for infants who were able to recall (imitate) complete event sequences one month after the ERP test.</td>
</tr>
<tr>
<td>Study</td>
<td>Age</td>
<td>n</td>
<td>Female Faces</td>
<td>Presentation</td>
<td>Mother’s and Dissimilar Stranger’s Faces</td>
<td>Amplitude/Latency</td>
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<tr>
<td>Nelson et al., 2000</td>
<td>6 months, n = 34</td>
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<td>30%</td>
<td>400–800</td>
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<td>Mothers’ and dissimilar strangers’ faces (500 ms)</td>
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<td></td>
<td></td>
<td>Mother’s and dissimilar stranger’s face presented 50/50</td>
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<tr>
<td></td>
<td>also tested 26 infants of diabetic mothers</td>
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<td>for entire study</td>
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<tr>
<td>Webb &amp; Nelson, 2001</td>
<td>Adults 17–28 yrs, n = 30</td>
<td>Adults: 21%</td>
<td>female faces presented upright and inverted (500)</td>
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<tr>
<td></td>
<td>Babies 6 months, n = 24</td>
<td>Babies: 44%</td>
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<tr>
<td>Snyder et al., 2002</td>
<td>6 months, n = 94 (see individual studies)</td>
<td>Mothers’ and dissimilar strangers’ faces (500 ms)</td>
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</tbody>
</table>

**Amplitude larger over anterior leads and latency increased from anterior to posterior leads.**

**Amplitude larger to mother and stranger over C4 (and over right hemisphere generally when leads were collapsed by within hemisphere).**

**At lateral leads amplitude larger at fronto/central than temporal leads.**

**Amplitude for upright faces larger than inverted faces.**

**At lateral leads larger amplitude for novel than primed faces regardless of orientation.**

**Expt 1:** Amplitude largest anteriorly, and trend for largest amplitude to be for familiar faces over the right hemisphere.

No difference between first and second blocks.

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<thead>
<tr>
<th>Authors</th>
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<th>Montage (reference)</th>
<th>Time window of Nc</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Bauer et al., 2003</td>
<td>9.5 months, n = 57</td>
<td>39%</td>
<td>Same as Carver et al 2000.</td>
<td>Familiarisation to event sequence in 3 distributed, real life demonstrations of the event, then both immediately and one week after last exposure ERP test with still images of familiar and novel events presented 50/50</td>
<td>Oz Cz Pz Fz, T3/4, T5/6 C3/4 (linked ears)</td>
<td>260–870</td>
<td>Exp 2: Amplitude larger and latency shorter for the 61–80 trials group than the group who saw fewer trials. The latency to the novel face decreased with increasing number of trials included. The latency was faster to the novel face only in the group who saw the most trials. At immediate test, Ne amplitude larger for novel for all groups. At delay test no amplitude differences, but for children who were able to recall the events in the deferred imitation test, the latency is longer for old than new events.</td>
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</table>

Exp 2: Examined how response differed depending on the number of total trials viewed (<60, 61–80, 81–100)
Also only for the infants who recalled the events, latency was longer for old events at delayed than immediate test. The difference in peak amplitude between old and new events predicted the number events recalled in correct order.

| Carver et al., 2003 | 18–24 months, 24–45 months and 45–54 months | n = 14 per age group | Mother’s and strangers’ faces and familiar and unfamiliar toys (500 ms) | Mother’s and dissimilar stranger’s face presented 50/50 and in a separate session familiar and unfamiliar toy presented 50/50 | 64 electrodes (average reference) | 360–920 |

Faces: Younger group showed larger amplitude to mother than stranger, middle group showed no difference, and older group showed larger amplitude to stranger than mother.

Toys: Amplitude larger over right than left hemisphere. Amplitude larger for unfamiliar than familiar toys.

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<table>
<thead>
<tr>
<th>Authors</th>
<th>Age and number of subjects</th>
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<th>Montage (reference)</th>
<th>Time window of Nc</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Richards, 2003</td>
<td>4.5, 6, and 7.5 months</td>
<td>4.5 months: 12.5%</td>
<td>Video ‘Follow that Bird’, and 16 computer generated geometric patterns overlaid on the video (500 ms)</td>
<td>Familiarisation to two patterns (20 sec accumulated looking time trials then brief alternating presentations 5 times each) followed by ERP with one familiar 60%, one 20% and trial unique images for the remaining 20%</td>
<td>20 electrodes (averaged mastoids)</td>
<td>450–550 [analysed 250–750]</td>
<td>No differences between stimulus conditions. Amplitude at fronto-central and frontal lateral leads larger during orienting and sustained attention than inattention. Amplitude increased with age during periods of attention but not inattention.</td>
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<td></td>
<td>n = 16 per age group</td>
<td>6 months: 25%</td>
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<td>7.5 months: 25%</td>
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<tr>
<td>Stolarova et al., 2003</td>
<td>6 months, 4 months and preterm corrected age 4 months, n = 20 per group</td>
<td>Fullterms: 59%</td>
<td>Female faces (500)</td>
<td>62 different faces were presented, with 20 repeated immediately after the first presentation, another 20 repeated</td>
<td>Fz, Cz, Pz, Oz, F3/4, C3/4, T3/4, T5/6, P3/4, EOG (linked mastoids)</td>
<td>400–770</td>
<td>Amplitude larger over fronto-central than parietal sites Latency longer for 4-month-olds and preterms than 6-month-olds (by</td>
</tr>
</tbody>
</table>
After 4 intervening faces, and 22 not repeated.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, n</th>
<th>% Female</th>
<th>Condition Description</th>
<th>Electrodes (Reference)</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Haan et al., 2004</td>
<td>7 months, n = 40</td>
<td>63%</td>
<td>Female faces posing happy, fearful or neutral expressions (500 ms)</td>
<td>62 electrodes (average reference)</td>
<td>400–600</td>
<td>Amplitude larger anteriorly; larger over right than left side at temporal electrodes, but opposite pattern at parietal sites. Amplitude larger to fearful than happy faces (responses to neutral not reported). Amplitude was affected by infant temperament and maternal personality.</td>
</tr>
<tr>
<td>Goldman et al., 2004</td>
<td>27 months, n = 14</td>
<td>46%</td>
<td>Stuffed animals</td>
<td>Oddball with one stuffed animal presented frequently (70%) and additional, trial-unique stuffed animals presented the remaining 30%</td>
<td>Fz, Cz, Pz, F3/4, F7/8, P3/4, O1/2, EOG (linked mastoids)</td>
<td>400–800</td>
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<table>
<thead>
<tr>
<th>Authors</th>
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<th>Montage (reference)</th>
<th>Time window of Nc</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Lukowski et al., 2005</td>
<td>9.5 months, n = 79</td>
<td>64%</td>
<td>Same as Carver et al. (2000), (500 ms)</td>
<td>Familiarisation by watching real-life 2-step action sequences in 2 separate sessions. Half the infants allowed to imitate after watching, half not allowed. Immediately and one week after last familiarisation session ERPs recorded to still images of the familiar action sequence and a novel action sequence presented with equal probability.</td>
<td>25 electrodes (average reference)</td>
<td>260–700</td>
<td>Amplitude for novel sequences at immediate test. Larger amplitude for imitate group than watch only group for familiar sequences at one-week delay.</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Gender</td>
<td>Stimulus Description</td>
<td>EEG Parameters</td>
<td>Results and Findings</td>
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<tr>
<td>Parker &amp; Nelson, 2005</td>
<td>8- to 32-month-olds, n = 33</td>
<td>57%</td>
<td>Female faces posing happy, sad, angry or fearful expressions (500 ms)</td>
<td>Cz, Pz, Fz, O1/2m T7/8, P3/4, C3/4, F3/4, EOG (average mastoids)</td>
<td>Amplitude larger for younger than older infants but no age-related changes in latency</td>
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<td></td>
<td>[also tested institutionalised children]</td>
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<td>Peak latency for fearful faces was quicker over the left than right hemispheres</td>
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<tr>
<td>Reynolds &amp; Richards, 2005</td>
<td>4.5, 6 and 7.5 months, n = 22 at each age</td>
<td>15%</td>
<td>Video ‘Follow that Bird’, and 16 computer generated geometric patterns overlaid on the video (500 ms)</td>
<td>124 electrodes (average reference)</td>
<td>Amplitude largest to novel, intermediate to infrequent familiar and smallest to frequent familiar at frontal and central leads, and this pattern occurred primarily for the infants who received familiarisation</td>
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<td></td>
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<td><strong>Familiarisation Group</strong>: Familiarisation to two patterns (20 sec accumulated looking time trials then brief alternating presentations 5 times each) followed by ERP with one familiar 60%, one 20% and trial unique images for the remaining 20%</td>
<td></td>
<td>Amplitude was larger during inattention then attention for 4.5 month olds at frontal and central electrodes; no difference by attention for other ages.</td>
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<td><strong>No Familiarisation Group</strong>: As above only without familiarisation</td>
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<td></td>
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<td></td>
<td>Also measured heart rate to define different phases of attention</td>
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<tr>
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<tr>
<td>Webb et al., 2005</td>
<td>4, 6, 8, 10 and 12 months longitudinal, n’s range from 16–28.</td>
<td>4% (96% had at least one good data point across the 5 ages &amp; 2 stimulus conditions)</td>
<td>Task 1: Mother’s face and dissimilar-looker’s face (300)</td>
<td>Familiar and unfamiliar images presented 50/50 in separate sessions for faces and toys.</td>
<td>Oz, Pz, Cz, T3/4, T5/6, C3/4, EOG (linked mastoids)</td>
<td>4 and 6 months: 350–750, 8, 10 and 12 months: 300–700</td>
<td>Larger amplitude at anterior than posterior electrodes and at right than left electrodes. Larger amplitude for objects than faces. Linear and cubic trends for change in amplitude with age: increases [i.e., becomes more negative] most marked between 4–6 months and 10–12 months, relatively flat 6–10 months. Latency faster for faces than objects. Linear and quadratic trends for change in amplitude with age: decrease most prominent 4–8 months.</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Group Size</td>
<td>Familiarisation Details</td>
<td>Electrodes Used</td>
<td>Time Window</td>
<td>Amplitude/Latency Details</td>
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<tr>
<td>Quinn et al., 2006</td>
<td>6.5 months, $n = 10$</td>
<td>68%</td>
<td>Images of familiarised cats, novel cats, and novel dogs (500 ms)</td>
<td>62 electrodes (average reference)</td>
<td>350–750 ms</td>
<td>Larger amplitude for novel dogs than familiar or novel cats.</td>
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</tr>
<tr>
<td>Wiebe et al., 2006</td>
<td>9 months, $n = 42$</td>
<td>11%</td>
<td>Images of a familiar 2-step action sequence plus end state observed over 2 real-life exposure sessions, images of a new 2-step sequence and trial-unique images of other unseen events (500 ms)</td>
<td>29 electrodes (averaged mastoids)</td>
<td>350–750 ms</td>
<td>Amplitude larger and latency slower at anterior compared to posterior midline electrodes. Larger amplitude in early versus later trials and midline ($p &lt; 0.06$) and lateral ($p &lt; 0.05$) leads. At lateral leads, larger amplitude for trial unique novel than familiar, with novel repeated intermediate between the two.</td>
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<tr>
<td>Bauer et al., in press</td>
<td>9.5 months at entry, $n = 11$ for Phase 1 and $n = 14$ for Phase 2</td>
<td>65%</td>
<td>Similar to Carver et al. 2001 except had only two exposure sessions, then given ERP test for immediate recognition and imitation test for recall one month later.</td>
<td>25 electrodes (average reference)</td>
<td>260–700</td>
<td>Latency tended to be longer for familiar than novel at midlines. Amplitude tend to be larger for novel than familiar images at 9 months but larger for familiar than novel images at 10 months at midlines (Continued Overleaf)</td>
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Participants given same procedure but with different event sequences at 9 and 10 months.

At 10 months the difference in latency between novel and familiar events at Cz predicted the number of actions recalled one month later; the same also for area scores at T5/6 and for peak amplitude at T6 with recall of order.

Davis, Karrer & Walker, unpublished ms 1998

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age and number of subjects</th>
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<tbody>
<tr>
<td>1 month, n = 20</td>
<td>1 month: 43%</td>
<td>Geometric shapes (1 month and 3 month) or faces (3 month and 6 month)</td>
<td>Oddball with 80/20 probability within stimulus type</td>
<td>Fz Cz Pz Oz, C3/4 EOG (linked ears)</td>
<td>1 month: 500–1000</td>
<td>Shapes: Area and amplitude bigger at 3 than 1 month over Fz and Cz and area the same at C3/4. Area larger for oddball than frequent and trend for latency to be longer for oddball than frequent. Overall, is indication that Nc for older infants viewing faces is larger and faster than for younger infants viewing geometric shapes.</td>
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<tr>
<td>3 month, n = 21</td>
<td>3 month: 37%</td>
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<td>3 month: 500–1100</td>
<td>Faces: Area and amplitude bigger for rare than frequent. Latency shorter at 6 than 3 months.</td>
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<tr>
<td>6 month, n = 18</td>
<td>6 month: 70%</td>
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<td>6 month: 400–800</td>
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REFERENCES


5 Auditory recognition memory in infancy

Raye-Ann deRegnier
Northwestern University Feinberg School of Medicine, Chicago, USA

In the adult brain, memory is a complex function that is subserved by several neural networks. Recognition memory is a function of the explicit memory or declarative memory network that is known to be dependent upon medial temporal lobe structures such as the hippocampus and the entorhinal cortex (Broadbent, Clark, Zola, & Squire, 2002; Clark, Broadbent, Zola, & Squire, 2002; Reed & Squire, 1997) and it is one of the earliest types of explicit memory to develop (Fagan, 1990; Nelson, 1995). As such, the evaluation of the development of recognition memory in the infant offers the opportunity to understand the evolution of the explicit memory network from the “ground up” and enhance our understanding of the role of memory in overall cognitive development. Understanding the memory abilities of the youngest infants also allows the researcher the opportunity to document perinatal brain injury to memory networks and to further evaluate the role of plasticity in neural development.

It is important to recognize that the immature memory network of the newborn infant is accompanied by immature sensory systems and limited experience. Thus, prerequisites to the study of memory in the newborn include sufficient maturity of the sensory organs and sensory brain pathways leading into the memory circuits themselves. Experiences to be remembered must be appropriate for the processing abilities of the infant, and methodology for testing must take all these factors into account.

Although most studies of infant recognition memory have focused on visual memory, there is evidence that the memory networks of the brain are amodal (Broadbent, Clark, Zola, & Squire, 2002) and are connected to each of the sensory pathways (also see Squire, Schmolck, & Stark, 2001). Although visual recognition memory is most commonly studied, in the newborn infant visual acuity is poor (Volpe, 2001) and visual experience is very limited. In contrast, hearing begins during the fetal period and by term gestation, the newborn has relatively good auditory acuity (Lary, Briassoulis, de Vries, Dubowitz, & Dubowitz, 1985, Starr, Amlie, Martin, & Sanders, 1977) as well as several months of prenatal auditory experience (Lecaunet & Schaal, 1996). Both of these features facilitate the study of auditory recognition memory.

This chapter will describe the development of the sensory and neural
networks that are thought to underlie the neurobehavioral manifestations of auditory recognition memory. Although auditory discrimination is likely required for recognition memory, it will not be discussed here as it is the focus of Dr Cheour’s chapter of this book (Chapter 6). The use of event-related potentials (ERPs) in the evaluation of auditory recognition memory in the newborn infant will be discussed, and behavioral, psychophysiological, and event-related potential evidence of early auditory recognition memory will be reviewed.

THE NEURAL PATHWAY FOR AUDITORY RECOGNITION MEMORY

Although many parts of the neural pathway for auditory recognition memory have been elucidated, the complete neural pathway for auditory recognition memory has not been described in either the adult or the infant. Through decades of work, the pathway for perception of environmental sounds from the ear to the primary auditory cortex has been established, and the development of this pathway has been studied using histological, behavioral, and neurophysiologic techniques. There is much less information regarding the central auditory processing leading into and including the memory network that is responsible for auditory recognition memory in the infant. Recent studies have detailed pathways linking perception and memory in animal models (Suzuki & Amaral, 1994) and in human adults, using functional magnetic resonance scanning (fMRI) (Daseeleer, Veltman, & Witter, 2004; Dolan & Fletcher, 1999; Lepage, Habib, & Tulving, 1998; Shah et al., 2001). The development of central auditory processing and recognition memory have not been as well described, but both ERPs and neuroimaging procedures have augmented the traditional procedures to improve our understanding of both anatomic and functional development.

A pathway of neural structures likely to be involved in auditory recognition memory is seen in Figure 5.1. The first part of the pathway (Hudspeth, 2000) involves the transformation of sound to neural impulses. Sound is transmitted to the outer ear via amniotic fluid, bone, or air, and transmitted through the external ear canal through the middle ear to the cochlea where the vibration of the middle ear ossicles is converted into neural impulses by vibration of the frequency-specific hair cells in the organ of Corti. These hair cells are innervated by bipolar neurons of the spiral ganglia which make up the auditory nerve. The auditory nerve terminates in the dorsal and ventral cochlear nuclei of the brainstem. At this point, the neural pathway divides into ipsilateral and contralateral tracts that ascend further through the superior olivary nucleus to the lateral lemniscus (where further crossing may occur), to the inferior colliculus and medial geniculate body of the thalamus, to primary auditory cortex found in the superior temporal gyrus where perception presumably begins.
The pathway from perception to auditory recognition memory is not as well known and is more complex, likely involving a network of brain areas that are variably activated, depending on the exact nature of the memory task. However, it is known that primary auditory cortex connects to higher-order auditory association areas and ultimately projects to the hippocampus and rhinal cortex through projections to area TH of the parahippocampal cortex (Squire et al., 2001; Suzuki & Amaral, 1994). Recognition of voices in the adult is also associated with activation of the posterior cingulate cortex and retrosplenial cortex of the limbic system (which also project to the perirhinal, parahippocampal, and entorhinal cortex) (Shah et al., 2001).

From this discussion it should be apparent that evaluation of recognition memory in the infant requires that the entire neural pathway is sufficiently mature before testing can be accomplished. In adults and older children this can be assumed. However, when discussing memory in the very young infant, it becomes important to understand what is known about the histological and functional development of these pathways during gestation and early infancy. This knowledge is helpful in preparing paradigms to be used to study this age group, and in understanding the variability that may be seen in ERP studies at these young ages.
ANATOMIC DEVELOPMENT OF THE NEURAL PATHWAY FOR AUDITORY RECOGNITION MEMORY

All parts of the ear begin to develop in the embryo, with the cochlea appearing to be functional by 18–20 weeks gestation. Inner ear function overall appears to be at mature levels by 36 weeks gestation (Lecaunet & Schaal, 1996). The brainstem also forms relatively early and has a short time course of myelination starting near 23–24 weeks gestation and completing at about 37 weeks gestation (Eggermont, 1988). In contrast, the cerebral cortex has a prolonged period of development. Neurons destined for the cerebral cortex proliferate from 7 weeks through midgestation and then migrate to their final destinations in one of the six layers of the cerebral cortex. Neurons migrate in the neocortex in an “inside-out” pattern, with the deepest layers (5–6) developing first and the more superficial layers developing later. By 32 weeks gestation, all six layers of the cerebral cortex can be observed. Once the neurons have formed and migrated, they extend axons and dendrites, form synapses, and undergo further differentiation and apoptosis (Nelson, 2002).

Synaptogenesis is critical in order for neural impulses to be transmitted throughout the nervous system. Although most synapses form after birth, Huttenlocher and Dabholkar (1997) demonstrated early synapse formation in all six layers of the auditory cortex beginning by 28 weeks gestation. Synaptic density was maximal in this area at 3 months of age, with synapse elimination appearing to be complete by 12 years of age. Thus, synaptic connections are known to exist from the auditory nerve through primary auditory cortex by mid to late gestation in the fetus.

There is less information regarding early histologic development in the auditory association areas or within the memory networks of the human brain. A notable exception to this is the development of the hippocampus, reviewed in detail by Dr László Seress of Hungary (Seress, 2001). The human hippocampus begins to develop during fetal life, with development continuing to adulthood. Most of the neurons in the hippocampal formation are formed in the first half of gestation, the exception being the dentate gyrus, where the neurons develop later. An “inside-out” pattern of neural migration is noted that is similar to that seen in the neocortical regions, except for the neurons of the dentate gyrus that migrate throughout the first postnatal year and develop from the outside in. Entorhinal-hippocampal projections are noted during midgestation (Hevnar & Kinney, 1996). These connections appear to be among the first cortico-cortical connections in the human brain. Although the human hippocampus is quite immature at birth, it appears that sufficient synaptic connections are present to support at least rudimentary recognition memory at term gestation.

Medial temporal lobe development has also been described in early infancy using magnetic resonance imaging (MRI). In one study of children from 3 weeks to 14 years of age (Utsunomiya, Takano, Okazaki, & Mitsudome, 1999), it was noted that the basic morphology of the hippocampal formation
was similar to that seen in adults. The volume of the hippocampal formation increased rapidly through age 2 and more slowly thereafter. The hippocampal formation composed a larger percentage of the temporal lobe in younger infants compared with older children. The right hippocampal formation was larger than the left in 91% of the children, beginning in early infancy. Early myelination was noted in the parahippocampal gyrus from age 3 months continuing through 2–5 years for the limbic system and related structures. These MRI data show a disproportionately large size for the hippocampus within the temporal lobe in very young infants, supporting a central role for this brain structure in early cognition.

Taken altogether, these anatomic studies show sufficient histologic development to support hearing and auditory perception by 28 weeks gestation. The hippocampus appears to have sufficient synaptic connections to support functional abilities by term gestation, if not earlier. Neurophysiologic and behavioral studies support these basic timetables and will be reviewed next.

BEHAVIORAL AND EVOKED POTENTIAL MEASURES OF AUDITORY PROCESSING

Fetal hearing has been tested using a variety of methods (reviewed in Lecanuet & Schaal, 1996), with the most common responses being fetal cardiac responses or motor responses. By 23–24 weeks gestation, some fetuses show an increase in heart rate or motor activity in response to sound, becoming more uniformly present over the next month of gestation (Hepper & Shahidullah, 1994; Lecanuet & Schaal, 1996). These behavioral studies are consistent with developmental studies of the auditory processing pathway through primary cortex and suggest that efferent pathways controlling heart rate and motor activity must be sufficiently developed as well. Further information about the development of hearing later in gestation can be gained through neurophysiologic assessment of premature infants, who are able to survive outside of the womb by about 23–24 weeks gestation (deRegnier, 2002). The auditory brainstem response (ABR) methodology has been used in a number of studies to evaluate the maturation of the auditory nerve through the brainstem. In an averaged ABR, a series of well-described, numbered peaks track the transmission of neural impulses from the auditory nerve (wave I) through the medial geniculate body of the thalamus (wave VI) (Counter, 2002). Although very young premature infants typically do not display all of these peaks in their ABR, even infants as young as 24 weeks gestation have shown reproducible waveforms indicating transmission of neural impulses through the brainstem (Amin, Orlando, Dalzell, Merle, & Guillette, 1999; Starr, et al., 1977). Similar to fetal behavioral studies, auditory brainstem responses become more robust by 27–28 weeks gestation. A great deal of maturation occurs in this part of the neural pathway continuing through gestation and the first year of life (Salamy & McKean, 1976).
thresholds improve from 40 dB nHL at 28–34 weeks gestation to less than 20 dB nHL by 2 weeks post term (Adelman, Levi, Linder, & Sohmer, 1990; Lary et al., 1985). Additionally, conduction time within the brainstem (assessed using the wave I–V latency difference) improves dramatically between 24 weeks gestation and term (Amin et al., 1999; Starr et al., 1977). This is thought to be reflective of increases in both synaptic density and early myelination (Eggermont, 1988). Lastly, the use of the ABR has also demonstrated that the brainstem has a slight but significant right ear advantage for auditory processing (Eldredge & Salamy, 1996).

Moving past the brainstem to cortical processing, long-latency ERP responses to sounds have also been generated as early as 23 weeks gestation (Weitzman & Graziani, 1968). In these extremely premature infants, a simple negativity with a long latency (180–270 ms) has been demonstrated over the midline and lateral electrode sites (denoted as N1 by these authors). Interestingly, at this very young age, these responses are more robust than those potentials arising from the brainstem (the ABR). With maturation, the latency of the N1 wave decreases over the posterior scalp, and a subsequent positive wave develops that becomes predominant over the midline. This positive component has been denoted as P2, and with further maturation the positive component also begins to predominate the lateral waveforms (Kurtzberg, Hilpert, Kreuzer, & Vaughan, 1984; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989). It has been speculated that this change from a predominant negative polarity to a predominant positive polarity may reflect development of specific laminae of the cerebral cortex. Initially, the thalamocortical innervation is limited to lamina IV. In the animal, this innervation generates a surface negative potential. As lamina III becomes innervated, this may result in a shift to a surface positive potential (Novak et al., 1989).

The Einstein group developed a scoring system to assess the maturity of the auditory cortical responses (Kurtzberg et al., 1984). In this system, level I is the most immature response, with predominantly negative responses over both midline and lateral scalp sites (Figure 5.2), level III indicates a positive midline but negative lateral response, and level V showing positive waveforms over both midline and lateral scalp sites from 100–400 ms post-stimulus. Using this classification scheme, most term newborns are in maturity level III but all levels from I to V are commonly seen at this age (deRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000; deRegnier, Wewerka, Georgieff, Mattia, & Nelson, 2002; Novak et al., 1989). Further dramatic maturational changes have been described over the first year of life (Kushnerenko, Ceponiene, Balan, Fellman, Huotilainen, & Näätänen, 2002), with increases in amplitude and shortening of latencies noted, although the time course for these processes appeared to differ for the different peaks noted in the waveforms. These changes in morphology occurring over a relatively short time period have been described by several authors and are important to note because they can introduce large amounts of variability into ERP waveforms obtained from very young infants.
Figure 5.2 ERPS from three individual infants illustrating maturity levels I, III, and V in response to a computer chime (400 ms, 80 db SPL). Reprinted with permission from deRegnier et al., 2000.
Interestingly, functional MRI studies of hearing in the fetus and newborn also demonstrate variable responses to auditory stimuli. The fMRI response is assessed through evaluation of the blood oxygenation level dependent (BOLD) imaging, which is a measure of blood oxygenation that is presumed to increase with increased neuronal activity (Casey, Davidson, & Rosen, 2002). Hykin and colleagues (1999) studied fetal MRI in response to the maternal voice. The four fetuses were studied at 38–39 weeks gestation, with the fetal head engaged in the maternal pelvis to reduce motion artifact. Of the three subjects with technically satisfactory scans, two showed significant activation of the temporal lobe that was also seen in the adult control subjects. In a study of 14 unsedated term newborn infants, Anderson and colleagues (2001) reported fMRI results using pure tone stimuli, compared with 4 adult control subjects. All of the adults, but only 5/14 neonates showed a positive increase in the MRI BOLD signal in the superior temporal region. In contrast, the majority of infants showed a negative BOLD signal in the same area of the brain. The significance of these variable responses in BOLD signaling is not well understood, but may be due to differences in methodology or as part of a developmental pattern that will emerge with more research. In support of this, Dehaene-Lambertz, Dehaene, and Hertz-Pannier (2002) studied unsedated infants using speech stimuli. The task did not require recognition memory. At 2–3 months of age, this group reported activations (with no significant inversions in polarity) in a large area of the left temporal lobe, with non-significant activation in the right temporal lobe. Thus, by 2–3 months of age, no negative inversions of BOLD polarity were noted. More research is needed regarding this topic, but it appears that fMRI may be a valuable method to study the development of regional specialization of brain functions, including infant memory.

In summary, the sensory organs and central nervous system of the fetus are prepared to receive auditory input in the mid to latter part of gestation, and the hippocampus appears to be sufficiently developed to support memory abilities by term. It is important to consider the types of sounds that the fetus is exposed to in utero as these sounds may be encoded into memory during the latter part of pregnancy. The fetal sound environment includes noises associated with the mother (speech, heart sounds, placental blood flow, and digestive sounds) as well as external noises that are transmitted through the uterus. The uterus acts as a low-pass filter for airborne extraterine sounds, with moderate attenuation of sound levels from 400–1000 Hz and further attenuation (up to 35 db SPL) at 10 kHz (Lecanuet & Schaal, 1996). Environmental voices near the uterus are therefore audible to the fetus, but since the higher frequencies are attenuated, voices are muffled, though prosody is preserved. Querleu, Renard, Versyp, Paris-Delrue, and Vervoort (1988) estimated that up to 30% of extraterine speech is intelligible in utero. The maternal voice is transmitted to the fetus through the airborne route but it is also transmitted through body tissue and bone, which results in less filtering of higher frequencies (Lecanuet & Schaal, 1996). The net result of this is that
the maternal voice is louder in utero than ex utero and less subject to distortion of the acoustic properties than are the airborne voices of others. Since the maternal voice is heard by the fetus whenever the mother speaks, the fetus has many weeks of experience of it by the time of birth. Although the duration of experience required for encoding in the newborn is not known, the fetal experience with the maternal voice should result in encoding if the neural mechanisms are sufficiently developed.

AUDITORY RECOGNITION MEMORY IN THE FETUS AND NEWBORN

Psychophysiologic and behavioral studies

Although the maternal voice has been used in a number of studies of the fetus, it has often been used to evaluate the infant for hearing and sound discrimination rather than memory (see Fifer & Moon, 1995, for a review). For any comparisons of the maternal voice and a stranger’s voice, it is important to utilize recordings of the maternal voice that can be played back ex utero to contrast with the stranger’s voice. Otherwise, as previously mentioned, the maternal voice will be louder than the stranger’s voice and will have different acoustic properties due to tissue and bone conduction. Kisilevsky’s group (2003) tested term fetuses with 2-minute tape recordings of the maternal voice, a stranger’s voice, and silence. The voice of the previous mother served as the stranger. They reported an increase in the fetal heart rate for the maternal voice for the 90 seconds post stimulus onset, whereas the stranger’s voice led to a fetal heart rate deceleration. No differences in body movements were noted for the two voices. These data show that, at term, the fetus is able to respond differently to the maternal voice than to a stranger’s voice, and this is suggestive of recognition memory.

After birth, recognition of the maternal voice and other fetal experiences has been tested by several authors. Querleu, Lefebvre, Titran, Renard, Morillion, and Crepin (1984) videotaped 25 newborn infants (< 2 hours of age) with no prior postnatal exposure to the maternal voice. Each infant listened to recordings of five voices, including that of the mother. The videotapes were scored by blinded observers who documented orienting movements to the maternal voice more often than to the strangers’ voices. DeCasper and Fifer (1980) tested 2-day-old infants with an operant sucking procedure and noted that the infants could learn to suck at a specific rate that would produce a recording of the maternal voice rather than a stranger’s voice. In this study it was unclear whether the results of the study reflected fetal or neonatal learning. However, DeCasper and Spence (1986) later showed that prenatal stimulation with specific speech sounds was associated with changes in newborns’ perceptions of those sounds. Fifer and Moon (1995) also tested newborn infants with a filtered version of the maternal
voice created to mimic conditions in utero compared with an unfiltered version. The newborns sucked preferentially to elicit the filtered version, providing additional evidence that intrauterine experience is encoded. Therefore, current psychobiologic and behavioral evidence supports the concept that the late gestation fetus and newborn is capable of encoding auditory stimuli and shows behavioral evidence of recognition memory.

**Evaluation of auditory recognition memory using event-related potentials**

There are a number of favorable attributes supporting the use of ERPs in the study of auditory recognition memory in the newborn. Compared with assessments such as MRI scanning, ERPs are relatively inexpensive. Furthermore, they are non-invasive, sedation is not needed, and behavioral responses are not required. ERPs are also known to have excellent temporal resolution. Lastly, sleeping newborns can be studied with minimal attrition. Because of these attributes, we have used ERPs to study recognition of the maternal voice in newborn infants.

There are several points of methodology that are important in testing auditory ERPs in the newborn infant. The first concerns the stimuli chosen. Although the fetal and behavioral studies use long segments of speech as stimuli, it is difficult to synchronize neural activity to a long segment of speech in an ERP study, and shorter segments are preferable. One-word utterances make up a significant part of the natural sound environment of young infants and are suitable for study (Korman & Lewis, 2002). Second, it is important to control sleep state. Although it would be optimal to study awake infants, the quiet awake state is unusual in a newborn (Thoman, 1990) and cannot be produced reliably in the laboratory. We have therefore studied newborns in the behavioral stage of active sleep, as cortical evoked potentials are similar in active sleep as in awake infants (Ellingson, Danahy, Nelson, & Lathrop, 1974). Furthermore, active sleep is abundant in the newborn, occurring about 50% of the time (Thoman, 1990).

To evaluate long-term memory abilities of the newborn, a paradigm was developed with no familiarization period. The maternal voice served as the familiar stimulus, with a stranger’s voice serving as the novel stimulus. The stranger was the previous mother. This means that in the course of the study, each voice was heard in both the mother and stranger conditions. The word “baby” was used as the stimulus, with the mother instructed to use prosody in the recording. Stimuli were digitized and then edited to 750 ms and 80 db SPL. The maternal and stranger’s voices were presented with equal frequencies so that there would be no differential encoding of one of the voices during the study. The interstimulus interval was varied randomly from 3900–4900 ms to prevent infants from anticipating the onset of the subsequent voice, and to allow evaluation of the long latency activity. Stimuli were presented to the right ear with an insert earphone to utilize the right
ear advantage for language processing (Ahonniska, Cantell, Tolvanen, & Lyytinen, 1993) and to prevent compression obstruction of the ear, which can be seen with external earphones. The ERPs were recorded from Pz, Cz, Fz, T3, and T4 (Jasper, 1958) in a behavioral state of active sleep.

The first study (deRegnier et al., 2000) tested the development of auditory recognition memory for the maternal voice in 28 normal hearing newborn infants born at term and tested at a mean age of 10.7 (± 2) days. In this group of infants (Figure 5.3), the maternal and stranger’s voices evinced positive components in the window from 150–400 ms, denoted as “P2”. Review of the waveform reveals that a negative slow wave (NSW) is also present in the ERP derived from the stranger’s voice. The negative slow wave begins early in the recording and results in a smaller amplitude P2 peak for the stranger’s voice and a more negative area under the curve for the entire recording. Additionally, the latency to the P2 peak at the Cz electrode site was shorter for the stranger’s voice than for the maternal voice.

Negative slow waves have been described in studies of visual recognition memory in early infancy (see Chapter 4, this volume, for further discussion). In a previous neonatal study, deRegnier (1993) reported that infrequent novel tones inserted into a train of frequent familiar tones elicited a negative slow wave, but only when a sequence of five or more repeated familiar tones preceded the novel tone. Additionally, deRegnier, Georgieff, and Nelson (1997) noted a negative slow wave in response to a novel visual stimulus in 4-month-old infants. Nelson and Collins (1991) similarly described a negative slow wave in response to unique novel faces (presented only once) in an ERP study of 6-month-old full term infants. Nelson has postulated that the negative slow wave is indicative of novelty detection, a function of the hippocampus (Dolan & Strange, 2002; Nelson, 1994; Nelson & deRegnier, 1992). If this speculation is correct, that means that even after hearing the stranger’s voice 60 times during the ERP testing session, the stranger’s voice remained a novel stimulus, corroborating behavioral evidence of very slow visual encoding in young infants.

In another experiment designed to further evaluate the role of experience and postmenstrual age on memory development, three groups of normal hearing infants were tested using the paradigm described above (deRegnier et al., 2002). To evaluate the effects of maturity and experience, minimally preterm infants (35–38 weeks gestation) were tested during the first postnatal week (mean age: 1.6 days at test) and compared with a group of full term newborn infants (mean gestation 40.1 weeks) tested at 2 days of age. This group was more mature, but still had little postnatal experience. The third comparison group also consisted of full term infants (tested at 40.9 weeks postmenstrual age) who had 2 weeks of postnatal experience. Thus, the minimally preterm group was immature and inexperienced; the full term newborn group was more mature but with little postnatal experience, and the experienced group was of similar postmenstrual age, but had more postnatal experience.
In this study, both the full term newborn group and the experienced group showed positive waves for the maternal voice and negative slow waves for the stranger’s voice, whereas the minimally preterm group did not show significant differences between the stimuli (Figure 5.4). The minimally preterm infants’ maternal and stranger ERPs were similar to the stranger ERPs in the full term

Figure 5.3 Grand mean ERPs for 28 newborn infants in response to the maternal (solid line) and stranger’s (dotted line) voices. Areas of significant difference between mother and stranger ERP areas under the curve are denoted NSW (negative slow wave). Reprinted with permission from deRegnier et al., 2000.
newborn and experienced groups. Hypothesizing that the negative slow waves are associated with novelty detection, the fact that the preterm infants’ maternal ERPs showed predominantly negative waveforms may indicate that these less mature infants have not fully encoded the maternal voice to the same degree as the older infants. Since we know that infants born at 35–38 weeks gestation have many weeks of prenatal experience with the maternal voice, experience would not be the limiting factor for these younger infants. Rather the results are consistent with immaturity of the memory network itself until close to term gestation. Thus brain immaturity (indexed here by postmenstrual age) appears to be an important determinant of recognition memory.

The study showed that postnatal experience was also important in maternal voice recognition. For the full term groups, the group with more postnatal experience showed a longer latency for the maternal voice than to the stranger’s voice. The latency to the stranger’s voice in the experienced group was similar to the latencies for the maternal and strangers’ voices in the newborn infants tested at 2 days of age. Thus, the effect of experience was to prolong the latency to the maternal voice. The grand mean figures (Figure 5.4) also show that the waveform in this group was more complex, with new peaks surfacing in the mid portion of the ERP. This may indicate a separate but overlaid response to the second syllable of the word “baby” in this group, and appears to be consistent with a greater depth of processing associated with postnatal experience.

Overall, this study showed that both maturation and postnatal experience have effects on neonatal auditory recognition memory. It is known from behavioral studies of visual recognition memory that newborns encode novel stimuli very slowly and that the speed of encoding improves dramatically over the first 6 months of life (Fagan, 1990). We speculated that immature encoding abilities might be overcome by additional familiarization with the stimulus, facilitating recognition memory. In a third study (Therien, Worwa, Mattia, & deRegnier, 2004), 40 full term newborns (2 days old at test) were studied using the basic paradigm described previously. However, half of the infants received a familiarization period with 60 trials of the maternal voice prior to the test phase in which the maternal voice alternated with a stranger’s voice. The additional familiarization did not produce any significant effects on the peak amplitudes, latency measurements, or areas under the curve of the ERP. In this study, the auditory cortical maturity level also did not correlate with the performance on the recognition memory task. These data, as well as the previously described study of minimally preterm infants, suggest that although neonates do show evidence of recognition memory, this seems to require very intensive exposure to a stimulus, such as occurs on a daily basis during the last trimester of pregnancy. This is substantiated by the behavioral studies of DeCasper and Prescott (1984) who demonstrated that newborn infants did not show behavioral evidence of recognition memory for the paternal voice, even with 4–10 hours of postnatal measured voice exposure prior to the testing.
Figure 5.4 Grand mean ERPs in response to the maternal (solid line) and stranger’s (dashed line) voices recorded from premature newborn infants, full term newborn infants, and full term experienced infants with 2 weeks postnatal experience. NSW indicates the area of the negative slow wave. Reprinted with permission from deRegnier et al., 2002.
ERP studies of recognition memory corroborate behavioral studies indicating neonatal recognition memory for the maternal voice at term. The ERP studies also indicate that recognition memory abilities in the newborn are the product of both maturation of the neural circuitry and experience, and that a great deal of experience appears to be necessary to demonstrate long-term memory in the immediate perinatal period. Further research is required to determine the neural structures responsible for this response, although neurohistologic and MRI studies implicate the hippocampus as an important structure in the development of cognitive function during infancy. The hippocampus and parahippocampal region both appear to be involved encoding and retrieval of memory in adults (Daseleer et al., 2004; Dolan & Fletcher, 1999), and further investigation is needed to determine if these structures are also responsible for these functions in the newborn as well. It is speculated that the negative waveforms seen on the infant ERP in response to novel stimuli may be due to the detection and subsequent encoding of novel stimuli, and that as the hippocampus matures, encoding also matures, and these waves will evolve into the positive slow waves seen in older infants in response to partially encoded stimuli in the older infant (Nelson, 1994; Nelson & deRegnier, 1992; see Chapter 4, this volume, for further discussion of positive slow waves).

STUDIES OF HIGH-RISK POPULATIONS

One advantage of developing techniques to study the development of memory in newborn infants is that these methods can be used to evaluate perinatal brain injury and plasticity. It is now known that infants with prematurity (Curtis, Lindeke, Georgieff, & Nelson, 2002; De Haan, Bauer, Georgieff, & Nelson, 2000; Isaacs et al., 2000; Rose, 1983; Rose, Feldman, & Jankowski, 2001, 2002), perinatal hypoxia-ischemia (Maneru et al., 2003; Nyakas, Buwalda, & Luidten, 1996), and poorly controlled maternal diabetes (deRegnier et al., 2000, Sidappa, Georgieff, Wewerka, Worwa, Nelson, & deRegnier, 2004; Nelson, Wewerka, Borschard, deRegnier, & Georgieff, 2003; Nelson, Wewerka, Thomas, Tribby-Walbridge, deRegnier, & Georgieff, 2000) are at increased risk for difficulties with memory. ERPs have been used to evaluate memory development in premature infants and infants of diabetic mothers.

Premature infants

Premature infants may experience multiple episodes of perinatal hypoxia-ischemia due to complications of labor and delivery, respiratory disorders, or recurrent episodes of apnea and bradycardia (Mattia & deRegnier, 1998). It is known that the hippocampus is vulnerable to hypoxia (Nyakas et al., 1996) and indeed, the increasing use of MRI scanning and the availability of volumetric
studies have demonstrated that premature children often have evidence of hippocampal injury and atrophy (Isaacs et al., 2000; Vargha-Khadem, Gadian, & Mishkin, 2001; Vargha-Khadem, Salmond, Watkins, Friston, Gadian, & Mishkin, 2003) as well as patterns of explicit memory deficits. Volumetric MRI studies have shown that significant memory impairments appear to be associated with a 20–30% reduction of bilateral hippocampal volumes (Isaacs, Vargha-Khadem, Watkins, Lucas, Mishkin, & Gadian, 2003). Interestingly, long before this was described, Susan Rose’s group demonstrated early and persistent deficits in visual recognition memory as well as cross-modal memory in premature infants (Rose, 1983; Rose, Feldman, McCarton, & Wolfson, 1988). De Haan and colleagues (2000) also described deficits in explicit memory, including ordered recall in 27–34-week preterm children at a mean of 19 months adjusted age. Premature preteen and teenage children also have been shown to have deficits in spatial memory span length and more forgetting errors on a spatial working memory task (Curtis et al., 2002), with some improvements noted with further development in adolescence.

We have studied auditory recognition memory in a group of premature newborns born at less than 32 weeks gestation (Therien et al., 2004). All underwent at least two cranial ultrasounds during the neonatal period and all had normal hearing. ERPs were recorded at 40 weeks postmenstrual age in a counterbalanced paradigm that included an auditory change paradigm as well as the maternal voice recognition paradigm. Compared with healthy term controls, the preterm infants demonstrated several differences in their ERPs. First, although they did show significant differences between the frequent and infrequent speech sounds in the auditory change paradigm, it was in the opposite direction from that seen in the control infants. Whereas control infants showed a positive wave for the infrequent stimulus, the preterm infants showed a negative wave that was similar to a mismatch negativity response. The preterm infants’ responses also were more widely distributed over the scalp than the control infants. In the recognition memory paradigm, preterm infants also did not show any differences between the maternal voice and a stranger’s voice, even when a familiarization period was provided at the beginning of the maternal voice recognition paradigm. The preterm infants had been discharged to home a mean of 17.5 days prior to the ERP study and also had weeks of postnatal exposure to the maternal voice that should have facilitated recognition providing that their neural substrate was intact and sufficiently mature. Evaluation of the maturity levels for the “P2” peak did not elucidate any significant differences between the control and preterm infants in maturity of the auditory cortex. Maturity levels also did not correlate with the presence of the negative slow wave. Thus, the alterations in auditory discrimination and memory noted in this study did not appear to be a simple function of maturity of the auditory cortex. Although further investigation is clearly required, these findings may be consistent with the memory deficits described in premature children by other authors.
The aforementioned data and the recent data of Fellman, Kushnerenko, Mikkola, Ceponiene, Leipälä, and Näätänen (2004) both indicate that auditory processing in premature children is altered compared with controls. Although the patients described by Vargha-Khadem and colleagues have shown isolated hippocampal atrophy (Vargha-Khadem et al., 2001), preterm infants are more typically at risk for a variety of brain abnormalities including intracranial hemorrhage, ischemic changes in the white matter, and decreased growth of gray matter (Maalouf et al., 1999; Peterson et al., 2000). It is most likely that the differences in auditory processing and recognition memory in preterm infants are due to overlapping problems of widespread brain injury or maldevelopment, and further investigation is required to elucidate both the types of insults that cause difficulties with recognition memory and the complex interactions between auditory processing and discrimination and recognition memory.

**Infants of diabetic mothers**

It has been known for many years that infants of poorly controlled diabetic mothers have lower scores on standardized tests of cognitive function (Ornoy, Wolf, Ratson, Greenbaum, & Dulitzky, 1999; Rizzo, Metzger, Dooley, & Cho, 1997). Poorly controlled maternal diabetes is associated with a number of fetal metabolic derangements including fetal hyper- and hypoglycemia, ketonemia, increased oxygen consumption, and chronic fetal hypoxia, as well as iron deficiency (Nold & Georgieff, 2004). Hypoxia and brain iron depletion both may target the hippocampus and other parts of the explicit memory pathway (Jorgenson, Wobken, & Georgieff, 2003; Rao, Tkac, Townsend, Gruetteer, & Georgieff, 2003; deUngria, Rao, Wobken, Luciana, & Georgieff, 2000), potentially resulting in difficulties with memory development in infants of diabetic mothers.

We have studied newborn infants of diabetic mothers (IDMs) using the maternal voice/stranger’s voice paradigm described above. In the first study (deRegnier et al., 2000), all infants of diabetic mothers were included, regardless of the degree of control of diabetes during pregnancy. The IDMs showed attenuation of the negative slow wave seen in the control infants (Figure 5.5). Additionally, the area of the negative slow wave was correlated to the 1-year Mental Developmental Index Score on the Bayley Scales of Infant Development in IDMs and control newborns. This study did not assess the role of fetal risk factors, and in a subsequent study (Sidappa et al., 2004), we demonstrated that infants with low brain iron stores showed near obliteration of the negative slow wave and no significant differences between the maternal and stranger ERP (Figure 5.6), whereas IDMs who were brain iron sufficient showed a normal appearance of the ERP. The degree of the brain iron deficiency, as assessed by neonatal ferritin levels, was associated with attenuation of the right temporal (T4) activity on the ERP.

These infants have been studied longitudinally, and showed abnormal
ERPs for visual recognition memory at 6 months of age and abnormal ERPs for cross-modal memory at 8 months of age (Nelson et al., 2003, 2000). Preliminary reports using elicited imitation paradigms have shown the emergence of behavioral evidence of deficits in delayed recall abilities at 1 year of age (DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005). These children are currently in long-term follow-up to determine if they are at significant risk for

Figure 5.5 Grand mean ERPs for 22 newborn infants of diabetic mothers in response to the maternal (solid line) and stranger’s (dotted line) voices. Note attenuation of NSW (negative slow wave) compared with control infants in Figure 5.3. Reprinted with permission from deRegnier et al., 2000.
behavioral manifestations of memory deficits, as this is not yet known. These longitudinal data will be helpful in establishing the role of plasticity in recovery from perinatal brain injury.

SUMMARY

In summary, recognition memory is one of the first cognitive functions to develop in the newborn. Auditory recognition memory becomes possible during pregnancy through sufficient maturation of the auditory perception pathways, auditory experiences are provided to the infant in utero, and early histologic and MRI data suggest that the hippocampus is sufficiently developed to begin to encode these auditory experiences by late gestation, if not earlier. ERP and behavioral data suggest that encoding is poor in the newborn, and intensive exposure to a stimulus may be required, such as the weeks of experience with the maternal voice that occur during late gestation.

ERPs have been useful in neonatal evaluation of high-risk newborns. Preterm infants are known to be at risk for memory deficits, and early ERP evidence suggests that this may be manifested in impairments of auditory recognition memory as early as term postmenstrual age. Infants of poorly controlled diabetic mothers have a well-studied pattern of perinatal brain injury that would theoretically lead to memory impairments. Early ERP studies appear to verify this, showing that early auditory, visual, and cross-modal recognition memory are impaired in these infants, possibly due to

Figure 5.6  Grand mean ERPs for newborn infants of diabetic mothers in response to the maternal (thick line) and stranger’s (thin line) voices for the brain iron deficient (BID) and (BIS) groups. Areas of significant difference between maternal and stranger’s ERPs are denoted by*. Note near complete obliteration of the negative slow wave in the BID group. Reprinted with permission from deRegnier et al., 2004.
deficiencies of hippocampal iron stores that occur as a result of the metabolic derangements.

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