How fast can we see?
The latency development in human infants to pattern, orientation, and direction-reversal Visual Evoked Potentials

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Preface

The studies described in this thesis were carried out at the Department of Psychology, University of Oxford, England, during the years 2008-2012, under the supervision of Professor Oliver J. Braddick.
The goal of the present project is to explore the early development of visual processing in infants by finding the developmental changes in the latency of pattern, orientation, and direction-reversal visual evoked potentials.

The results presented in Chapters 3 and 4 of this thesis have been published in full (Lee et al, 2012a and 2012b respectively). The result of Chapters 5 is in press for the Journal of Vision (Lee et al., 2013a) while Chapter 6 is under preparation for submission (Lee et al., 2013b). Moreover, the data of Chapters 6 and 7 have been presented at multiple conferences and published in abstract form.

Abstract

The goal of this thesis is to track latency changes in three visual evoked potentials (VEP) stimuli as an indication of overall brain development, in order to provide a normative baseline to differentiate visual and neurological development from pathological processes.

VEP- neural electrical activity recorded from the scalp surface and synchronized with visual stimulus transitions- is one of the common techniques in understanding infant vision development. Past work has concentrated on responses to pattern reversal and to the latency of the initial positive peak. Here we compare the timing of responses to pattern, orientation, and direction-reversal VEPs, and transient peak latencies to those calculated from the gradient of steady-state phase against reversal rate. The three stimuli were tested in 81 adults at 1- 16 r/s and 137 infants (3.6- 79.0 weeks) at 2- 8 r/s.

Initial responses to orientation and direction were as fast as for contrast- around 100 ms, consistent with other findings that V1 is orientation selective. Cortical processing for both OR and DR yielded longer latencies (200 ms) by the calculated method, perhaps reflecting more involvement of higher visual processing in comparison to PR. Orientation and direction latencies also had a delayed onset and longer developmental period to reach maturity. Infants reached adult transient PR latency values by 15 weeks, for OR by 50 weeks, and for DR by 10 weeks. For the calculated latency, infants reached both adult PR and DR latencies by 30 weeks while OR showed little change across age.

We successfully confirmed that (1) phase-based calculation of latency is effective, easy to use, and taps into a different cortical pathway; (2) motion processing has an additional, faster, subcortical pathway; (3) a parallel processing of initial contrast and orientation; and (4) later visual processing is not only developmentally delayed for all three stimuli but also more vulnerable to perinatal brain damage. These latency differences provided a baseline for clinical evaluations where identification of delayed latencies should aid early diagnosis and guide therapies for adults and infants.

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Glossary

CP	Cerebral Palsy
DR	Direction Reversal VEP stimulus
EEG	Electroencephalography
F2	Second harmonic (=reversal frequency)
F4	Fourth harmonic (= double of second harmonic)
fMRI	Functional magnetic resonance imaging
Hz	Hertz- unit of temporal frequency
LGN	Lateral Geniculate Nucleus
M	Magnocellular
MT	Middle Temporal area
OKN	Optokinetic Nystagmus
OR	Orientation Reversal VEP stimulus
P	Parvocellular
P100	Positive peak latency at ~100 ms
PR	Phase or Pattern Reversal VEP stimulus
r/s	Reversal per second
RF	Receptive Field
RM-ANOVA	Repeated-Measure ANalysis Of VAriance
SF	Spatial Frequency
SNR	Signal to Noise Ratio
SS-VEP	Steady-State Evoked Potential
TF	Temporal Frequency
TVEP	Transient VEP
VEP	Visual Evoked Potentials

Tables and Figures

1 INTRODUCTION

The goal of this thesis is to explore the early development of visual processing in infants, using developmental changes in the latency of visual evoked potentials (VEP) for three stimuli that test contrast, orientation, and direction functions.

Background information on VEP is presented in Chapter 1. Full details on the methodology and materials are described in Chapter 2. Results and discussion of pattern, orientation, and direction-reversal VEPs are discussed in Chapters 3, 4, and 5 respectively. The comparison between these three VEP stimuli is examined in Chapter 6. Chapter 7 studies the use of VEP in tracking atypical infant development while Chapter 8 explores the factors affecting VEP latency. Finally Chapter 9 sums up the whole thesis.

1.1 Infant visual development

Vision is essential to our daily living. As human infants are extremely vulnerable at their early stage, infants depend heavily on their vision to navigate the world. Back in 1762, a baby was described as "a perfect idiot" according to Jean-Jacques Rousseau. Then in 1890 William James described a baby's mind as "a great blooming, buzzing confusion." Today we know that infants exhibit specific visual capabilities that underpin their behaviour at each developmental stage. For example, Atkinson and Braddick have showed that neonates are capable of crude orientation discrimination at birth (Atkinson et al., 1988) but only has specific VEP responses to orientation at 3 weeks (Braddick et al., 1986). Babies are able to make behavioural directional discrimination by 7 weeks of age (Atkinson & Braddick, 1981) but significant VEP responses are not obtained until 10

weeks (Wattam-Bell, 1991). As for binocular correlation and disparity, infants showed both behavioural discrimination (Braddick et al., 1980) and VEP response at 11-13 weeks (Braddick et al., 1983). Because of these distinctive visual developments, infant vision measures are crucial in understanding ophthalmic and neurological functions in the infant.

1.1.1 Paediatric vision testing

The main hurdle in studying infant development is the difficulty of getting precise measurements from infants. As their visual ability changes with age, the developmental stage at which these measurements are taken becomes critical. Young infants also have reduced spatial acuity (Dobson & Teller, 1978), immature smooth pursuit (Hainline, 1993), absent stereopsis (Birch, 1993) and other inadequacies in comparison to the visual functions of adults.

Babies' control over their own bodies is limited. One behaviour that they can control at birth is their own eye movements. Preferential looking (PL) paradigms have been devised to record infants' preferred response for one stimulus over another. PL requires an infant to use their extra-foveal vision to fixate on either the stimulus or a uniform grey background (Fantz, 1958). PL tests how well a stimulus engages a baby's attention after the baby has been fixated foveally, as well as attracting fixation from an extra-foveal location (Atkinson & Braddick, 1977). Fixation signifies the baby's interest and ability to discriminate the stimulus from the background (Atkinson, 2000).

At birth, infants' acuity is around 20/600 (legally blind in an adult). By 3 months, babies' acuity has improved to 20/200, then at 6 months to 20/100, and at 12 months to

about 20/50. This enhancement slows down after the first year of life until they reach adult level acuity by age 6-7 years (Atkinson, 2000). Acuity may also be limited by refractive errors.

One of the most widely used noninvasive techniques in tracking infant visual development is visual evoked potentials (VEP). Unlike the behavioural studies, VEP is a complementary and efficient method to measure and track neural activity in real – time.

1.2 Visual neurophysiology

In the complex process of seeing, light rays travel through an individual's cornea, pupil, biconvex lens, and are focused precisely on the retina- a neuroprocessor on the inner surface of the eye. The electrical signals received from the retina's 130 million photoreceptors (rods and cones) then travel through 1.2 million ganglion cells that form the optic nerve, which in turn is connected to many subcortical regions and nucli including the lateral geniculate nucleus (LGN), the primary visual cortex (V1), and finally higher visual pathways within the brain (Regan, 1989).

Neurons from the earlier visual pathways such as the retina, LGN, and the simple cells in V1 have all been found to show linear behaviour, in which the response to a stimulus can be predicted from the additive sum of the responses to its components (Carandini et al., 1997). In contrast, complex cells in V1 are nonlinear, where the summated response cannot be predicted by the simple addition of the individual responses to stimulus components. For example, unlike the simple cell where its receptive fields can be divided into on-and off- regions which summate linearly, a complex cell responds to its optimal stimulus anywhere in its large receptive field and so

cannot be analyzed in terms of on-and off regions (Hubel, 1963). Retinal magnocells respond to the timing both on and off of contrast changes. Cortical processing is required for true motion detection at least in higher mammals. V1 is important for form, color, orientation, local motion and depth (Livingstone & Hubel, 1988; Trotter et al., 1992; Zeki, 1993). Higher visual areas then integrate the V1 outputs to analyze edges, surface curvature, textures, stereopsis and other visual information (Palmer, 1999; Ungerleider et al., 1998).

There are many parallel pathways in the visual system. From the retina, there are the on- and-off pathways in which light in the receptive field centre either stimulates or suppresses the cell's response; tonic and phasic ganglion cells which respond in a transient or sustained fashion; and the X and Y cells where the X type cells summate light from every point with perfect linearity while the Y type is nonlinear. These two ways of classification strongly overlap each other. The parallel pathways continue in the LGN and the visual cortex. Starting from the ganglion cells, the parvocellular (P) pathway is responsible for detail vision while the magnocellular (M) pathway is mainly for motion perception (Regan, 1989; Zeki & Shipp, 1988). M cells have larger receptive fields and a higher sensitivity to achromatic contrast (Shapley & Perry, 1986) and a faster temporal response in comparison to P cells (Schiller & Malpeli, 1977).

M and P pathways have different terminations in primary visual cortex. The M pathway sends its output from cortical layer 4Cα within layer 4B and layer 6 which directly feed into V5 (responsible for direction selectivity) and V3 (orientation) and indirectly to some areas through the thick dark stripes of V2 (responsible for direction selectivity). Direction selectivity is also found in the V1 cells that project to V2 thick

stripes and middle temporal visual motion area MT/ V5. Both the orientation- and direction-selectivity are found in V1 but not in precortical stages of the visual pathway (Hubel & Wiesel, 1977).

In contrast, the P pathway sends its outputs to the dark blobs and lighter interblobs of the upper layers of V1. The interblobs are usually orientation selective and respond to contours with different wavelength or luminance. The upper layers of V1 are needed to analyze colour and form (Zeki & Shipp, 1988). Ungerleider and Mishkin (1982) suggested from primate lesion experiments that the parietal cortex is associated with the representation of a spatial array, or the 'where' aspect of visual processing which receives input mainly from the M pathway. On the other hand, the temporal lobe is responsible for processing features such as form and colour for object recognition, or the 'what' aspect of vision based on input from the P cells. In the 1980s to 1990s, it became more accepted that the dorsal stream is connected to the parietal cortex responsible for spatial arrangements, and visuomotor control (where), while the ventral stream connects to the temporal lobe that is mainly for object recognition (what) (Goodale & Milner, 1992). The dorsal stream can also be termed as the 'how' stream as its main property is to guide visual direction of attention, eye and limb movements (Milner & Goodale, 1995).

The visual cortex is also highly tuned to spatial frequency (Campbell & Blakemore, 1968; De Valois et al., 1982). The overall envelope of spatial-frequency channels can be used to describe the contrast sensitivity function. Masking experiments have also shown that the channels are tuned to specific spatial frequency (SF) and orientation (Stromeyer et al., 1982; Wilson et al., 1983).

1.2.1 The developing visual brain

Based on eye movement studies and adult cortical lesion studies, Bronson (1974) suggested that neonatal visual behaviour is mediated by a subcortical system. The main visual pathway consists of LGN, striate cortex, and various visual cortical areas, that are responsible for analysis, encoding, identifying and recognising pattern information and voluntary regulation of eye movement. The subcortical pathway comprises the superior colliculus and other motor nuclei in the mid brain, where it is responsible for localizing stimuli and interaction with the primary visual system to control eye movements. Atkinson (1984 & 2000) hypothesized that during the first two months of life, vision is dominated by the subcortical system. The subsequent maturation of cortex then enables increasing coordination of eye movements. Cortical modulation and control of the subcortical mechanism begins to become functional between 2-4 months postnatally (Atkinson, 1984 & 2000).

Infants can make saccadic eye movement at birth and turn their head toward the high contrast stimuli such as pattern reversal. Infants show crude orientation discrimination between 45° and 135° oriented static grating patterns at birth (Atkinson et al., 1988) but do not exhibit the dynamic orientation-specific VEP responses to stimuli alternating at 4 reversals/s (r/s) until 3 weeks of age and 8 r/s until 6 weeks of age (Braddick et al., 1986). This frequency dependence indicates that the dynamics of the cortical orientation response changes with development. The difference seen between the static and dynamic patterns suggests different temporal properties of the neuronal origins of the responses.

In order to analyze translational motion, the visual system has to process not only pattern changes and orientation filtering within a neuron's receptive field, but also the interaction between time and space. Atkinson (1979) showed that newborns have a nasal-ward bias toward monocular optokinetic nystagmus (OKN), indicating that it is a subcortically driven process. Habituation and preferential looking studies showed that OKN continues until about 7 weeks of age when the emergent of symmetrical responses indicated the cortical processes becoming more dominant than the subcortical. Around the same time, infants can generate smooth pursuit eye tracking on moving objects (Rosander & von Hofsten, 2002).

The motion neurons also begin to set the limits of one's direction response around two-months of age (Wattam- Bell, 1996). Braddick et al (2005) demonstrated that DR-VEP has lower amplitude and sensitivity than orientation reversal-VEP in early development. Onset of DR is around 7-9 weeks for 2 Hz and about 9-11 weeks for 4 Hz at 5.5°/s, 3 weeks later than OR (Braddick et al., 2005; Wattam-Bell, 1991). Infants use motion as a means of organizing object perception by 4 months of age (Kellman & Spelke, 1983). With age, infants' motion sensitivity extends to both higher and lower speeds (Braddick et al., 2003 & 2005; Wattam-Bell, 1992 & 1996)

Pattern	Function	Onset Age
Pattern-Reversal (PR)	Spatial contrast processing – input to cortex- not necessarily cortical	Late preterm/ term
Orientation-Reversal (OR)	Cortical pattern processing	~1-3 months (temporal frequency dependent)
Direction-Reversal (DR)	Cortical motion processing	~2-3 months (temporal frequency dependent)

Table 1.1: The three stimuli used in the present thesis (Braddick et al., 2005).

1.3 Visual Evoked Potentials (VEP)

VEP are neural electrical activity recorded from the scalp surface, identifiable by being synchronized with repeated presentations of visual stimulus transitions (Bodis-Wollner et al., 1986; Regan, 1989). There are two types of brain activity that can be recorded from the scalp, (1) spontaneous activity that can be measured with EEG and (2) event related potentials (ERP) with lower amplitude that are synchronized with a stimulus event. To enhance signal quality, the technique of signal averaging is used. VEP amplitude depends on neuronal synchronization and background brain noise. Compared to the EEG signals of 20-100 μV, the VEP signal is much smaller at about 1-20 μV.

Ever since Campbell and Maffei (1970) found a linear relation between the logarithm of contrast and amplitude of VEP response to a sine wave, VEP has been widely used among visual scientists. To determine the limit of one's visual acuity,

extrapolation can be done on a graph of VEP amplitude as a function of spatial frequency (SF) to the 0 microvolt (Norcia & Tyler, 1985).

While VEP acuity maybe more limited by structural and neural changes in the ocular media and visual pathway, behavioural acuity is also limited by attention and oculomotor development. Nonetheless, VEP and behavioural measures complement each other in determining visual development. Harris, Atkinson, and Braddick (1976) found that VEP measurements could provide similar data on contrast sensitivity to that obtained by behavioural methods. They suggested that at low to medium (0.1-15 cpd) SF, infant contrast sensitivity reached adult level by 6 months.

For this thesis, I used three visual stimuli (pattern, orientation, and direction-reversal) with two temporal types of VEP recordings: Transient VEP (TVEP) and steady-state evoked potential (SS-VEP) to track infant visual development.

1.3.1 Physiological basis of VEPs

VEP responses, like the EEG, are generated by postsynaptic currents from massive synchronous activity. The signals travel through various spatial filters- all the cortical layers, dura, and skull before reaching the scalp where they can be measured. This limits spatial resolution and source localization of EEG. Nicholls et al. (1992) proposed that VEP arise from pyramidal cells that are located outside of layer 4. Layer 4 receives most of the cortical inputs, and contains mostly small spiny stellate cells that have small potentials (Nunez & Srinivasan, 2006).

VEP can provide information regarding the temporal sequence of neural processing. It has a clear advantage to using fMRI, which measures blood flow rather than direct

electrical activity of the neuronal response. Moreover, VEP records in real time. Unlike fMRI that takes 5-6 seconds to achieve peak response, VEP response can be recorded in milliseconds. Nicholls et al (1992) postulated that while fMRI emphasizes synaptic input to an area, EEG like VEP, record activity from pyramidal cells that carry the output from V1. However, unlike MRIs, all EEG have poorer spatial localization of the neuronal generators.

1.3.2 Visual stimuli

1.3.2.1 Pattern-reversal VEP

Pattern or phase reversal (PR) is commonly used to test responses to contrast changes. The stimulus is typically either a checkerboard pattern or a grating (sine- or square-wave), in which the luminance of adjacent checks or grating stripes are periodically interchanged by 180° phase flips (Regan, 1989). In the present study, the grating is oriented at 45° with phase changing at a fixed frequency of one half of a cycle , resulting in a bi-stable moving grating illusion (Chapter 3; Lee et al., 2012a). While others found smaller VEP amplitude and longer latency associated with oblique orientations, the oblique effect is more prominent at low temporal frequency (TF) (Arakawa et al., 2000; Moskowitz & Sokol, 1985) and high spatial frequency (SF) (Essock & Lehmkuhle, 1982). As this thesis uses a range of TF from 1-16 r/s, the oblique effect is not likely to significantly affect latency measures. Because this thesis compares PR with OR, both gratings were made oblique for an easier comparison.

A typical PR response has a positive peak, P1 (typically around 100ms in adults), and two negative deflections- N1 (N70- N75) and N2 (N135-N150). Several studies suggested that the P1 originates from the primary visual cortex (Di Russo et al., 2002; Magoon et al., 1981) while N1 contribute to the subcortical V1 input (De Haan, 2007; Regan, 1989). P1 is reported to be generated in the occipital cortex (Di Russo et al., 2002; Magoon & Robb, 1981), and is dependent upon stimulus luminance, contrast (Morrone et al., 1996), orientation, and spatial frequency (Kenemanas et al., 2000). Yet the precise location within V1 remains unknown. This thesis focuses on the changes in P1 as cortical contributions to other latencies (N1 and N2) are less well documented in psychophysics and in clinical settings.

PR produces responses at the retinal level in on- and off- ganglion cells (Kuffler, 1953). While the PR-VEP response indicates that these contrast signals have arrived at the cortex, the response does not necessarily reflect processing at the level of the visual cortex.

1.3.2.2 Orientation-reversal VEP

Orientation change, however unlike pattern, can only be processed in V1 and in further extra-striate visual areas (Hubel & Wiesel, 1962). Orientation detection is essential for object recognition- to define shapes in extrastriate areas and the temporal lobe of the ventral stream (Ungerleider & Mishkin, 1982). The onset of cortical orientation selectivity can be assessed by using orientation-reversal (OR) VEPs. The OR stimulus, introduced by Braddick et al (1986), uses a grating whose orientation switches between 45° and 135° and includes jitter (random phase shifts of the grating) to isolate

response components that are specific to orientation changes by using Fourier analysis (Fig. 3). The existence of the orientation response is inferred from the statistical presence of a frequency component at the orientation-reversal rate. To measure waveform characteristics (eg. transient latency), the component at the jitter frequency can then be filtered out to obtain an OR-specific response (Chapter 4; Lee et al., 2012b).

The oblique angle was used to reduce any contrast difference between gratings seen by infants with astigmatism. Infants younger than 6 months commonly have astigmatism in the horizontal or vertical meridians (Howland et al., 1978).

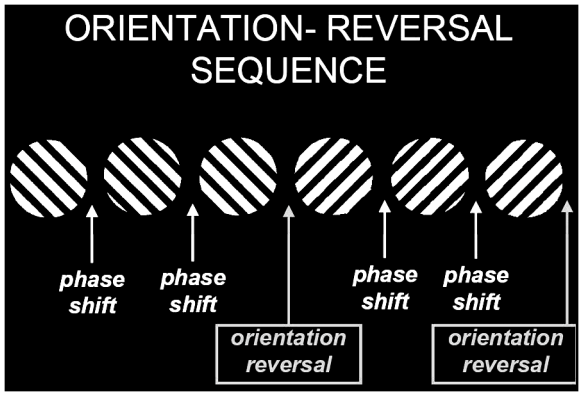


Fig. 1.1: The OR sequence used in the thesis (adopted from Braddick et al., 1985).

1.3.2.3 Direction-reversal VEP

In order to see translational motion, the visual system has to recognize not only pattern changes, but also the relation between time and space. Direction-reversal VEP was used to check motion processing generated in V1 and higher visual cortices. The DR stimulus used in the study includes a series of reversals in the motion of a random pixel pattern with random contrast changes or 'jumps' (the introduction of a new random pixel

array) embedded in the sequence to control for local contrast changes occurring at the direction reversals (Fig. 2, Wattam-Bell, 1991& 1996). The random dot kinematogram (RDK) is a widely used stimulus for activation motion-selective neurons, e.g. in area MT (Newsome et al., 1989). A directional shift of all the pixels should contain enough motion energy to excite sufficient amount of motion sensors that are tuned to that particular direction and speed. To measure waveform characteristics, DR- specific response at the jitter frequency can be filtered out by removing recording section with the random contrast changes to obtain a DR-specific response, whose peak latency can then be measured (Chapter 5; Lee et al., 2013a; Wattam-Bell, 1991 &1996).

DR-VEP is an example of first order motion where motion perception is the result of the difference in luminance of the object from its background. First order motion begins with orientation filtering in simple cells that respond to average luminance difference within a neuron's receptive field, acting as a linear filter (Kaneko et al., 1997). Direction selective filters like complex cells in V1 then summate the spatiotemporal sensitive simple cells, which can also be direction selective. The projections from V1 directly and indirectly connect to MT and integrate the local directional signals from V1 into larger receptive fields. (Lamme et al., 1993). Newsome et al (1989) showed in monkeys that the directional threshold of individual MT neuron is the same as that of the whole animal.

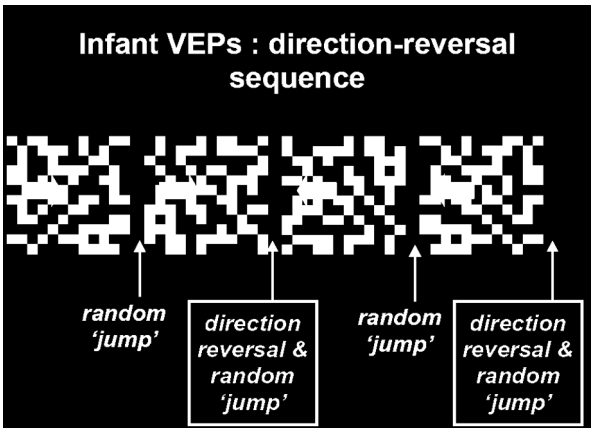


Fig. 1.2: The DR pattern used in the thesis (adopted from Wattam-Bell, 1991).

1.3.3 Transient and Steady-state VEPs

We used two types of VEP recordings: transient VEP and steady-state evoked potential (SS-VEP).

1.3.3.1 Transient VEP

In transient VEP (TVEP), the brain mechanism generating the signal returns to the resting state before the next stimulus, producing a brainwave with distinct VEP components. A temporal frequency (TF) of < 2 Hz (4 r/s) is used (Atkinson, 2000). In our work latency is determined from the most prominent peak (P1), typically around 100 ms in adults.

1.3.3.2 Steady-state VEP

Steady-state evoked potential (SS-VEP) is the response to rapid repeated stimulation, with TF >2 Hz, that produces quasi-sinusoidal waveforms in responses to overlapping stimulus presentation (Bodis-Wollner et al., 1986; Celesia, 1984; Porciatti, 1984; Regan, 1989). The brain responds rhythmically at the frequency of the repeated stimuli, and the peaks of separate components that appear in the transient VEP are not distinguished. SS-VEP generates a periodic neural response at the stimulus frequency and its harmonics, from which signal amplitude and phase at the stimulus frequency was computed using Fourier analysis. Phase unwrapping is required to calculate the latency of VEP, as described below.

1.3.3.3 Comparison between transient and state-state VEPs

Because TVEP requires low TF to generate clear complete VEP waveforms, its recording time is much longer than SS-VEP. While latency and waveform are directly determined from TVEP, the quasi-sinusoidal waveforms produced by SS-VEP are difficult to interpret without Fourier analysis and further mathematical manipulation. However, the presence of an SS-VEP response at a particular frequency can be tested statistically, while the evaluation of transient VEP is generally more subjective. Due to the nonlinearities in the visual system, the second harmonic response is most often the major component of the VEP (Marx et al., 1986; Strasburger et al., 1993)- especially for the three stimuli tested in this thesis. Over the years, TVEP has gained popularity in clinical ophthalmology and neurology while SS-VEP tends to be favored by the visual scientists.

1.3.4 VEP latency

Latency of VEP waveforms is a more robust measure compared to amplitude, for amplitude is more affected by participant cooperation, background noise (Ciganek, 1969), and individual physiological differences such as the thickness of one's skull (De Haan, 2007). Several studies have shown that the peak latency is less variable than amplitude both within and between subjects (Sarnthein et al., 2009; Strasburger et al., 1988; Tomoda et al., 1999). VEP latency has been used as an important measure in studies of attention (Di Russo & Spinelli, 1999 & 2002), binocularity (Tobimatsu and Kato, 1996), visual development (Fiorentini & Trimarchi, 1991; Porciatti, 1984), luminance and colour contrast (Morrone et al., 1996), clinical evaluation (Falsini & Porciatti, 1996; Tobimatsu et al., 1990), spatial frequency (Simon, 1992; Tobimatsu et al., 1993), and ageing (Porciatti et al., 1992).

Infants develop different VEP components at different developmental stages. Infants can successfully produce N1 by 8-14 weeks and N2 within the first 2 months (Sokol & Jones 1979). Yet a prominent P1 peak can be seen at birth (McCulloch et al., 1991 & 1999; Moskowitz & Sokol, 1983; Porciatti, 1984). Previous studies on infant visual development have reported that the transient peak latency (P100 or P1) for PR - VEP decreases from 260 ms at birth to around 100 ms (adult values) at around 4 months (Chapter 3, Lee et al., 2012a; McCulloch et al., 1991 & 1999; Moskowitz & Sokol, 1983; Porciatti, 1984). This rapid change may be attributed to various factors: retinal development, especially the cone photoreceptors (Magoon & Robb, 1981; Yuodelis & Hendrickson, 1986) and progressive myelination of the optic nerve and radiation (Dubois et al., 2008) which increase processing speed.

1.3.5 Latency analysis

Most of the studies done on latency are based on the time to the P1 peak of transient VEP (transient peak latency), which is a problematic measure in developmental studies. First, the shape and number of peaks varies with age (Moskowitz & Sokol, 1983), making adequate comparisons across ages difficult. The use of different stimuli, which may be expected to generate different waveforms, accentuates this problem. To provide an alternative measure, the present study also measured latency indirectly. The phase of the SS-VEP was analysed at two or more different TFs, giving a phase versus TF plot, whose slope provides a calculated value of apparent latency (Spekreijse, 1978; Regan, 1966). The rationale and significance of the calculated value is discussed below.

Phase has been found to be reliable between (Strasburger et al., 1987; Tobimatsu et al., 1993) and within subjects (Simon, 1992). Phase is also linearly related to the stimulus' TF (Regan, 1966) and latency (Di Russo & Spinelli, 1999; Fiorentini & Trimarchi, 1991).

Phase measurements are ambiguous. Since phase values cycle every 360°, a measurement of 75° can also correspond to 75°+ 360°= 435°, etc. (Strasburger et al., 1987). In order to "unwrap" the phase, some multiples of 360° must be subtracted from the subsequent phase, changing the slope and the calculated latency. Current literature offers no rigorous method for resolving this ambiguity. In previous studies using steady state phase to calculate latency, multiples of 2π radians (or 360°) were subtracted to "sort [phase] over the whole TF range" (Falsinin & Porciatti, 1996) and "produce maximum orderliness" (Morrone et al., 1996; Porciatti et al., 1992) or minimize the distance to the

preceding point (Strasburger, 1987). The criteria used in the present study are described in the methods section.

It should be noted that the gradient of phase with TF corresponds to the transient measure of latency only if the temporal dynamics of the response can be modelled by a pure delay (Strasburger, 1987). Unlike the P1 (or any other individual peak), the phase measurement is determined by the entire time course of the VEP response. The P1 will primarily reflect the arrival time at the cortex of the barrage via the optic radiation - the latency of retinal events, the transmission time from retina to cortex, and perhaps the initial dynamics of the cortical activation by this barrage. P1, however, is not the first input to the visual cortex. The phase-based measure can be expected to have a greater contribution from subsequent components of cortical processing. Transient latency and the phased-based calculated latency are expected to be different but complementary to each other. Comparison of the two measures, particularly in development, should reveal any differences in the maturation between different levels of processing in the visual pathway.

1.4 Atypical Infant Development

Cerebral Palsy (CP), often related to brain injury around birth, is one of the commonest causes of childhood disability in industrialized countries. Children with CP often have severe motor deficits and visual impairments, ranging from a complete lack of visual awareness to milder spatial problems (e.g. Schenk-Rootlieb et al., 1993; van Nieuwenhuize et al., 1984). One way of identifying visual deficits and tracking general

visual-neuro development is through recording visual brainwaves, for example VEP. Since Halliday et al's (1972) first application of pattern reversal-VEP to diagnose patients with optic neuritis, VEP, especially using either a checkerboard or a grating pattern, has been widely used in evaluating patients' visual-neuro changes (Regan, 1989).

In typical development, the latency delay of this response decreases from 250ms in newborns to adult level of 100 ms at 4 months of age (McCulloch & Skarf, 1991; Moskowitz & Sokol, 1983). Measuring latency in infants at risk for CP will further clarify the potential factors underlying the changes in infants' visual cortex. By applying two latency techniques, this thesis hoped to provide some evidence of the efficacy of latency measures in clinical babies. In particular, since premature infants at risk for CP have mostly white-matter fibre-tract problems, the latency measure may be particularly revealing of these.

1.5 Objectives

The present thesis will add to the current data on these latency changes by testing a much wider age group of healthy full term infants, to provide a normative baseline in differentiating visual and neurological development from pathological processes. More importantly, in addition to using PR-VEP, we will examine, for the first time in the field, the latency of responses to orientation-reversal (OR) and motion direction-reversal (DR), which isolate specific cortical mechanisms.

Because all three processes - pattern, orientation, and direction responses - receive visual information from the retina and optic nerve, the contribution of retinal processing and transmission time to latency should not differ among the different mechanisms.

However, since orientation selectivity develops earlier compared to direction (Braddick et al., 2005), and both develop after the appearance of PR-VEP responses in development, changes in the overall brain development and timing of cortical processing would be expected to be different among the PR, OR, and DR processes.

This thesis investigates: (1) the efficacy of the slope method to calculate latency in adults and infants and the best way to analyse phase; (2) the relationship between calculated and transient latencies; (3) the relationship between the timing of direction, orientation, and contrast VEP responses; and finally (4) the relationship between the developmental courses of the PR, OR, and DR latencies.

A further aim of this work is to provide the means for investigating atypical development in infants at risk for CP. More specifically, we would track the difference in the latency development of the clinical infants compared to the normal controls, and examine the latency delays in relationship to their visual and cognitive abilities.

This project aims to provide new insights into human visual cortical development. The neonate visual system is a dynamic state where deprivation during critical periods can result in permanent visual impairment. Identification of delayed maturation of VEP latencies may aid in early diagnosis and guide therapies in pediatric ophthalmology and neurology.

2 METHODS

2.1 Participants

2.1.1 Adults

While most adult subjects were recruited to complete their psychology experimental credits in Oxford and UCL, others joined the study through responding to our advertisements hung in the psychology departments. 81 adults were tested (median age 21, range16-43 years) with normal or corrected to normal vision. Some subjects did not show measurable peak response from a record with a significant component at the reversal frequency from all temporal frequencies (TF).

2.1.2 Infants

Infant subjects were recruited from a database of families who had volunteered for research while in the postnatal wards of the Women's Centre at the John Radcliffe Hospital, Oxford. 137 healthy full term infants (age 3.6-79.0 weeks) born within 14 days of their due date were tested. ANOVA revealed no significant effect of pre/post-maturity within this range affecting latency. Not all 137 infants were tested for all three VEP stimuli.

Specific numbers of participants for particular studies are described in detail in the individual VEP chapters. For the study on orientation-reversal VEP (chapter 4), the transient peak latencies of OR responses at 4 r/s were analysed from the data of 123 infants (4.0-20.3 weeks) tested previously (Braddick et al., 2005) in addition to those tested in the current experiments. In the study on atypical infants (Chapter 7), 50 infants

(adjusted age: 0.9 to 129 weeks post-term) with perinatal brain damage were recruited for the clinical group, as part of the 'Dolphin' study on nutritional supplements for at-risk infants.

2.2 Stimuli

2.2.1 Pattern-reversal VEP

The PR stimulus was a sine wave grating, with a spatial frequency of 0.24 cpd (comparable to 81 minute of arc checks), oriented at 45°, and alternated with periodic 180° phase shifts. It had a mean luminance of 31 cd/m^2 at 93% contrast.

2.2.2 Orientation-reversal VEP

Like the PR stimulus, the OR stimulus consisted of a sine wave grating with a spatial frequency of 0.24 cpd with a mean luminance of 31cd/m^2 at about 93% contrast. In OR, the grating alternated between 45° and 135° at the test frequency. Between orientation changes, the grating underwent random phase shifts (jitter) at a rate of 25 per second with no overall change in the luminance of the screen (Braddick et al., 1986). Oblique orientations were used to avoid the risk of any horizontal-vertical anisotropy, including that caused by the common astigmatic refractions seen in infants.

2.2.3 Direction-reversal VEP

The DR stimulus was composed of a 0.44° pixel-size random checkerboard pattern, where the pattern displaced horizontally at 5.5 deg/sec. Jumps, or introduction of new

random pixel array, occurred at a rate twice of the DR frequency (i.e. the random contrast changes appeared every 125ms for a 4 r/s DR). The DR stimulus used in this paper is similar to the stimulus studied by Wattam-Bell (1991) and the same as the one used in Braddick et al. (2005) (Fig. 2).

Each of the three stimuli was displayed on a computer monitor 40 cm from the participant's eyes. Stimuli were generated using the LUA scripting language (ver. 5.1; www.lua.org) running on a PC (Windows XP; Microsoft, WA, USA), and presented on a 17" CRT monitor (800 x 600 pixels resolution, viewable area 323 x 240 mm (18.4 deg x 13.7 deg at the viewing distance of 40 cm) at nominal 100 Hz frame rate. The display computer was coupled to a PC (Windows 2000, Microsoft, WA, USA) for recording the VEP responses.

2.3 VEP recording

Three gold cup electrodes were used to record VEP: one on the vertex, one 1 cm above the inion, and a ground electrode positioned high on the forehead. The signals were recorded using a computer-based acquisition system (Espion; Diagnosys, Cambridge, UK). Impedance was measured with an applied voltage at 1000 Hz and electrodes were adjusted until this was < 10 kΩ. Signals were amplified (20,000x), band pass filtered between 0.5 and 30 Hz, and sampled at 1000 Hz. In a separate test using a square-wave input to the amplifier, the phase response of the system was measured for the range of temporal frequencies (TF) to ensure that it was not affected by the band pass filtering. The phase shift introduced was found to be less than 5° for all TFs used, except at 1 r/s where it was approximately10°. It was checked that these phase shifts would have no

significant effect on the calculated latency values. Measurement using a photoelectric photometer revealed that there was a systematic software delay of 45 ms between the stimulus event at the middle of the computer screen and the recording cycle for the PR and OR stimuli, and 25 ms for the DR stimulus. This was taken into account in computing latency values.

One hundred epochs (2 cycles per epoch) were averaged on the computer. Any epoch containing signals greater than 200 μV in amplitude was automatically rejected from the signal averaging as artefact. The operator could use the computer mouse button to reject the current epoch if the participant was inattentive. To minimize onset effects, recording began a few seconds after the stimuli appeared. The order of testing the three stimuli at different TFs was randomized to minimize any systematic adaptation effects. Because each recording contained two complete cycles, the total recording epoch was 2 sec for 1 r/s, 1 sec for 2 r/s, 0.5 sec for 4 r/s, etc. By averaging signals over 100 sweeps, the signal builds up relative to random noise in the averaging process.

For adults, up to twelve different TF of 1, 2, 3, 4, 6, 8, 9.6, 10.7, 12, 13.7, 16, and 19.2 r/s were used. For infants, up to seven different TF of 2, 3, 4, 6, 8, 12, and 16 r/s were tested. A small noisy toy was shaken in the centre of computer screen to attract their attention. Recording was interrupted when subjects became inattentive. Fewer TFs were used with infants because their limited attention span restricted the total recording time available.

2.4 VEP analysis

Relevant response frequencies were first extracted from the record using Fourier

analysis. The presence of a statistically measurable peak response from a record with a significant component at a particular TF was calculated using the Mann-Whitney U test, a circular variance test of consistency of the signal phase (Moore, 1980; Wattam-Bell, 1985). This test determines the presence of a statistically significant response with a consistent phase across the run as a whole, by taking the amplitude and phase measured at the reversal frequency within each sweep as a sample. Signal/noise ratio (SNR) was calculated based on measurements of noise power in a band 1 Hz either side of the stimulus frequency (Braddick et al., 2005). Any runs with $P > 0.05$ on the U test or an SNR < 1.5 were discarded.

Both transient and steady state latency measures were corrected for the systematic software delay between the stimulus event and the recording cycle, of 45ms for PR and OR stimuli and 25 ms for the DR. All other delays have been accounted for, including those from the background Windows, recording delays, and the amplifier for the various temporal frequencies. Conditions and age groups were then compared by ANOVA (multivariate and repeated-measure (RM)) using SPSS 18.

2.5 Transient peak latency

For the transient VEP, the timing of the highest positive peak values in the computed waveform was manually selected for the low TFs: 1-4 r/s in adults and 2-4 r/s in infants for PR and OR. At high TFs, the waveform around the initial peak cannot be separated from the effects of preceding stimuli. Since DR latencies were generally longer, 4 r/s was too high a rate to separate peaks from successive reversals, so transient peak latencies were computed only for 1-3 r/s in adults and 2 and 3 r/s in infants. The

early peak was manually selected between the time-window of 50-100 ms while P1 was taken between 100-150ms. As each recording contained the responses to two stimulus reversals, an average latency of the two peaks within the record was used for subsequent analysis. The mean latencies across these low temporal frequencies were calculated and used in subsequent analysis, after confirming that there was no significant difference of P1 latency among the different temporal frequencies.

The waveform for OR and DR stimuli reflects the effects of the phase shifts or 'random contrast changes' incorporated in the stimulus sequence as described above. The orientation reversal event was accompanied by simultaneous local contrast changes, which may also contribute to the initial peak. The jitter at a multiple of the grating reversal rate was included in the stimulus to allow the effects of these contrast changes to be removed. For the transient analysis, the recorded responses were "dejittered" by using a MATLAB where the Fourier-Analysis transformed the averaged waveform and removed the component at the jitter frequency (25 reversal /sec) and its harmonics at 50 and 100 Hz. The peak latency was then measured from this modified waveform.

In the DR stimulus sequence, each reversal of direction was accompanied by simultaneous replacement of the random pixel pattern (Fig. 1). This allows the use of interleaved 'random contrast changes' to exclude non-directional effects associated with the reversal. However, this means that the reversal is accompanied by simultaneous local contrast changes, and these may contribute to the initial peak response. To remove the random contrast changes, i.e. isolate the component of the peak due to direction reversal, the second half of the recorded waveform, which contains the effects of contrast changes without direction reversal, was subtracted from the first half of the VEP recording for one

reversal cycle (reversal + contrast changes) (Fig. 2; Braddick et al., 2010). For example, a recording of 2 r/s with two complete reversals would be divided into 4 chunks: DR response and random contrast changes for the first 25 to 256 ms, contrast-change-only response for 257-491 ms, DR and contrast change for 492-726ms, and finally contrast-change-only for 727- 961 ms. By dividing the DR record into 4 chunks to remove the random contrast changes, the analyzed waveform can be recorded only up to 160 ms at 3 r/s. Any peak after this time would not be detected using this method.

2.6 Phase-based calculated latency

The phase of the averaged signal components at the second harmonic frequency, F2, was measured for each stimulus temporal frequency, from 0 to 360°. The phases were calculated using the arctangent of sine / cosine amplitude. Although arctangent is bounded between ± 180°, an infinite series of phase values separated by 360° exist with the same tangent. Because the slope of the phase plotted against TF is proportional to delay (Porciatti, 1984; Regan, 1966), we assume that our phase values should reduce with TF in a similar linear fashion. Therefore, to choose the appropriate phase, the difference between two adjacent frequencies' phase values was calculated. If this difference was positive, multiples of 360° were subtracted from the phase value of the higher frequency until the difference became negative. 360 degree was also subtracted from the phase value of the next higher frequency, and the next difference then tested in the same way (Porciatti et al., 1992; Strasburger, 1987). The phase values 'unwrapped' in this way were plotted against TF and the slope of this function derived by linear regression. Finally, the slopes of the phase plot were converted into apparent latency in ms by using the formula:

$$Latency(ms) = -(\frac{Phase\Delta}{TemporalFrequency\Delta}) \times (\frac{1000}{360°}) - 45ms Software Delay$$

(or 25 ms Software Delay in the case of DR-VEP).

As many closely spaced TF values as possible were chosen for this study to minimize the risk of any data point being misplaced by 360° (Chapter 3, Lee et al., 2012a; Simons, 1992). When the calculated latency derived from the whole slope was greater than three standard deviation from the mean slope of the entire sample, the outlier was eliminated from the data pool.

3 PATTERN-REVERSAL VEP

3.1 Background

Pattern or phase reversal (PR) is the most common type of VEP stimulus currently used. The stimulus is either a checkerboard pattern or a simple sine or square grating, where the luminance is varied by waveforms that differ in phase by 180 degrees between adjacent checks or grating stripes (Regan, 1989). The pattern reversal stimulus consists of black and white gratings that abruptly alternate, with no overall change in the luminance of the screen. A typical response has a positive peak, P100, and two negative deflections: N1 or N75 and N2 or N135 (Fig. 3.1).

P100 transient peak latency has been found to decrease from ~260 ms at birth to ~100 ms (adult values) at 4- 5 months (McCulloch et al., 1999; Moskowitz & Sokol, 1983; Porciatti, 1984). This rapid decrease in latency may been attributed to various factors: the structural development of retinal processing, especially the cone photoreceptors (Yuodelis & Hendrickson, 1986); progressive myelination of the optic nerve and optic radiation (Dubois et al., 2008; Magoon & Robb, 1981), and rapid synaptogenesis (with maximum density by 8 months of age) (Huttenlocher et al., 1982). It should be noted, however, that the PR stimulus would generate responses at the retinal level from on and off responses in the ganglion cells (Kuffler, 1953). PR-VEP is thus useful in demonstrating that contrast information has arrived at the cortex, but need not reflect any processing within the visual cortex.

In addition to finding the transient P1 peak in the PR VEP response, this study calculates phase-based latency through the gradient of phase at different temporal

frequencies. The present study investigates: (1) the efficacy of the slope method to calculate latency in adults and infants, and the best way to analyse phase; (2) the relation between calculated and transient latency; and (3) the developmental courses of PR latencies as measured with both approaches.

3.1 Methods

Please refer to Chapter 2 for detailed descriptions for methods and materials used throughout this thesis.

3.1.1 Participants

81 adults were tested (median age 21, range16-43 years) with normal or corrected to normal vision. Healthy full term infants born within 14 days of their due date were recruited. 137 individual infants (3.6-79.0 weeks) were tested (Table 3.1). Twenty-five of these infants were tested at two ages, six infants were tested at three ages, and five infants were tested at four different ages.

3.1.2 Stimulus

The PR stimulus was a sine wave grating, with a SF of 0.24 cpd (comparable to 81' of arc checks) and mean luminance of 31cd/m^2 at about 93% contrast. It was oriented at 45° and alternated with periodic 180° phase shifts.

3.1.3 VEP recording

For adults, up to twelve different TF at 1, 2, 3, 4, 6, 8, 9.6, 10.7, 12, 13.7, 16, and 19.2 r/s were used. For infants, up to seven different TF at 2, 3, 4, 6, 8, 12, and 16 r/s were tested.

3.1.4 VEP analysis

For the transient VEPs, the timing to produce the highest positive peak values in the modified waveform was manually selected for the low TFs, that is 1-4 r/s in adults and 2-4 r/s in infants.

To calculate apparent latency, phase values were unwrapped as described in Chapter 2. The unwrapped phase values were then plotted against TFs. Finally, the slopes of their linear regression were converted into apparent latency using the formula:

$$Latency(ms) = -\left(\frac{Phase\Delta}{TemporalFrequency\Delta}\right) \times \left(\frac{1000}{360^{\circ}}\right) - 45ms SoftwareDelay$$

3.3 Results

3.3.1 Response rate

Among the 81 adults tested, transient responses were obtained from records with a significant second harmonic component for 74 (91.4%), calculated latencies were obtained from all 78 (96%), and data for both transient and calculated latencies were obtained for 71 (87%). Of the 137 infants aged 3.6-79.0 weeks, 101 infants (73.7%) yielded significant response for obtaining transient latencies while 85 infants (62.0%)

yielded calculated latency values. 74 infants (54.0 %) yielded data for both the transient and calculated responses (Table 3.1). For the calculated latency analysis, 26 infants gave data for the phase at only two temporal frequencies; the handling of these data is discussed below. Three of the 81 adults and two of the 137 infants were completely eliminated from the analysis due to high values for the calculated latencies (>3 SD above the mean).

Age (wks)	Tested	Transient	Calculated	Transient & Calculated
3.6-4.9	5	4	4	3
5-9.9	19	10	13	9
10-14.9	20	10	10	10
15-19.9	16	11	10	10
20-29.9	27	25	21	19
30-39.9	14	11	11	8
40-49.9	10	7	3	3
50-59.9	10	7	5	4
60-69.9	10	10	4	4
70-79.9	6	6	4	4
Infants Total	137	101	85	74
Adults Total	81	74	78	71

Table 3.1: Response rate: number of adults and infants in each of the 11 age groups with significant components at the reversal frequency in transient, calculated, and both transient and calculated latencies.

3.3.2 Transient versus calculated latencies

3.3.2.1 Transient P1 latency

VEP waveforms showed classical PR responses with a prominent, easily identifiable P1 peak (Fig. 3.1). One-way ANOVA showed that the mean differences among the latency values for this peak between the low TFs in adults was not significant (1, 2, 3, 4 r/s; $F(3, 81)= 2.2$, $P> 0.1$). In infants, a two-way ANOVA was performed with age treated as a between-subjects factor. The peak latency differences among the low TFs (2, 3, 4 r/s) were not significant ($F(2, 130)= 2.0$, $P> 0.1$), nor was the interaction effect between age and TFs ($F(2, 130)= 0.7$, $P> 0.1$). Therefore, we used the combined average of the four TFs in each adult and of the three TFs in each infant as the subject's transient peak latency value. Significant responses at the second harmonic of the reversal frequency were also observed in some instances at all TF tested for both infants and adults (Fig. 3.1A- right panel).

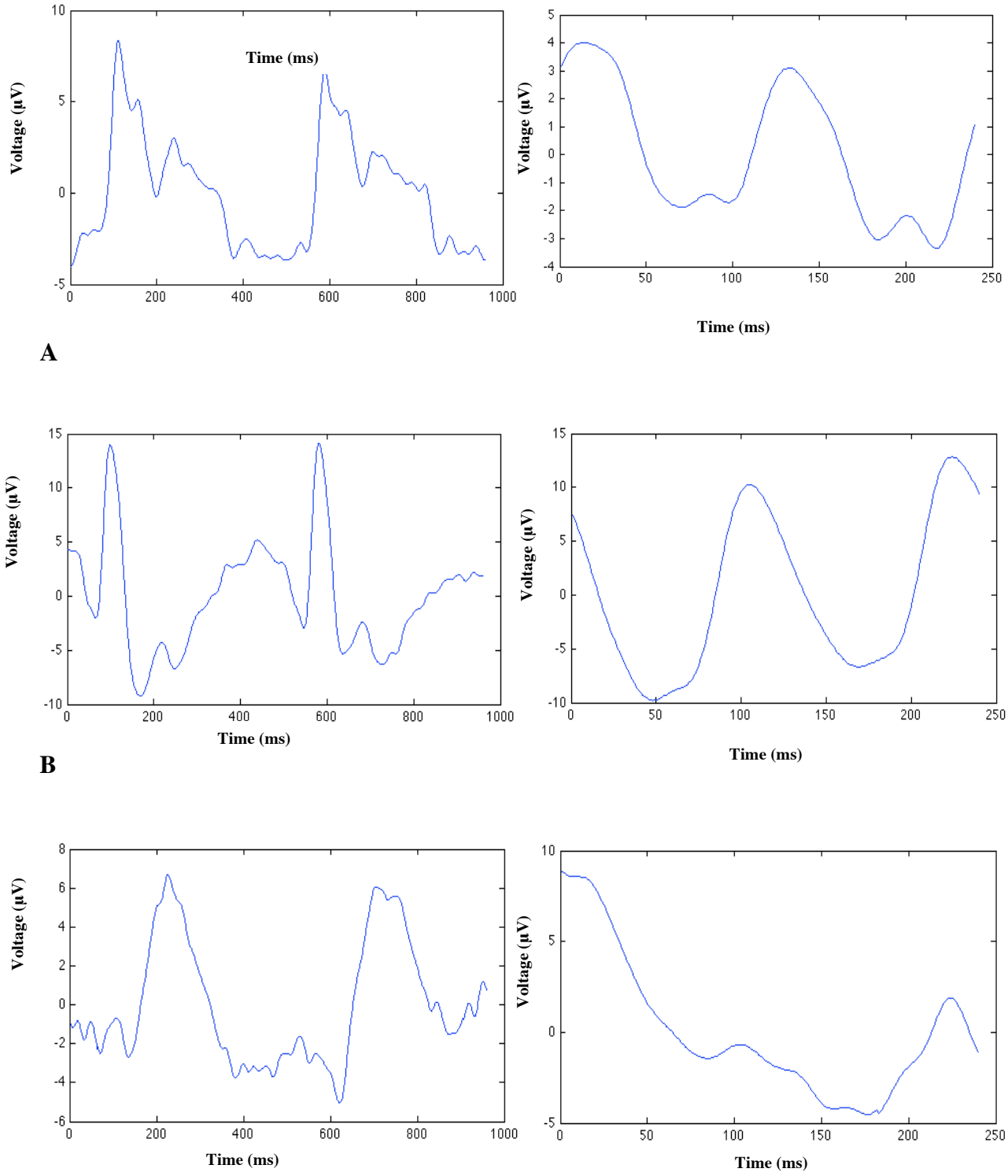


Fig. 3.1: A representation of two PR-VEP waveforms at 2 r/s (left) for an: (A) adult with an average peak transient latency of 109 ms; (B) 20-week-old infant, peak 112 ms; and (C) 8-week-old infant, peak 265 ms. Transient latency was selected manually by placing

a cursor on the most prominent positive peak of the two averaged cycles. Representative steady state waveforms of 8 r/s are presented to the right side for the same participants.

3.3.2.2 Phase-based calculated latency

In both adults and infants, the slope method proved effective in calculating an apparent latency value. Examples of plots for individual adults and infants are shown in Fig. 2. The absence of any clear split in the slope between the upper and lower part of the TF range (as reported by Fiorentini & Trimarchi, 1991; Regan, 1966) seen in these examples was characteristic of the data. It suggests that any difference between transient and calculated latencies was not simply due to the different TF ranges used.

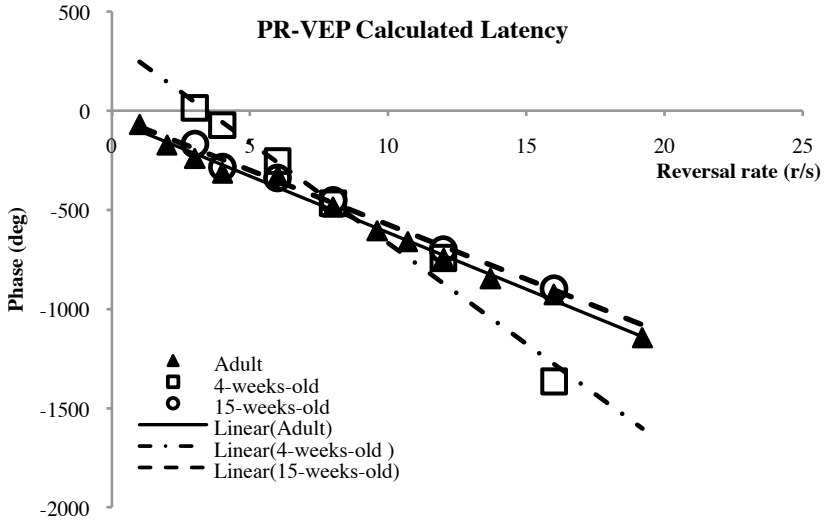


Fig. 3.2: Illustration of the slope method for an adult and two infants (4 & 15 weeks old). The adult was tested with 12 different TFs from 1-19.2 r/s (R^2= 0.99, slope= -57.0, latency= -(-57.0)* 1000/ 360- 45= 113.4 ms. 45 ms is the correction for software delay). The infants were tested with 6 different TFs from 3-16 r/s. The 4-week-old had R^2= 0.98, slope= -101.6, latency= 237.3ms. The 15-week-old had R^2= 0.99, slope= -54.9, latency= 107.5ms.

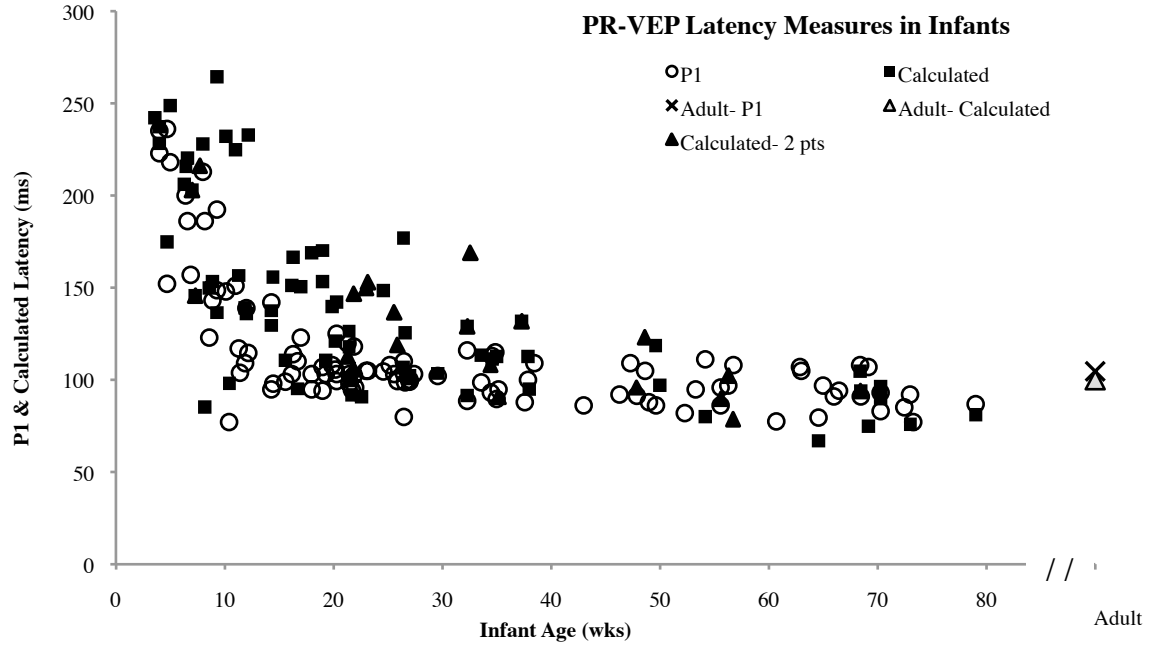
Although an increased number of TFs will enhance the accuracy of the calculated latency, a latency value can be derived from as few as two TFs. These values are shown with distinctive symbols in Fig. 3,3A, indicating their consistency with the data set as a whole. In infants, a comparison by ANOVA (with age as a covariate) between the calculated latency derived where only two TFs were available vs. those derived from more than two TFs indicated no significant difference between the two methods (F (1, 112)= 0.1, P> 0.1) nor any significant interaction between age and method (F (1, 112)=

0.3, P> 0.1). We conclude that appropriate latency values can be achieved from as few as two TFs.

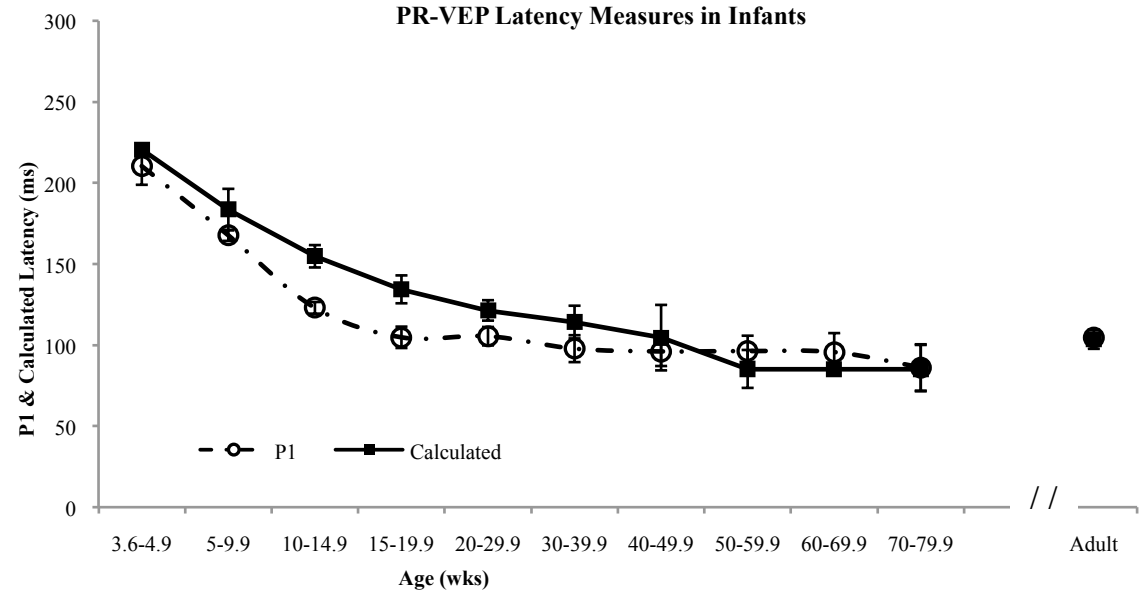
3.3.3 Adult versus infant latencies

3.3.3.1 Adults

In adults, the range of transient peak latency ± SE (104.6 ± 1.7ms; 95% CI= 100.8-106.9 ms) and calculated latency (103.6 ± 3.0ms; 95% CI= 97.2- 107.3 ms) were similar to the range (100-115 ms) found in the literature (McCulloch et al., 1999; Morrone et al., 1996; Tobimatsu et al., 1991 & 1993) (Figs. 3.3 A & B). Similar to Tobimatsu et al.'s (1993) findings, no significant difference between the two latency methods was found, using RM-ANOVA (F (1, 69)= 0.4, P> 0.1).



A



B

Fig. 3.3: P1 and calculated latency of PR- VEP in infants as a function of (A) continuous age range (all infants) and (B) 10 age groups (mean± SE) (see Table 3.1). The transient

(104.6±1.7 ms) and calculated latency (103.6 ±3.0 ms) values of adults are shown for comparison.

3.3.3.2 Infants

Compared to adults, the response waveform for young infants is prolonged (Fig. 3.2). In the latency of the first positive peak, we found similar age trends to other published studies (Fiorentini et al., 1991; Porciatti, 1984; McCulloch et al., 1999; Morrone et al., 1996; Moskowitz & Sokol, 1983; Sokol & Jones, 1979), with a steep decrease over the first few months of life (Fig. 3.4 A & B). Longitudinal data from four infants with four repeated sessions at different ages (Fig. 3.5A & B) showed a similar developmental trend to that of the overall cross-sectional data (Fig. 3.4B).

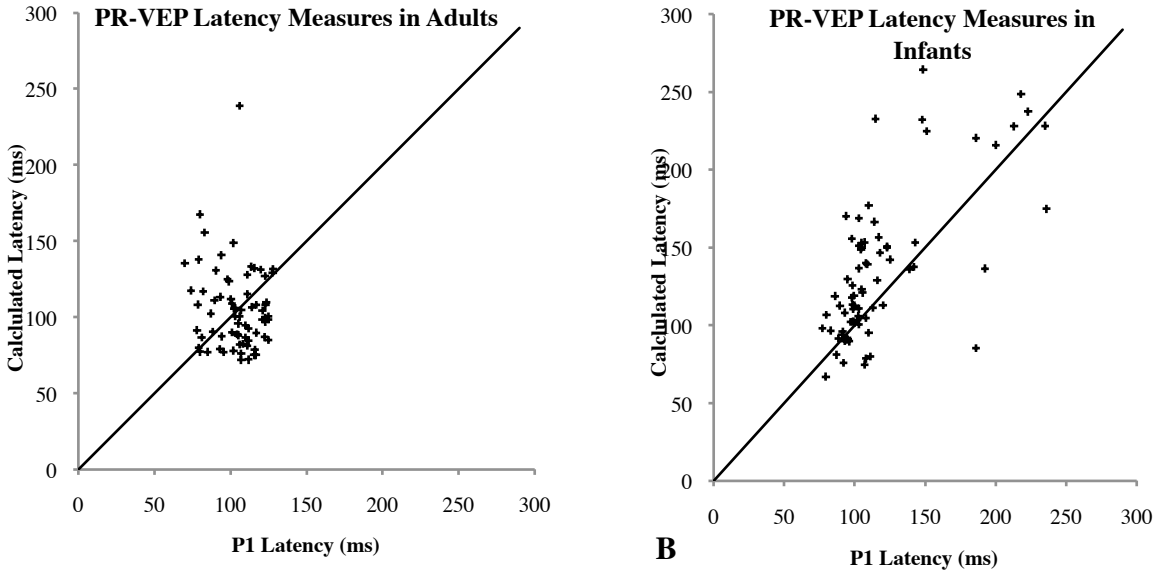


Fig. 3.4: Scatter plot of transient peak latency versus calculated latency in (A) adults (N= 71, R^2= 0.01) and (B) infants (N= 74, R^2= 0.4). The linear relationship primarily reflects the significant effect of age on both measurements. The 45° angle line shows equality of

the latency measures (slope of 1) so that for points above this line, the calculated latency is greater than the measured P1 latency.

The infants were divided into ten age groups (Table 3.1). RM-ANOVA using all the age groups as a between-subjects factor confirmed a significant overall difference between the two latency methods ($F(1, 64) = 4.5$, $P = 0.04$), and a significant interaction effect of method and age groups ($F(9, 64) = 2.8$, $P = 0.01$). Nonetheless, both P1 and calculated latency decreased with age, from mean latency of about 215ms at 3.6 weeks to 86ms at 80 weeks of age. Although P1 latency seems to decrease at a faster rate, post hoc analysis (Games-Howell) revealed both latencies merged at 50 weeks ($P > 0.1$) (Fig. 3.4).

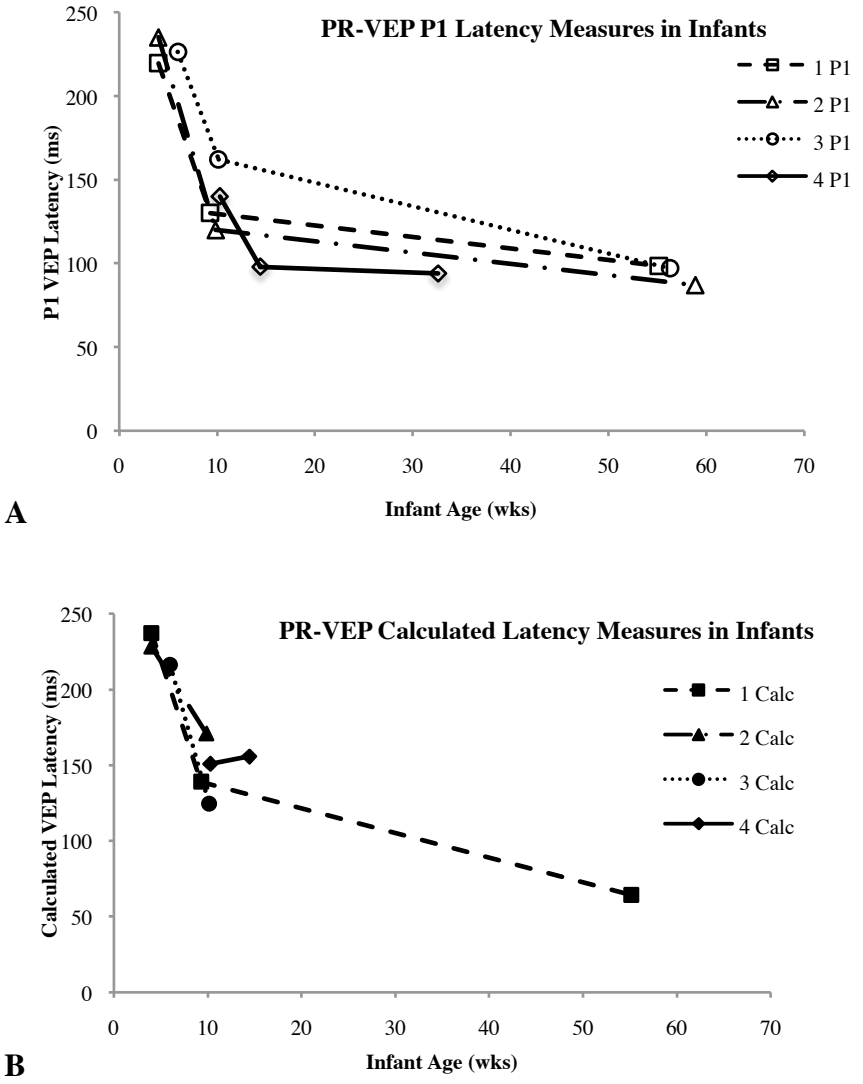


Fig. 3.5: Longitudinal data of (A) P1 and (B) calculated latency of PR- VEP from four infants (marked 1, 2, 3, 4 in key) with four repeated sessions at different ages, resulted in 2-3 data points per individual infants.

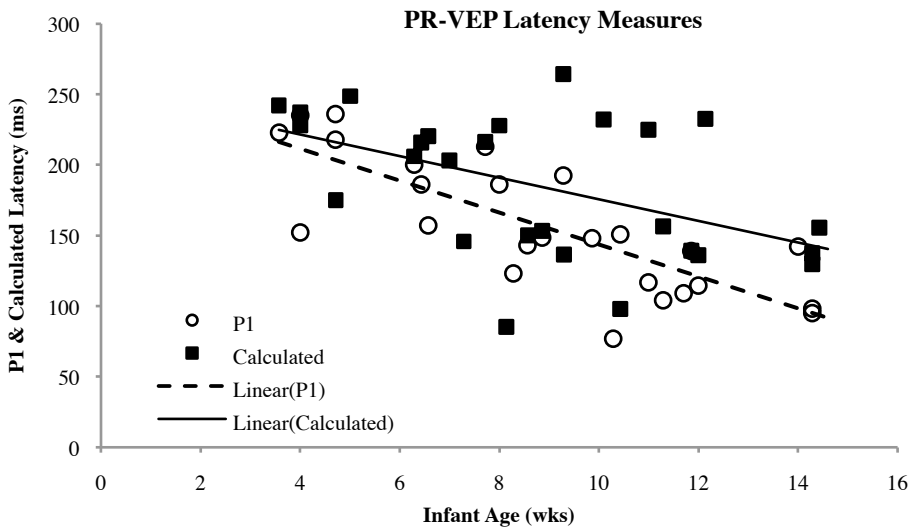


Fig. 3.6: Linear regression for infants <15 weeks of age showed that the transient latency decrease at about 11.6 ms/wk (P< 0.001), and the calculated latency decreases at about 7.6 ms/wk (P= 0.01).

3.3.3.3 Comparison between adults and infants

Calculated PR latency was found to be significantly longer than transient latency in infants but not in adults. The infant data showed overall higher variance than the adults', especially the infants' calculated latency.

Post hoc analysis (Games-Howell) revealed that the infant transient peak latency was significantly different from adult values until 15 weeks of age (P< 0.001). Infants' phase-based calculated latency was significantly different from adults' until 30 weeks of age, (P< 0.001) (Fig. 3.4). Latencies were significantly different from adults at all younger ages.

As the latency of transient VEP is not significantly different from adults' after 15 weeks, linear regression was fitted between latency and age over the range of 3.6 to 14.4 weeks. This is in line with other published practice (Fiorentini et al., 1991; McCulloch et al., 1999; Morrone et al., 1996) (Fig. 3.6). The latency values showed a significant downward trend for both transient ($r= 0.8$, $F(1, 23)= 41.4$, $P< 0.001$, latency= -11.6* age + 261.8) and calculated latency ($r= 0.5$, $F(1, 25)= 7.9$, $P= 0.01$, latency= -7.6* age+ 252.1). While the transient latency decreased 11.6 ms per week, the calculated latency decreased 7.6 ms per week for the first 15 weeks of life (Lee et al., 2012a).

3.4 Discussion

We obtained response latencies for PR-VEP in both adults and infants through two methods: transient peak latency for the first positive peak in the waveform and calculated apparent latency from relative phase measurements.

3.4.1 Transient P1 latency

The traditional P1 latency from transient VEP reflects the arrival time of the visual stimulus at the visual cortex from the eye. The elapsed time represents early retinal processing of contrast; transmission through optic nerve, tract, and radiation; and sufficient activation of visual cortical cells in the feed-forward pathway to generate postsynaptic currents for a large-scale synchronization to be detected at the scalp (Wood & Allison, 1981; Tobimatsu et al., 2006). While studies have found P1 to arise from area V1 and its surroundings, the precise area of origin of adults' P1 within the occipital lobe is not fully resolved (Bodis-Wollner et al., 1997; Bonmassar et al., 1999; Di Russo et al.,

2007).

3.4.2 Phase-based calculated latency

Similar to others (Fiorentini & Trimarchi, 1991; Di Russo & Spinelli, 1999; Porciatti, 1984; Simon, 1992; Tobimatsu et al., 1991), our data could be well fitted with a single regression line. Some published data have been fitted by different gradients in the low versus high TF ranges: in infants (Morrone, et al., 1996), in young adults (Tobimatsu et al., 1993), in older adults (mean age 72) (Porciatti et al., 1992), and in rats (Pizzorusso, et al., 1997). However, the discontinuities in these studies seemed to occur around 20-30 r/s, above the TF range (1-19.2 r/s) used in this study. Moreover, careful examination revealed that some 'split slopes' in the cited studies were so close that the full range could also be well fitted by a single regression line. This suggests that across the range 1-19 r/s, our measured VEPs are most likely to be driven by a comparable population of neurons.

3.4.3 Latency Development

Similar to Moskowitz and Sokol's (1983) findings, VEP morphology in our data develops from a single late positive peak at birth to an adult-like double peak-and-trough complex. While the transient latency asymptoted to the adult value at 15 weeks, the calculated latency did not reached adult values until around 30 weeks. The two latencies then merged at about 50 weeks of age (Fig. 3.3B) (Lee et al., 2012a).

While both transient and calculated methods yielded latency approaching 100 ms in adults, the calculated measure was significantly longer in comparison to the transient

value in infants. Linear regression for the first 15 weeks showed that the calculated latency decreases at about 7.6 ms/wk and transient peak latency decreases at about 11.6 ms/wk (Lee et al., 2012a).

3.5 Summary

Our results showed that a single linear slope fitting a phase versus temporal frequency plot is an effective approach for calculating apparent latency in both adults and infants. From the P1 peak latency comparisons, infants showed two types of functional changes in development that are reflected in the temporal properties of the PR-VEP. First, the dramatic reduction in the transient peak latency during the first 4 months of life can be attributed to the progressive development of conduction time in the afferent visual pathways and concurrent maturation of synaptic transmission within the visual pathway and cortex. The adult value is reached around 15 weeks of age for low spatial frequencies. Second, the maturation of later cortical processing (including feedback loops, recurrent processing, and horizontal connections) that contributes to the overall VEP waveform, and hence to the latency calculated for relative phase, has a slower developmental rate. For this latter measure, the adult value is reached around 30 weeks. The two latencies began to merge around 50 weeks of age. However, the similarity of calculated and transient latency in adults implies that in the mature system, the timing of the cortical response may be mostly dominated by transmission delays that determine the timing of the initial transient. Better understanding of the factors determining latency measures of the PR-VEP during development will help to interpret the relation between normative baselines and individuals' results in future clinical evaluations.

4 ORIENTATION-REVERSAL VEP

4.1 Background

Most of the current literature focuses on the Pattern or Phase Reversal (PR) VEP, which tests responses to contrast. However, because PR produces responses at the retinal level in on- and off- ganglion cells (Kuffler, 1953), the PR response, while indicating that contrast signals have arrived at the cortex, need not necessarily reflect processing at the level of the visual cortex.

Orientation-specific responses, however, can be generated only in the primary visual cortex and in further extra-striate areas (Hubel & Wiesel, 1962). Orientation detection is essential for object recognition. The onset of cortical orientation selectivity has been assessed by the use of orientation-reversal (OR) VEPs. The orientation-reversal stimulus, introduced by Braddick et al. (1986), uses a grating whose orientation switches between 45° and 135°. The OR stimulus sequence includes 'jitter', or random phase shifts of the grating at a higher frequency than these switches, which can be filtered out later to isolate response components that are specific to orientation changes. Infants show VEP responses to the OR stimulus at 3 reversals/second (r/s) at 3-4 weeks and to 8 r/s steady state VEP at about 8 weeks (Braddick, 1993). This frequency dependence indicates that the dynamics of the cortical orientation response change with development.

The experiments described in the previous chapter confirmed earlier findings that the latency of the first positive peak in the transient PR response decreases rapidly with age, and provided new information of a somewhat more prolonged decrease for the PR latency calculated from phase values. This chapter

will consider the developmental course for the OR-VEP, which has not yet been studied. In addition to revealing aspects of underlying cortical processing, OR-VEP has a strong clinical value as an indicator of cerebral development. It has been strongly correlated to changes seen on neonatal images in children with focal brain injury (Mercuri et al., 1996) and hypoxic-ischaemic brain damage at term (Mercuri et al., 1997) and predicts later neuro-developmental outcome of this group when the infants turned two years of age (Mercuri et al., 1996). OR is also a better indicator than PR for visual and neurocognitive development of prematurely born infants with white matter injuries (Atkinson et al., 2008; Lee et al., 2011).

Identifying the latency of the first positive peak in the VEP responses requires transient recording at low temporal frequencies. This latency reflects the initiation of cortical processing. Another latency measure uses the phase versus frequency plot (Chapter 3, Lee et al., 2012a; Regan, 1966; Spekreijse, 1978). This measure is derived from the waveform as a whole, and so reflects the overall cortical dynamics of the response, not just its initiation. The present study measured both the transient P1 latency and the calculated latency from the phase versus frequency plot, in the same adult and infant participants.

This chapter investigates: (1) the relation between calculated and transient peak latencies in the response to orientation reversal; (2) the relative timing of the orientation (OR) and contrast (PR) responses; and (3) the relationship between the developmental courses of PR and OR latencies. The detailed analysis of the two methods for adults' and infants' latencies for PR has been presented in the previous chapter and in Lee et al (2012a).

4.2 Methods

Please refer to chapter 2 for detailed descriptions for methods and materials used throughout this thesis.

4.2.1 Participants

Eight-one adults (median age 21, range 16- 43 years) with normal or corrected to normal vision were tested. Ninety-four full term infants (4.0- 79.0 weeks) born within 14 days of their due date were tested (Table 1). Many of these participants also provided data for the PR study of chapter 3; the detailed comparison of these two responses is discussed in chapter 6 and in Lee et al., 2013b. In addition to the 94 infants recruited for this study, the transient peak latencies of OR responses at 4 r/s were analysed from the data collected from 123 infants (4.0- 20.3 weeks) tested previously (Braddick et al., 2005).

4.2.2 Stimulus

The OR stimulus is based on that of Braddick et al (1986 & 2005). Both the OR and the PR stimuli consisted of sine wave gratings with a spatial frequency of 0.24 c/deg, mean luminance of 32 cd/m^2, and a contrast of 93%. The grating orientation in the OR stimulus alternated between 45° and 135° at the reversal frequency. The grating underwent random phase shifts at a rate of 25 per second between the orientation changes.

4.2.3 VEP recording

For the transient VEPs, each adult was recorded at 1, 2, 3, and 4 r/s, while each infant was tested only at 2, 3, and 4 r/s. As for the PR recordings, because each recording contained two complete cycles, the total recording epoch is 2 s for 1 r/s, 1s for 2 r/s, 0.5 s for 4 r/s, etc.

For the steady-state VEPs, up to seven different temporal frequencies at 1, 2, 3, 4, 6, 8, and 12 r/s were used in adults. In infants, up to five different temporal frequencies at 2, 3, 4, 6, and 8 r/s were tested.

4.2.4 VEP analysis

4.2.4.1 Transient P1 latency

For the transient analysis, the recorded responses were "dejittered" by using a MATLAB script that Fourier-transformed the averaged waveform and removed the component at the jitter frequency (25 reversal /sec) and its harmonics at 50 and 100 Hz. Fig. 4.1 illustrates examples of the waveform before and after this dejittering process. The time of the first positive peak values from the dejittered waveform were manually selected for the low temporal frequencies (adults- 1, 2, 3, 4 r/s; infants- 2, 3, 4 r/s).

4.2.4.2 Phase-based calculated latency

Calculated latency did not require dejittering, since it was derived only from the component of the response at the reversal frequency. Instead, the phase values of this response component at all tested reversal frequencies were analysed. Phase

values were 'unwrapped' using the same procedure as described in Chapter 2, and the latency calculated from the slope of the regression line using the same formula:

$$Latency(ms) = -(\frac{Phase\Delta}{TemporalFrequency\Delta}) \times (\frac{1000}{360°}) - 45msSoftwareDelay$$

4.3 Results

4.3.1 Response rate

The OR responses have a generally lower amplitude than PR, and so a reduced number of participants gave usable results. Out of a total of 81 adults, 66 (81.5%) adults had significant components at the reversal frequency at frequencies used for transient measurements, 64 (79.0%) for calculated latencies, and 62 adults (76.5%) for both the transient and calculated latencies. Among the 94 infants tested in the present study, 83 infants (88.3 %) showed significant responses for transient measurements while 58 infants (61.7%) yielded calculated latency values. Fifty-five infants (58.5%) yielded data for both the transient and calculated latencies. An additional 123 infants tested at 4 r/s from the study of Braddick et al. (2005) were incorporated into transient data for subsequent analysis, making a total of 217 infants (Table 4.1). For the calculated latency analysis, 18 out of the 58 infants yielded phase measurements from significant responses at only two temporal frequencies.

Age (wks)	Tested	Transient	Calculated	Transient & Calculated
4-4.9	7	6	0	0
5-9.9	61	54	5	4
10-14.9	53	52	9	9
15-19.9	24	20	10	10
20-29.9	25	22	15	13
30-39.9	16	14	9	9
40-49.9	13	10	3	3
50-59.9	10	9	4	4
60-69.9	4	4	1	1
70-79.9	4	4	2	2
Infants Total	217	195	58	55
Adults Total	81	66	64	62

Table 4.1: Age distribution of participants and response rate: number of infants in each of the 10 age groups and number of adults with significant components at the reversal frequency in transient, calculated, and both transient and calculated latencies.

4.3.2 Transient versus calculated latencies

4.3.2.1 Transient P1 latency

In adults, the raw VEP waveform (before dejittering) showed no peak response to the orientation reversal that could be distinguished from the jitter responses (see the example in Fig. 4.1). For the infants, on the other hand, a prominent peak for the orientation reversal was clearly identifiable (presumably because the infants had a weaker response to the high frequency jitter). After the components at the jitter frequency and its harmonics (multiple of 25 Hz) were removed, OR-VEP waveforms showed features similar to the classical PR responses in both participant groups, as they all displayed prominent P1 peaks (Fig. 4.1). Similar to the case for PR (Chapter 3, Lee et al., 2012a),

the transient P1 latency is much longer in infants (Fig. 4.1).

In adults, one-way ANOVA (Welch) showed no significant variation among the latencies of this peak measured at different low temporal frequency values (1, 2, 3, & 4 r/s; $F(3, 116) = 2.0$, $P = 0.1$). In infants, ANOVA (with age group as a between-subjects factor) yielded non-significant latency differences among the low temporal frequencies used in the analysis of transient latencies (2, 3, & 4 r/s; $F(2, 47) = 2.1$, $P = 0.1$). The interaction between the 10 age groups and temporal frequency was also not statistically significant ($F(14, 219) = 1.1$, $P = 0.4$). For the subsequent analysis, therefore, the transient latency was taken as the average of the results at four temporal frequencies in each adult and three temporal frequencies in each infant.

4.3.2.2 *Phase-based calculated latency*

In both adults and infants, the slope method proved effective in calculating the apparent latency (Fig. 4.2). For the 1 - 9.6 r/s tested in the present paper, a good linear fit (high R^2) for phase versus temporal frequencies was found, consistent with the findings for the PR latency (Di Russo et al., 1999; Chapter 3, Lee et al., 2012a; Fiorentini et al., 1991; Porciatti, 1984; Porciatti et al., 1992; Tobimatsu et al., 1991). Repeated-measures ANOVA indicated that the OR response showed a significantly longer calculated latency than peak latency for both adults ($F(1, 61) = 174.5$, $P<0.001$) and infants (with age group as the between-subject factor, $F(1, 46) = 44.5$, $P< 0.001$) (Fig. 4.3B).

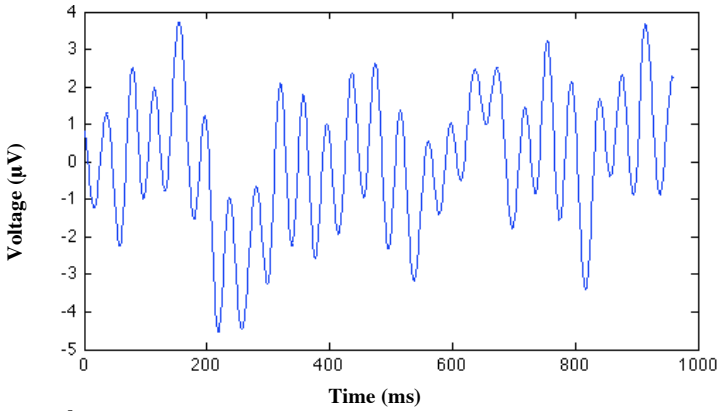


Fig. A1

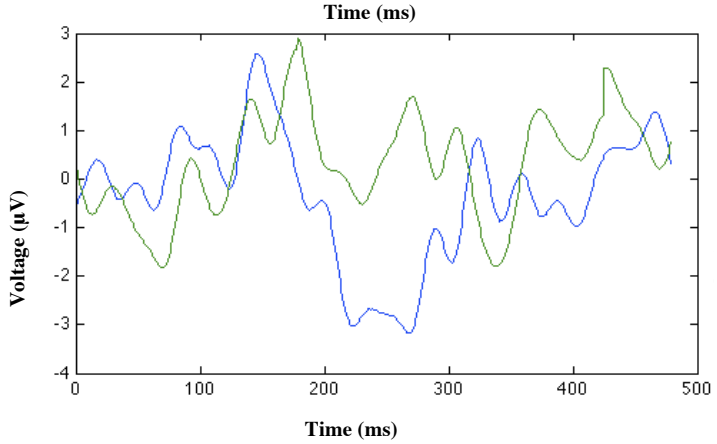


Fig. A2

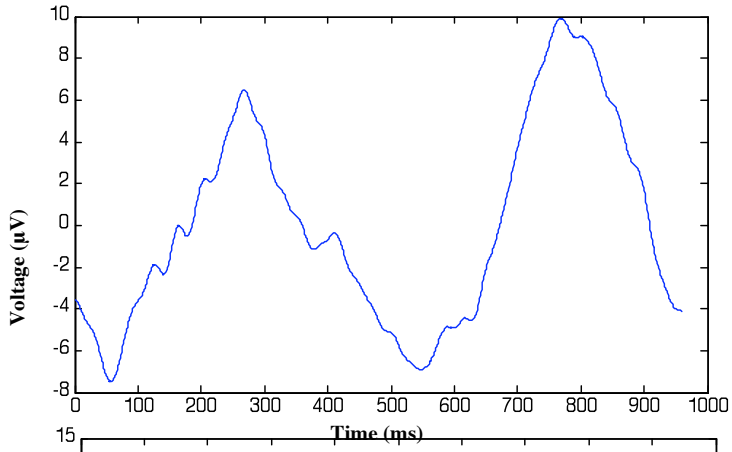


Fig. B1

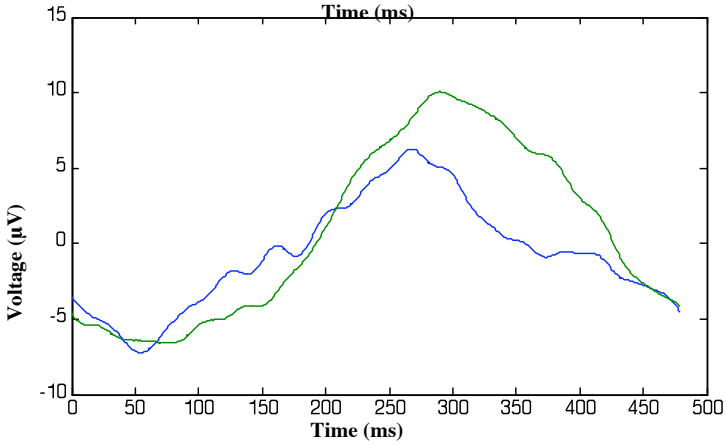


Fig. B2

Fig. 4.1: Example samples of OR-VEP waveforms. A1 is a sample from an adult at 2 r/s, showing two cycles of orientation reversal. The jitter response was prominent at 25 /s. (A2) is the result of Fig. A1 after filtering out the jitter frequency and its harmonics. The two superimposed traces in A2 represent the first and second halves of the record, illustrating the consistency of the waveform with an average peak transient latency of 100 ms from the two cycles (45 ms was subtracted due to systematic software delay). Similar to A1 and A2, B1 and B2 illustrate the OR response at 2 r/s from a 6.6-week old infant with a peak at an average of 240 ms. Transient latency was selected manually by placing a cursor on the most prominent P1 of each the two averaged cycles.

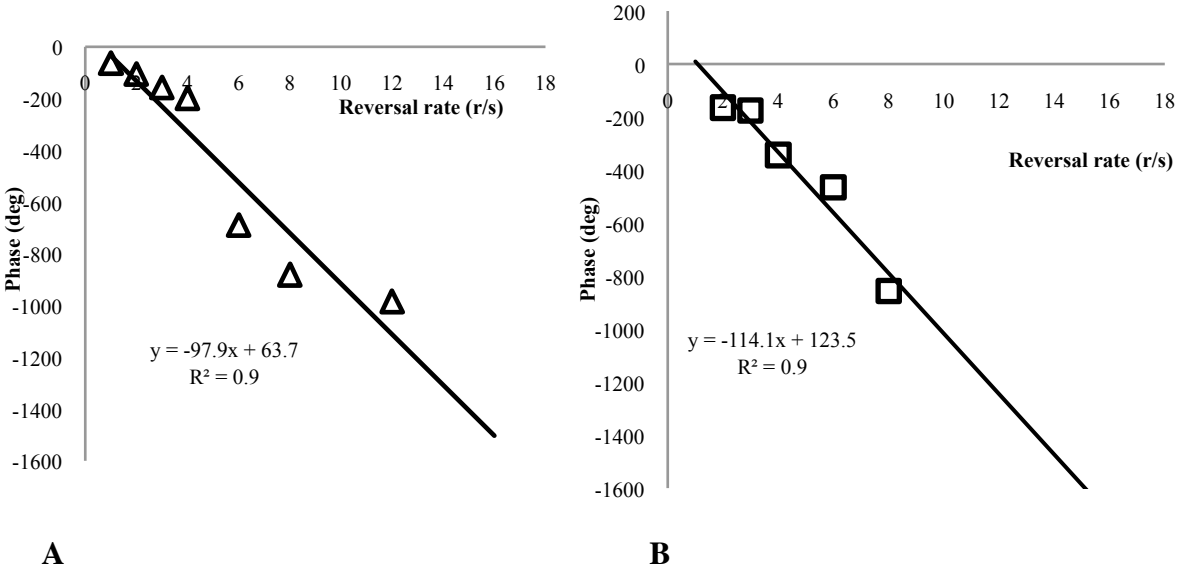
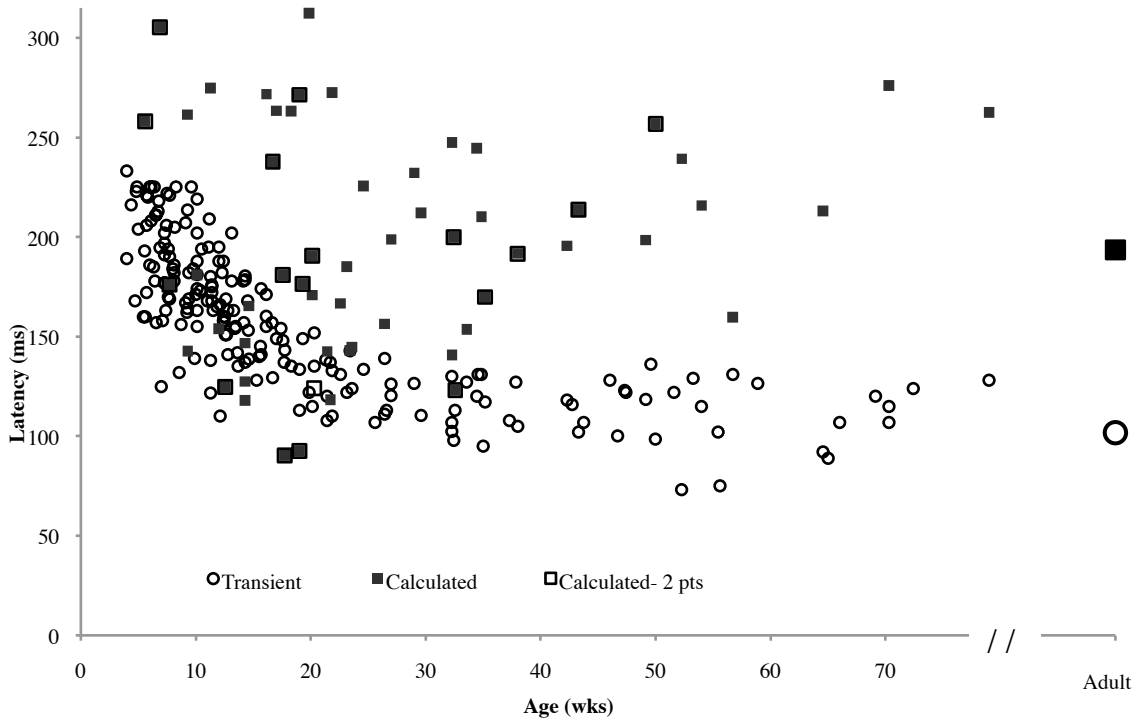
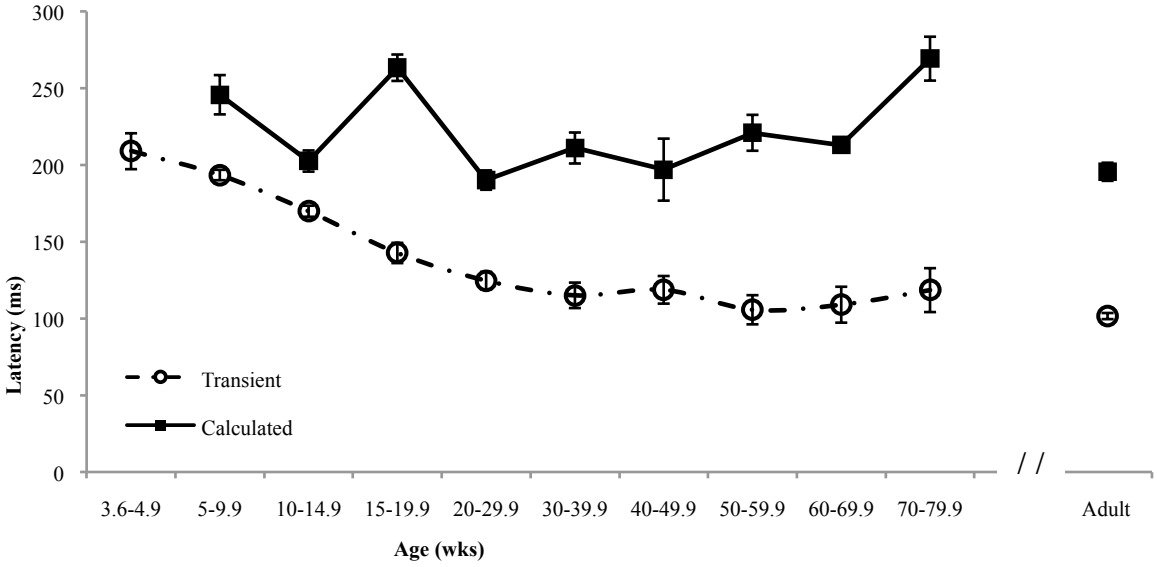


Fig. 4.2: Illustration of the slope method to calculate apparent latency for an adult (A) and a 16-week-old infant (B). The adult was tested with seven different TFs from 1-12 r/s (R^2= 0.9, slope= -97.9, latency= - (-97.9)* 1000/ 360- 45= 226.9 ms; 45 ms was the correction for software delay). For this study, the infants were tested with five different

TFs from 2-8 r/s. The 16-week-old had R^2= 0.9, slope= -114.1°/reversal rate, latency= - (-114.1)* 1000/ 360- 45= 271.9 ms.



A



B

Fig. 4.3: Transient and calculated latency in infants as a function of (A) continuous age range (all infants) and (B) 10 age groups (mean± SE). Small open circles represent transient P1 latency while the small filled squares represent phase-based calculated latency. In (A) the data points obtained from calculated latencies from only two frequencies have been plotted with small open square symbols to illustrate that they are consistent with the values obtained from fuller data sets. The mean transient P1± SE (102.0 ± 2.0 ms; large empty circles) and mean calculated latency ± SE (195.6 ± 5.9 ms; large filled squares) values of adults have been added for comparison.

4.3.3 Adult versus infant latencies

4.3.3.1 Adults

The mean transient peak latency for OR ± SE (101.4 ± 2.0 ms) was significantly lower than the calculated latency of OR (193.3 ± 6.3 ms), using Repeated-measure-ANOVA ($F(1, 61)= 174.5$, $P<0.001$) (Fig. 4.4A). This contrasts with adults' PR responses (Chapter 3, Lee et al., 2012a), where the transient peak latency and calculated latency were similar.

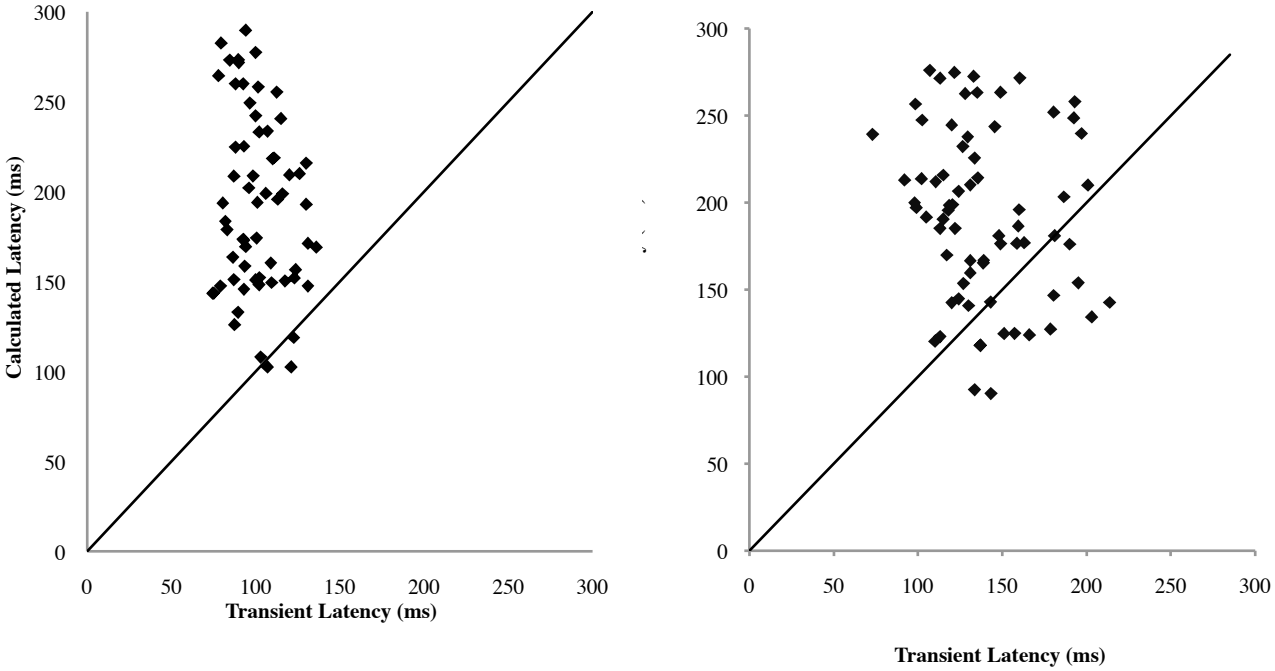


Fig. 4.4: Scatter plot of calculated phase-based latency against transient P1 latency in (A) adults (N= 62, R^2= 0.03) and (B) infants (N= 72, R^2=0.03). The 45° angle line shows equality of the two latency measures (slope of 1); so that for points above this line the calculated latency is greater than the measured P1 latency.

4.3.3.2 Infants

The infants were divided into ten age groups (Table 4.1). Repeated-measures-ANOVA (age as a between-subjects factor) revealed significant differences between the transient and calculated values (F (1, 46)= 44.5, P< 0.001) (Fig. 4.4B) and a significant interaction effect of method and age groups (F (8, 46)= 2.4, P= 0.03). Figure 4.3A shows individual data points and Figure 4.3B the mean for each age group to illustrate this comparison. This difference between the two measures of latency was also found in the

OR adult data and in the infant data for PR (Chapter 3, Lee et al., 2012a). Similar to PR (Chapter 3, Lee et al., 2012a), OR-VEP latencies were prolonged in infants compared to those of adults, as shown in the example waveforms of Figure 4.1 (Lee et al, 2012b).

As found for PR (Chapter 3, Lee et al., 2012a), calculated latency can be derived using as few as two temporal frequencies. In infants, ANOVA (with age as a covariate) was performed to compare the calculated latency derived from the 26 infants having results from only two temporal frequencies versus those infants with more than two temporal frequencies. No significant difference between results obtained from the two methods was found ($F(1, 18)= 0.3$, $P= 0.6$) nor any significant interaction between age and method ($F(6, 60)= 0.4$, $P= 0.9$) Figure 4.3A shows data from these two groups of infants with distinctive data points.

4.3.3.3 Comparison between adults and infants

For both infants and adults, the calculated OR latency was significantly longer than transient latency. In PR, however, no difference between the transient and calculated latencies was found in adults (Chapter 3, Lee et al., 2012a).

Post-hoc analysis (Games-Howell) revealed that the infant transient latencies were not significantly different from adult values after 50 weeks of age ($F(1, 84)= 3.4$, $P= 0.07$). The infants' calculated OR latencies were not significantly different from adult values after 80 weeks of age ($F(1, 151)= 0.7$, $P= 0.4$) (Figs. 4.3A & B).

As the mean latencies suggest that most of the drop in the transient latencies occurs within the first 30 weeks of life (Figs. 4.3A & B), linear regression was fitted

between latency and age over the age range from 3.6 to 30 weeks (Fig. 4.5). The latency values showed a significant downward trend for the transient latency only ($r = 0.8$, $F(1, 177) = 262.4$, $P < 0.001$), with latency decreasing at 4.2 ms/ week over this period.

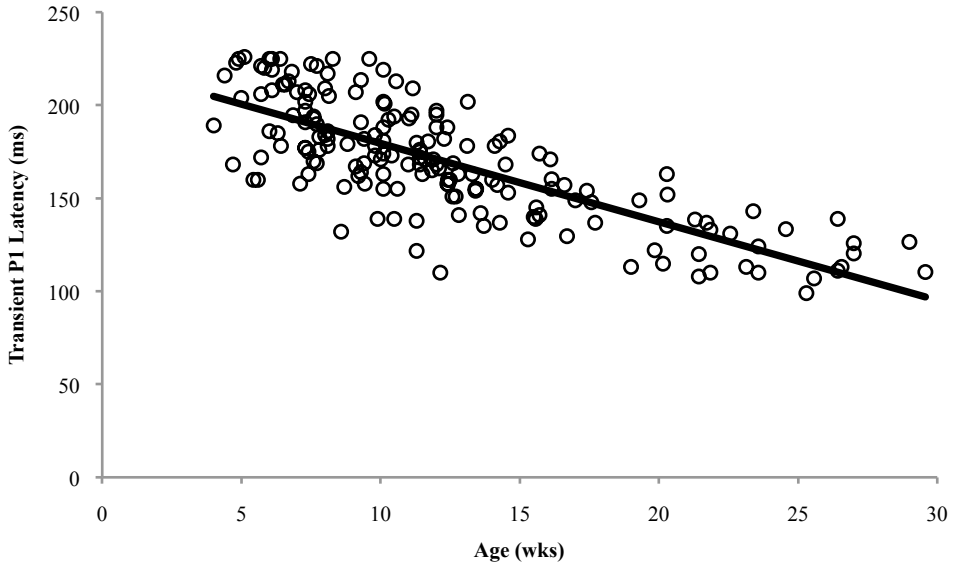


Fig. 4.5: Linear regression for infants less than 30 weeks of age showed that the transient latency decreases at about 4.2 ms/wk ($r = 0.8$, $P < 0.001$; latency= -4.2* age+ 221.6).

4.4 Discussion

We obtained a normative baseline of response latencies to orientation change in both adults and infants through two different methods– transient P1 and phase-based calculated latencies.

4.4.1 Transient P1 latency

The dejittered transient response of OR-VEP closely resembles the classical PR-VEP responses (Fig. 4.1). P1, around 100 ms, was prominent in both PR and OR (Lee et al., 2012b). The adults showed similar P1 latencies for both stimuli. This suggests that this component of each response arises at a similar level in the processing pathway. This is consistent with physiological data from monkeys, which has shown the earliest impulses in V1 cells to be orientation selective (Celebrini et al., 1993).

4.4.2 Phase-based calculated latency

Unlike the transient P1 latency which reflects the time needed to elicit the initial response at the occipital lobe, the phase of the fundamental component, hence the calculated latency, is derived from the whole waveform and so reflects the overall time course for the entire VEP response. In adults, this calculated latency (~200 ms) was almost twice as long as the transient P1 latency (~100 ms) (Fig. 4.4A) (Lee et al., 2012b). The longer OR latency (150-200 ms) has also been found in the VEP generated by the onset of orientation-defined texture segregation (Lachapelle et al., 2008).

The need to introduce jitter into the OR stimulus means that the orientation-specific response must be associated with neurons having a component of their response that is invariant with spatial phase (Braddick, 1993), a characteristic of complex cells (Movshon et al., 1978; Pollen & Ronner, 1982). Some of the differences in OR and PR responses, and their development, may therefore reflect differences in response properties between simple and complex cortical cells. There may be a later maturation of complex cells required for the phase-invariant OR response, consistent with the developmental

trend for higher temporal frequency OR response to emerge later than the response to lower temporal frequencies (Braddick, 1993). Simple cells and X-type optic radiation afferents, whose spatially linear response is dependent on spatial phase, may play a larger role in determining the PR response.

There are many interactions that may contribute to the temporal course of the orientation-selective response. Orientation responses can be enhanced by cells with similar preferred orientations in two ways: (1) from the summation of cell responses with slightly different orientation tuning; (2) by inhibition from cells with different preferred orientation (Ferster & Koch, 1987). In addition to activation of V1 through feed-forward processes, feedback loops and horizontal connections may play important but different roles in determining the calculated latencies for different visual stimuli (Gilbert & Wiesel, 1989; Lamme & Roelfsema, 2000; Lund & Levitt, 1996). Orientation-selective pattern masking is believed to reflect inhibitory interactions in cortex; such masking has been found in infants around 3 months of age for cross-oriented stimuli and for same-orientation by about 5-6 months (Candy et al., 2001; Morrone & Burr, 1986).

4.4.3 Latency development

4.4.3.1 Transient P1 Latency

VEP latency proved to be a more sensitive indicator of visual development than measures related to amplitude. No significant age changes have been found for SNR and amplitude of transient and steady-state OR-VEPs in 5-18 week-old infants (Braddick et al., 2005; Birtles et al., 2007). This study, however, demonstrated a clear latency decrease

in the first year of human life. Infants' transient P1 latency asymptoted to the adult value at about 50 weeks of age. Although Fig. 4.3B shows that it appears to approach the adult value as early as 30 weeks, it remains statistically different from the adults for all age groups under 50 weeks (Lee et al., 2012b). Similar to PR (Chapter 3, Lee et al., 2012a), the P1 latency decrease could be because of the progression of myelination with age (Dubois et al., 2008; Kos-Pietro et al., 1997; Tsuneishi & Casaer, 1997).

4.4.3.2 Phase-based calculated latency

Unlike the transient P1 latency, the relatively invariant calculated latency of the OR response within the first 18 months of life in infants showed little change (Lee et al., 2012b). Cortical processing of orientation apparently involves stages beyond the initial response, such as recurrent processing by top-down feedback loops or long-range horizontal connections (Gilbert & Wiesel, 1989; Lund & Levitt, 1996), which introduce additional delays and do not become significantly faster in the course of development.

4.5 Summary

The differences in the timing of VEP responses between infants and adults indicate functional and possibly structural changes during development. Detection of pattern reversal develops earlier than orientation reversal, possibly reflecting later maturation of complex cells required for the phase-invariant OR response, compared to simple cells in V1. During infancy, the peak latency depends on the transmission delay resulting from the immature physiology, for example incomplete myelination. The initial peaks in both contrast and orientation responses may arise from the same level of cortical processing.

In OR, we suggest that the lack of change between infants and adults results from the important contribution of later cortical processing to the temporal response and the overall waveform throughout development.

5 DIRECTION-REVERSAL VEP

5.1 Background

The previous chapter examined the timing of the VEP arising from orientation-specific responses of cortical neurons. The inclusion of jitter in the OR-VEP meant that only cells with spatial phase invariance can respond at the reversal rate. Another important form of complex processing in visual cortex is direction-specific motion responses. To understand motion processing and its development, Wattam-Bell (1991) designed direction-reversal (DR) VEPs. While contrast responses can be achieved by simple cells within V1, directional responses arise mostly from orientation specific complex cells in V1 and MT/V5 areas (Milner & Goodale, 1995; Movshon & Newsome, 1996). DR can be used clinically to examine cortical development in premature infants (Birtles et al., 2007) and early dorsal-stream vulnerabilities (Braddick et al., 2003).

DR has lower amplitude (Braddick et al., 2005) but more sensitivity to age (Birtles et al., 2007) than orientation reversal (OR)-VEP. At 5.5°/s, the onset of DR response was around 10-11 weeks for 4 r/s (Braddick et al., 2005), which is about 6 weeks later than OR. Older infants were able to respond to higher and lower velocities (Wattam-Bell, 1996). The latency development of DR remains unknown.

The DR stimulus used in the present study includes a series of direction-selective components, or random changes of pixel array that are embedded in the local contrast changes (Wattam-Bell, 1996). Response at the jitter frequency can be filtered out to obtain a DR-specific response, whose peak latency can be measured (Wattam-Bell, 1996).

DR-VEP is an example of first order motion where motion perception is the result of the difference in luminance of the object from its background. First order motion began with orientation filtering in simple cells that respond to average luminance difference within a neuron's receptive field, acting as a linear filter (Baker et al., 2001). Direction selective filters like complex cells in V1 then summate the spatiotemporal sensitive simple cells, which can also be direction selective (Lamme et al., 1993).

The latency of VEP responses to directional change has not previously been studied. In this study, transient P1 latencies were measured using the low temporal frequency of 1-3 r/s while calculated apparent latencies were calculated from the slope across a much wider temporal frequency range (Chapter 3, Lee et al., 2012a). As in the preceding analyses of the timing of PR and OR responses, this chapter investigates: (1) the relation between the phase-based calculated and transient P1 latencies in DR-VEP and (2) the developmental courses of DR latencies as measured using both approaches.

5.2 Methods

Please refer to Chapter 2 for a detailed description of the methods used.

5.2.1 Participants

Sixty-one adults (median age 21.4, range 17-43 years) with normal or corrected to normal vision and visual acuity (20/20) and 76 healthy full term infants (7.0- 79.0 weeks) born within 14 days of their due date were recruited.

5.2.2 Stimulus

The DR stimulus was composed of a random pattern of 0.44° black and white pixels, where the pattern displaced horizontally at 5.5 deg/sec. A change between left and right directional shift, accompanied by replacement of the random pixel pattern, occurs at the designated reversal rate. Random replacement of all the pixels was introduced at twice the reversal rate.

5.2.3 VEP recording

For adults, up to eleven different temporal frequencies at 1, 2, 3, 4, 4.8, 6, 6.86, 8, 9.6, 12, and 16 r/s were used. For infants, up to five different temporal frequencies at 2, 3, 4, 6, and 8 r/s were tested. The electrode array and recording arrangements were as described in previous chapters.

5.2.4 VEP analysis

5.2.4.1 Transient P1 latency

To remove random contrast changes, i.e. isolate the component of the peak due to direction reversal, the second half of the recorded waveform, which contains the effects of random contrast changes without direction reversal, was subtracted from the first half of the VEP recording for one reversal cycle (reversal + random contrast changes) (Braddick et al., 2010). By dividing the DR record (which contains two reversals) into 4 chunks to perform this subtraction to remove the random contrast changes, the analyzed waveform can be recorded only up to 160 ms at 3 r/s (Fig. 2). Any peak after these times

would not be detected using this method. The timing to produce the highest positive peak values in this modified waveform was manually selected for the low temporal frequencies (adults-1, 2, and 3 r/s; infants–2 and 3 r/s).

5.2.4.2 Phase-based calculated latency

To calculate apparent latency, the phase of the second harmonic of the sweep frequency at each temporal frequency was measured. As there are infinite series of phase values separated by 360°, phase was unwrapped. The unwrapped phase values were then plotted against temporal frequencies. Finally, the slopes of their linear regression were converted into apparent latency by the formula:

$$Latency(ms) = -(\frac{Phase\Delta}{TemporalFrequency\Delta}) \times (\frac{1000}{360^\circ}) - 25msSoftwareDelay$$

5.3 Results

5.3.1 Response rate

Out of 61 adults that were tested, 29 (47.5%) adults yielded records from which peak latency could be obtained with a statistically significant response at the reversal frequency based on the Mann-Whitney U Test; 44 (72.1%) had significant phase measurements where latency can be calculated, and 24 (39.3%) had additional early transient P1s that were easily identifiable. In total, 26 (42.6%) adults had records that yielded both transient and calculated latencies, while 22 (36.1%) adults had records yielding three latencies (Table 1).

Among the 76 infants tested, 27 (35.5%) infants showed significant components at

the reversal frequency that yielded peak values, 37 (48.7%) yielded calculated latencies, and 13 (17.1%) infants showed additional early transient P1s. While 17 (22.4%) infants showed both transient and calculated latencies, only 9 (11.8%) infants had significant components at the reversal frequency for all three latencies (Table 1).

Age (wks)	Tested	Transient	Calculated	Early Transient	Transient & Calculated	All 3 Latencies
7.7-9.9	4	1	2	1	0	0
10-14.9	7	6	7	5	3	2
15-19.9	3	3	2	2	3	3
20-29.9	10	4	10	0	3	0
30-39.9	10	5	6	1	4	1
40-49.9	15	3	3	3	2	2
50-59.9	11	1	4	0	0	0
60-69.9	9	1	0	0	0	0
70-79.0	7	3	3	1	2	1
Infants Total	76	27	37	13	17	9
Adults Total	61	29	44	24	26	22

Table 5.1: Response rate – the number of adults and infants in each of the 9 age groups with significant components at the reversal frequency in transient, calculated, early transient, both transient and calculated, and all three latencies.

5.3.2 Transient versus calculated latencies

5.3.2.1 Transient P1 latency

The more prolonged waveform for DR compared to PR (Chapter 3; Lee et al., 2012a) and OR (Chapter 4; Lee et al., 2012b) meant that the response to a reversal was

not complete by 250 ms. In the 4 r/s recording, therefore, the transient peak was likely to be confounded with the response to the preceding stimulus, and this reversal rate, unlike for PR and OR, could not be taken as contributing to the estimate of transient latency; instead it has to be treated as a frequency for steady-state analysis only.

VEP waveforms from low temporal frequencies were more complex than the classical PR responses, in which the P1 peak is prominent and easily identifiable (Fig. 5.1). The mean latency of the P1 in adults' DR recordings is 125.6 ± 4.8 ms. 9/22 (40.9%) of the adults who showed significant transient responses also showed a more prominent early peak (with higher amplitude) at 91.7± 4.6 ms. 4/27 (14.8%) infants (12.4- 79.0 weeks) had the early transient peak being more prominent than the latter peak.

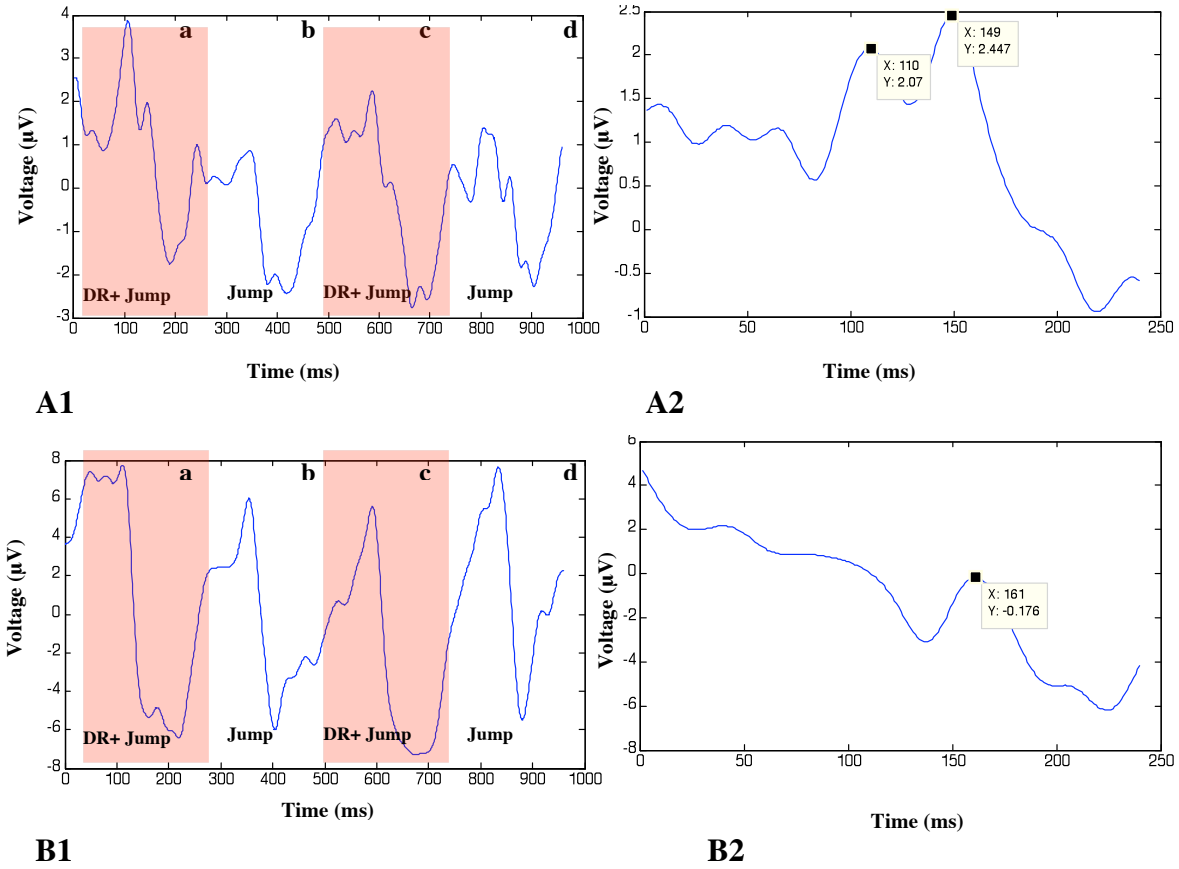


Fig. 5.1: Example samples of DR-VEP waveforms.

(A) An example of a DR response for an adult at 2 r/s: (A1) original response and (A2) filtered response after removing the random contrast changes or jumps. A2 is the result of subtracting sections within A1: (a + c) - (b + d). When the software delay of 25 ms was taken into account, the transient peak of the two averaged cycles was 149-25= 124 ms and the early transient was 110- 25= 85 ms. Transient latencies were selected manually by placing a cursor on the most prominent peaks of the two averaged cycles.

(B) A DR response at 2 r/s from a 12.6-week-old infant (B1), with an averaged peak of 137 ms (B2) and no significant early peak.

In adults using temporal frequencies as the within-subject variable, ANOVA (Welch) showed no significant differences between the transient latencies for DR at low temporal frequencies (1, 2, and 3 r/s; $F(2, 36)= 3.8$, $P= 0.1$), and for that of early peaks ($F(2, 42)= 0.1$, $P= 0.9$) at these frequencies. Similarly for the infant group, using age as a covariate, no significant difference was found between the transient latencies at 2 and 3 r/s ($F(1, 24)= 0.001$, $P= 0.98$), or for the interaction effect between temporal frequencies and age ($F(1, 24)= 2.2$, $P= 0.1$). For the early peaks in infants, the latencies at 2 and 3 r/s were not significantly different ($F(1, 13)= 0.6$, $P= 0.5$); nor was the interaction between temporal frequencies and age ($F(1, 13)= 2.1$, $P= 0.2$).

For the subsequent analysis, the average of P1 latencies at the three temporal frequencies in each adult and two temporal frequencies in each infant were defined as the transient latency. Unlike the phase and orientation- reversal responses (Chapters 3 & 4; Lee et al., 2012a & 2012b), 4 r/s gave the equivalent of a steady state response in the direction reversal stimulus. The DR response to 4 r/s started to exhibit quasi-sinusoidal waveforms rather than complete VEP waves with clear peaks and troughs in respond to individual stimulus events.

5.3.2.2 Phase-based calculated latency

In both adults and infants, the slope method proved effective in calculating an apparent latency value of 194.9 ± 6.2 ms (Fig. 5.2). For the eleven temporal frequencies ranging from 1-16 r/s, a single linear fit between phase and temporal frequencies was found. This was consistent with other studies of PR-VEP (Chapter 3; Di Russo &

Spinelli, 1999; Fiorentini et al., 1991; Lee et al., 2012a; Tobimatsu et al., 1991) and OR- (Chapter 4; Lee et al., 2012b). The absence of split slopes suggests that the difference between transient and calculated latency methods was not simply a result of different temporal frequency ranges, as in the parallel measurements for PR (Chapter 3; Lee et al, 2012a).

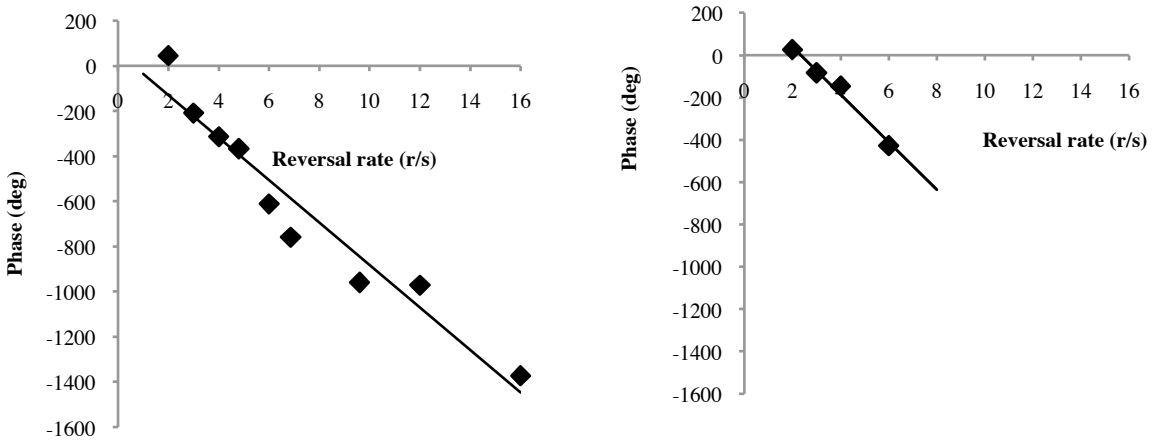
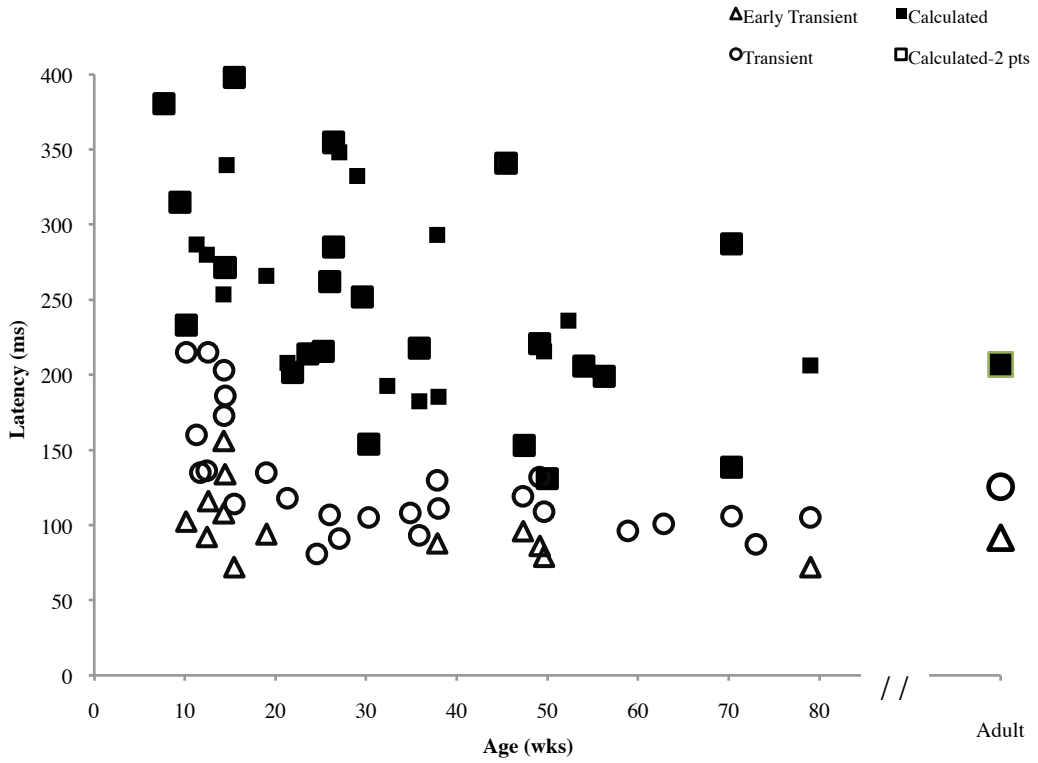
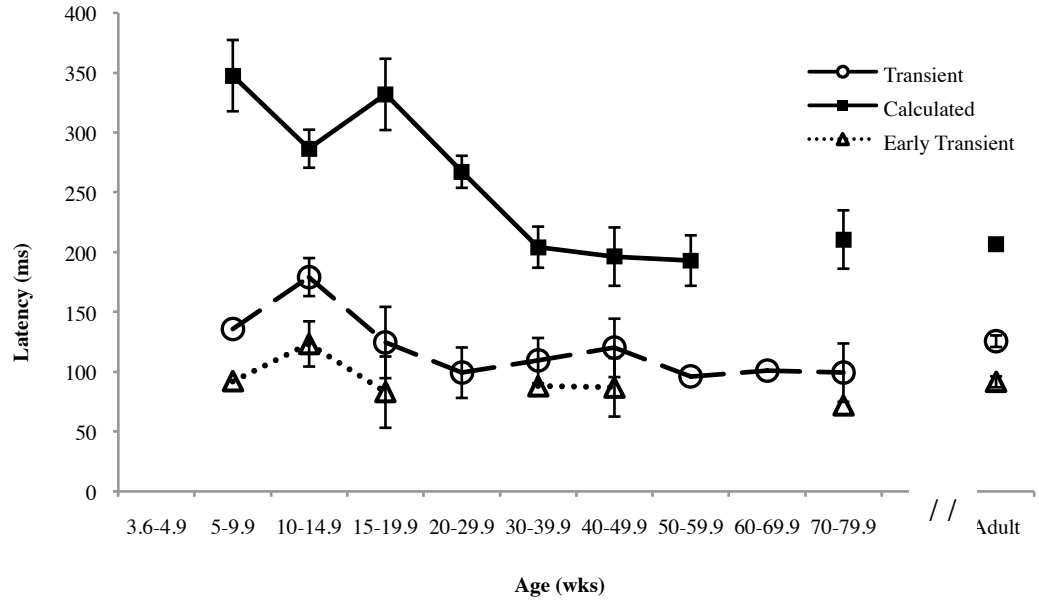


Fig. 5.2: Illustration of the slope method to calculate apparent latency for an adult (A) and an 11.3-week-old infant (B). This adult was tested with 9 different temporal frequencies from 1- 16 r/s (R^2= 0.94, slope= -94.1, latency=- (-94.1)* 1000/ 360- 25= 236.4 ms. 25 ms was the correction for software delay). The infant was tested with four different temporal frequencies from 2- 6 r/s. The 11.3-week-old had R^2= 0.98, slope= -112.3˚/reversal rate, latency= 286.9 ms.

Similar to PR (Chapter 3; Lee et al., 2012a) and OR (Chapter 4; Lee et al., 2012b), apparent latency can be calculated using merely two temporal frequencies. In infants, ANOVA (with age as a between subject factor) comparing the calculated latency derived from the 21 infants with only two temporal frequencies, versus those infants with more than two temporal frequencies, showed no significant difference between results obtained from the two data sets ($F(1, 31)= 0.04$, $P= 0.8$) nor any significant interaction between age and method ($F(1, 31)= 0.1$, $P= 0.7$) (Fig. 5.3A).


Early Transient
Calculated
Transient
Calculated-2 pts
Latency (ms)
400
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Adult
Age (wks)

A


Transient
Calculated
Early Transient
Latency (ms)
400
350
300
250
200
150
100
50
0
3.6-4.9
5-9.9
10-14.9
15-19.9
20-29.9
30-39.9
40-49.9
50-59.9
60-69.9
70-79.9
Adult
Age (wks)

B

Fig. 5.3: Transient and calculated latencies of DR-VEP in infants as a function of (A) continuous age range (all infants) and (B) 9 age groups (mean± SE). The average transient (125.6 ± 4.8 ms), calculated (206.8 ± 3.7 ms), and early transient (91.68 ± 4.6 ms) latencies from the adult group have been added for comparison.

5.3.3 Adult versus infant latencies

5.3.3.1 Adults

The mean transient P1 latency ± SE for the adults was 125.6 ± 4.8 ms, 91.7 ± 4.6 ms for the early transient peak, and 194.9 ± 6.2 ms for the calculated latency. Using latency methods as the within-subject variable, repeated-measure ANOVA (Greenhouse-Geisser) showed significant differences among the three methods ($F(2, 42) = 103.40$, $P < 0.001$) (Figs. 5.4 A & B). Calculated latency was significantly longer than the transient P1 latency ($F(1, 25) = 77.7$, $P < 0.001$). This was similar to the relationship in the adults' OR responses (Chapter 4; Lee et al., 2012b) but different from the case of PR (Chapter 3; Lee et al., 2012a).

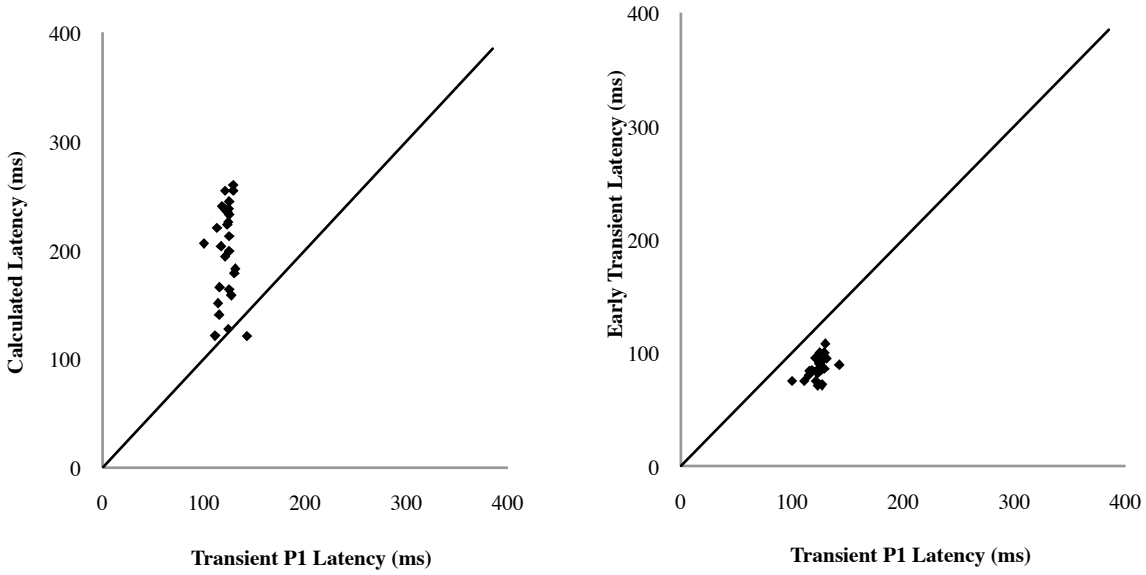


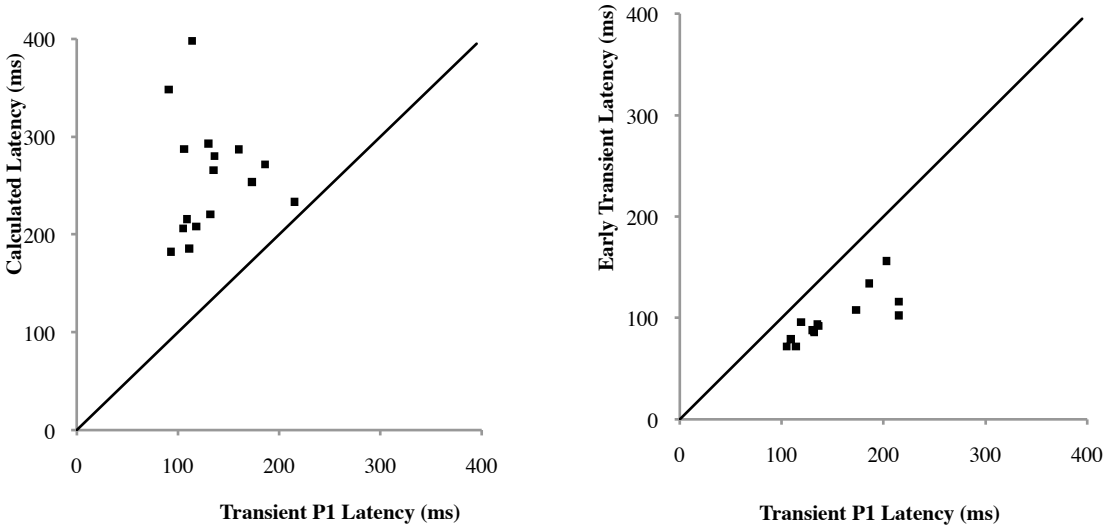
Fig. 5.4: Scatter plot of adult (A) calculated phase-based latency against transient P1 latency (N= 26, R^2= 0.0) and (B) early transient latency against transient P1 latency (N= 25, R^2= 0.2). The 45° angle line shows equality of the latency measures (slope of 1); so that for points above this line the calculated latency is greater than the measured P1 latency.

5.3.3.2 Infants

The transient response to DR was prolonged in infants compared to adults (Fig. 5.1), just as in the PR (Chapter 3; Lee et al., 2012a) and OR (Chapter 4; Lee et al., 2012b) studies. The onset of DR-VEP was around 7.7 weeks for the calculated latency and 10 weeks for the transient latency, much later than the 3-4 weeks for the OR (Braddick, 1993), and around birth for the PR responses (McCulloch et al., 1999; Moskowitz &

Sokol, 1983; Porciatti, 1984) but comparable with the findings of Braddick et al (2005) and Birtles et al (2007).

The infants were divided into nine age groups (Table 5.1). RM-ANOVA (age as a between-subjects factor) revealed significant effects of age on the transient P1, early peak and calculated latencies ($F(2, 8)= 49.6$, $P< 0.001$) but no significant interaction effect among the three methods and age groups ($F(8, 8)= 1.8$, $P= 0.2$) (Figs. 5.5A & B). Using latency methods as the within-subject variable, RM-ANOVA for the transient and calculated latencies also revealed a similar pattern: significant difference for the method ($F(1, 11)= 68.4$, $P< 0.001$) but not for the interaction between the two methods and the age groups ($F(5, 11)= 1.7$, $P= 0.2$).



A **B**

Fig. 5.5: Scatter plot of infant (A) calculated phase-based latency against transient P1 latency ($N= 16$, $R^2= 0.03$) and (B) early transient latency against transient P1 latency ($N= 11$, $R^2= 0.6$).

5.3.3.3 Comparison between adults and infants

Both adults and infants had significantly longer calculated latencies than their transient latencies. Post-hoc analysis (Games-Howell) revealed that the infant transient and early transient latencies were not significantly different from the adult values at the onset of the DR response, which is around 10 weeks of age, (P= 0.8). However, infant calculated latency was similar to adult values only after 30 weeks of age (P= 0.3) (Fig. 5.3B).

The average mean latencies in infants suggest that most of the drop in transient latencies was within the first 30 weeks of life (Figs. 5.3A & B). Linear regression was then fitted between latency and age from 10 to 27 weeks (Fig. 5.6). The latency values showed a significant linear trend for only the transient latency (r= 0.8, F (1, 14)= 17.4, P= 0.001, latency= -5.1* age + 235.6), with no such significant linear component for the calculated latency due its large variance.

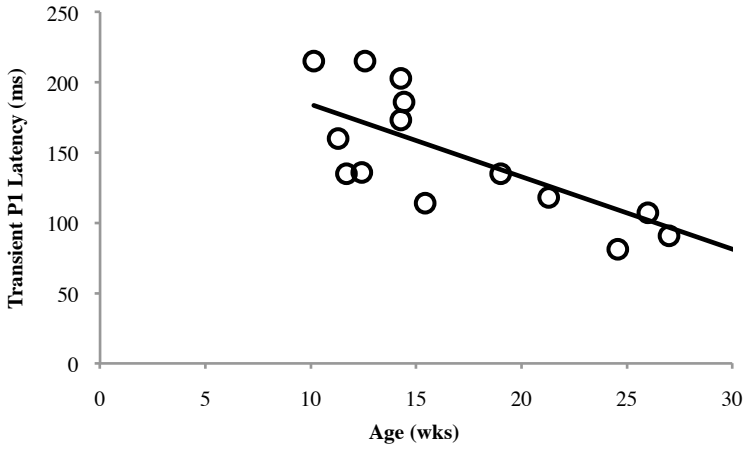


Fig. 5.6: Linear regression for infants less than 30 weeks of age showed that the transient latency decreases at about 5.1 ms/wk (r= 0.8, P= 0.001).

5.4 Discussion

Normative direction reversal-VEP responses and two different latency values were obtained from 61 adults and 76 infants under 18 months of age. The lower DR response rate, compared to PR and OR, could be the result of difficulty in attending to the DR stimulus and the smaller mean DR responses of 2.4 μV in comparison to PR's 3.2 μV and OR's 2.9 μV for adults. For infants the difference in amplitude is even larger, as DR produces 0.9 μV while PR has an average of 12.3 μV and OR has an average of 7.2 μV (Lee et al., 2013a).

5.4.1 Transient P1 latency

Unlike classical pattern-reversal responses in which the P1 peak, typically around 100 ms, is easily identifiable, the transient response of DR exhibited a peak with smaller amplitude around 126 ms in adults (Fig. 5.1). While 39.3% of the adults had an additional early peak around 92 ms, only 17.1% of the infants showed additional early peaks (Lee et al., 2013a). If we accept the suggestion that the early peak may represent fast transmission to MT that by-passes V1, this may be a hint that the direct route to the MT region is slower to develop in comparison to the route to MT via V1.

VEP may be dominated by V1 and V2 but responses to directional changes may still be contributed by extrastriate areas such as V5/MT. The additional early peaks may hint at a faster track of motion processing bypassing V1 while the transient P1 is reflective of the V1 to the MT pathway. Single cell recording has shown that different hierarchical levels can be simultaneously activated by visual stimuli (Mountcastle, 1998). The early peak may be representative of the motion processing in MT/V5 from a route

bypassing V1 through pulvinar (Kass & Lyon, 2007) or directly from the LGN (Sincich et al., 2004). Sincich et al (2004) found a direct projection in monkey from LGN to MT by konicellular neurons (which was the slowest pathway), which send almost no axons to V1. This K pathway has been proposed to explain motion perception in blind-sight patients (Stoerig & Cowey, 1997) and in those who showed close to normal activity in hMT+ and V4 without much remaining V1 (Barbur et al., 1993; Bridge et al., 2010; Goebel et al., 2001).

5.4.2 Phase-based calculated latency

Unlike the transient P1 latency that is determined by the timing needed to produce the initial highest peak, the phase-based calculated latency reflects the entire processing time course seen in the VEP waveform. Our results have shown that the calculated method can yield usable results even with only two temporal frequencies in pattern (Chapter 3; Lee et al., 2012a), orientation (Chapter 4; Lee et al., 2012b), and direction-reversal VEPs (Chapter 5; Lee et al., 2013a).

In addition to a direct route from the superior colliculus and afferent from V1, MT may also have feed-forward modulation from V2 and V3. Several studies have found motion responses in the V2/V3 area. Plomp et al (2010) found motion responses in the right hemisphere overlapping V5, V3a, similar to the finding of MRI (Tootell et al., 1995), fMRI (Braddick et al., 2000 & 2001), MEG (Ahlfors et al., 1999), and EEG (Mercier et al., 2009). The comparison between these effects in the three kinds of processing we have examined (contrast, orientation, and direction) are discussed in Chapter 6 and Lee et al., 2013b.

5.4.3 Latency development

Calculated latency has a delayed developmental course in comparison with the transient P1 latency in the pattern-reversal (Chapter 3; Lee et al., 2012a) and direction-reversal VEPs (Lee et al., 2013a), but not for the orientation-reversal (Chapter 4; Lee et al., 2012b). The calculated latency in DR reached adult values at about 30 weeks of age. Yet both the transient and early transient latencies were similar to their respective adult values at the response onset of about 8-10 weeks of age (Figs. 5.3A & B). For the initial 30 weeks of life, the linear decrease in DR latency of 5.1 ms/wk is steeper than for OR 4.2 ms/wk (Chapter 3; Lee et al., 2012b), suggesting a more rapid initial maturation of motion before form processing. This is consistent with results on infants' responses to global form and motion (Braddick et al., 2003; Lee et al., 2013a; Wattam-Bell et al, 2010).

The time course of latency maturation can be considered in relation to other findings on the development of motion processing. Rosander & von Hofsten (2002) found that at two months or 8.7 weeks of age, infants were able to generate smooth pursuit eye tracking of a moving object. This early motion response is similar to the 8-10 weeks of onset age found in this study and in Braddick et al (2005). Nonetheless, the small subsequent decrease of peak latencies seen in this study may largely reflect of the progression of myelination with age (Dubois et al., 2008; Kos-Pietro et al., 1997; Magoon & Robb, 1981; Tsuneishi & Casaer, 1997).

5.4.4 Factors affecting latency

Infant data showed an overall higher variance than that of adults. This was especially evident for the calculated latency of infants (Fig. 5.5A). This is in line with other studies. PET scans (Hasnain et al., 1998), MEG studies (Bundo et al., 2000), and statistical analysis using DESI (distributed electrical source imaging) have all found large individual variances in motion sensitive areas. While motion onset VEPs peak at 170 ms (Plomp et al., 2010), translational motion reversal VEPs such as the DR stimulus used in this study peak around 120 ms.

Since speed is a key variable for motion stimuli, and the temporal properties of the visual system are known to change with age, the developmental transition may also be speed dependent. Using translational motion VEPs, Lorteije et al. (2008) showed that ventral areas are selectively activated by low speeds (3.5°/s) while dorsal areas are activated by both high (32°/s) and low speeds. As the DR stimulus used in this study has a constant, moderately low, speed of 5.5°/s, the VEP responses probably originate from both the ventral and dorsal areas.

5.5 Summary

Similar to pattern and orientation reversal VEPs, the phase-based calculated latency of direction-reversal was much more prolonged compared to its transient P1 latency. Unlike PR and OR- VEPs, DR responses also had an earlier transient peak that may reflect an additional processing route from the subcortical to the MT area. While the peak latencies maybe mature at their response onset at 8-10 weeks of age, the temporal

sequence of cortical motion processing appears not to be fully developed until after 8 months of age. A better understanding of DR-VEP may serve as future clinical tool to detect cortical abnormalities in motion development, as motion processing appears particularly sensitive to neurodevelopmental disorders (Braddick et al, 2003).

6 COMPARISON OF PATTERN, ORIENTATION, & DIRECTION-REVERSAL VEPs

6.1 Background

The previous three chapters have examined the development of the timing of VEP responses to contrast, orientation-reversal, and direction-reversal. In this chapter we compare directly these three data sets to test the developmental relationship between the processing of these three types of information in the visual pathway. By comparing the VEP response to PR, OR, and DR using the same participants, we hope to tease out the specific neurological pathways contribute to their respective latencies and their developmental progression.

A phase-reversal (PR) response can be induced from retinal ganglion cells (Kuffler, 1953) and so may provide an indication of contrast information arriving at the cortex, but not of specifically cortical function. In order to definitively test cortical function, orientation-reversal (OR) VEP is a better indicator. Unlike PR, orientation responses cannot be found in lower (subcortical) visual areas (Hubel & Wiesel, 1977). Introduced by Braddick et al. (1986), the OR stimulus uses a grating pattern that switches between 45° and 135°, embedded in jitter or random phase shifts of the grating pattern. To test visual cortical function for motion processing, a different type of VEP is needed. In 1991, Wattam-Bell devised direction-reversal (DR) VEP to investigate motion processing. The DR stimulus includes a series of random changes in pixel arrey that are embedded in the

local contrast changes of a dense random pixel array (Wattam-Bell, 1996). The jitter in OR and the random contrast changes in DR can be filtered out upon subsequent analysis to obtain true orientation and direction VEP responses.

P1 or P100, the highest peak around 100ms, can be measured from transient VEPs. P1 for pattern reversal is known to vary with age (McCulloch et al., 1999; Moskowitz & Sokol, 1983) and with different stimulus parameters (Fiorentini et al., 1996; Tyler, 1985). Others have proposed to calculate latency by finding the slope of two or more phase values at different temporal frequencies (TF) (Chapter 3, Lee et al., 2012a; Regan, 1966; Spekreijse et al., 1978). Unlike the peak latency, the phase-based latency can be calculated at any TF and reflects the time course of all the processing that contributes to the VEP.

In pattern reversal VEPs, the peak latency (P1) for large checks decreased from 260 ms at birth to around 107 ms (adult values) around 4 months (Chapter 3, Lee et al., 2012a; McCulloch et al., 1999; Moskowitz & Sokol, 1983; Porciatti, 1984). While the calculated latency was significantly longer in infants, both calculated and transient latencies were around 100 ms in adults (Chapter 3, Lee et al., 2012a). While the peak latency for orientation reversal decreased with a similar trend as for PR, the calculated latency of OR showed little change with age (Chapter 4, Lee et al., 2012b). For direction reversal, in addition to the 126ms P1 peaks, early peaks of about 92 ms were found. Unlike the latency for OR, the peak latency for DR showed little variation, while its calculated latency decreased with age.

To understand the relationship among contrast, orientation, and motion processes, this chapter compares (1) the relation between calculated and transient latency in all three

VEPs and (2) the developmental course of each latency as measured with both approaches.

6.2 Methods

The PR, OR, and DR stimulus sequences, the recording, and the analysis methods, have been fully described in the preceding three Chapters- 3, 4, and 5. A total of 61 adults (median age 21.4, range 17-43 years) and 76 healthy full term infants (3.6- 79.0 weeks) born within 14 days of their due date were tested with all 3 stimuli.

6.3 Results

6.3.1 Response rate

Out of 61 adults tested, 19 (31.1%) gave data on peak latency from significant component at the reversal frequency for all three stimuli, 39 (42.5%) yielded calculated latency from phase measurements of significant components at the reversal frequency for all three and 17 (27.9%) had both transient and calculated latencies to all three VEP stimuli (Table 6.1).

Among the 76 infants tested with all three stimuli, 19 (25.0%) of the infants gave data on transient peaks in all three stimuli, 19 (25.0%) with calculated latencies, and only 8 (10.5%) infants gave both transient and calculated latency data for all three stimuli (Table 6.1).

Age (wks)	Tested	Transient	Calculated	Transient & Calculated
3.6-4.9	0	0	0	0
5.0-9.9	4	0	1	0
10-14.9	7	6	5	4
15-19.9	3	1	1	1
20-29.9	10	3	6	1
30-39.9	10	2	3	0
40-49.9	15	2	0	0
50-59.9	11	1	1	0
60-69.9	9	1	0	0
70-79.9	7	3	2	2
Infants Total	76	19	19	8
Adults Total	61	19	39	17

Table 6.1: Response rate: number of adults and infants in each of the ten age groups with measurable peak responses from significant components at the reversal frequency in all three stimuli: pattern, orientation, direction-reversal VEPs. (Note: DR early transient was not accounted for).

PR induced the largest mean amplitudes for both the adults (3.2 μV) and infants (12.3 μV), followed by OR responses (adults: 2.9 μV; infants: 7.2 μV). DR produced the smallest response for both adults (2.4 μV) and infants (0.9 μV).

6.3.2 Adults: comparison of transient and calculated latencies across stimulus conditions

For 19 adults with measurable transient P1 latency from significant components at the reversal frequency for all three stimuli, the mean ± SE for PR was 110.8 ± 3.1 ms, for

OR was 102.4± 3.9 ms, for DR was 123.1 ± 2.1 ms. The mean differences were significant: ($F(2, 36) = 9.0$, $P = 0.001$). The early transient latency for DR was 86.4 ± 2.2 ms. There were similar significant differences among the calculated latencies: PR (100.1 ± 3.0 ms), OR (197.7 ± 8.0 ms), and DR (191.9 ± 6.6 ms), ($F(2, 76) = 63.8$, $P < 0.001$). However, post-hoc (Bonferroni) comparisons revealed that the difference between PR and OR transient latencies was not significant ($P = 0.6$), and neither were the differences between the OR and DR calculated latencies ($P = 0.5$). Yet there was an overall interaction effect between the two latency methods and the three stimuli: ($F(2, 32) = 28.5$, $P < 0.001$) (Table 6.2).

	Pattern	Orientation	Direction	N
Transient Latency ± SE (ms)	111.1± 2.8	103.7± 2.8	122.6± 1.9	19
Calculated Latency ± SE (ms)	100.1± 3.0	197.8± 8.0	191.9± 6.6	39

Table 6.2: Mean transient and calculated latencies (± standard error) for adults in pattern, orientation, and direction reversal VEPs. N= number of adults with measurable peak responses from records with significant components at the reversal frequency in all three stimuli.

6.3.3 Infants: comparison of transient and calculated latencies across stimulus conditions

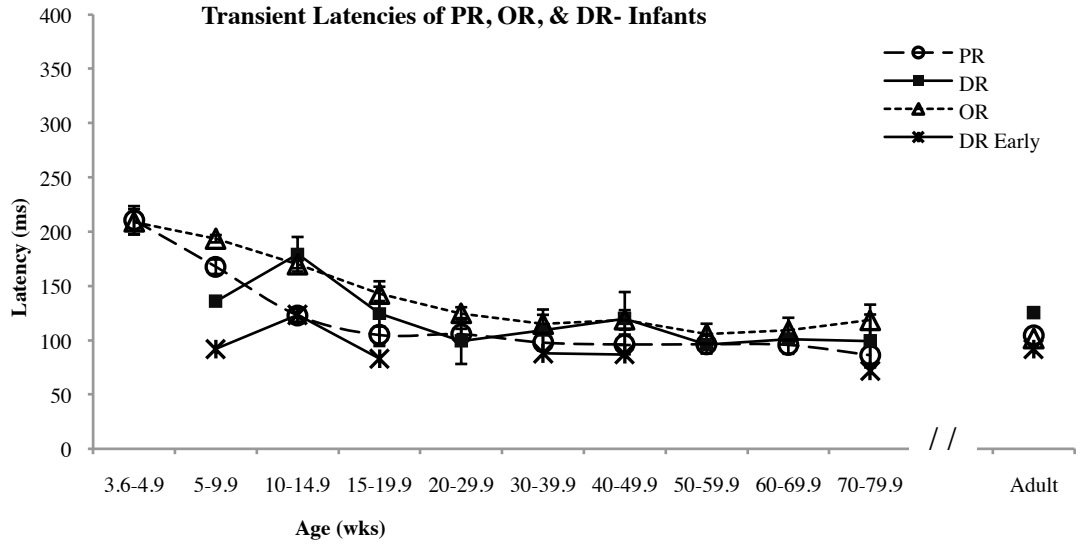
For the19 infants who showed significant transient P1 latencies for all PR, OR, and DR- reversal VEPs, RM-ANOVA (with age as a between-subjects factor) revealed

significant mean differences ($F(2, 22) = 8.9$, $P = 0.001$), but not for the interaction between the latencies and age: ($F(14, 22) = 1.8$, $P = 0.1$). There were similar significant differences among the calculated latencies, PR, OR, and DR: ($F(2, 24) = 20.8$, $P < 0.001$), and also for the interaction between the 3 stimuli and age: ($F(12, 24) = 2.5$, $P = 0.02$). However, post-hoc (Bonferroni) comparisons revealed that the difference between OR and DR transient ($P = 0.2$), PR and DR early transient latencies ($P = 0.997$) was not significant, nor was that between OR and DR calculated latencies ($P = 0.07$). Yet there was an overall interaction effect between the latency methods and the three stimuli and age: ($F(6, 8) = 6.3$, $P = 0.01$). This was in line with adult data (Figs. 6.1 & 6.2).

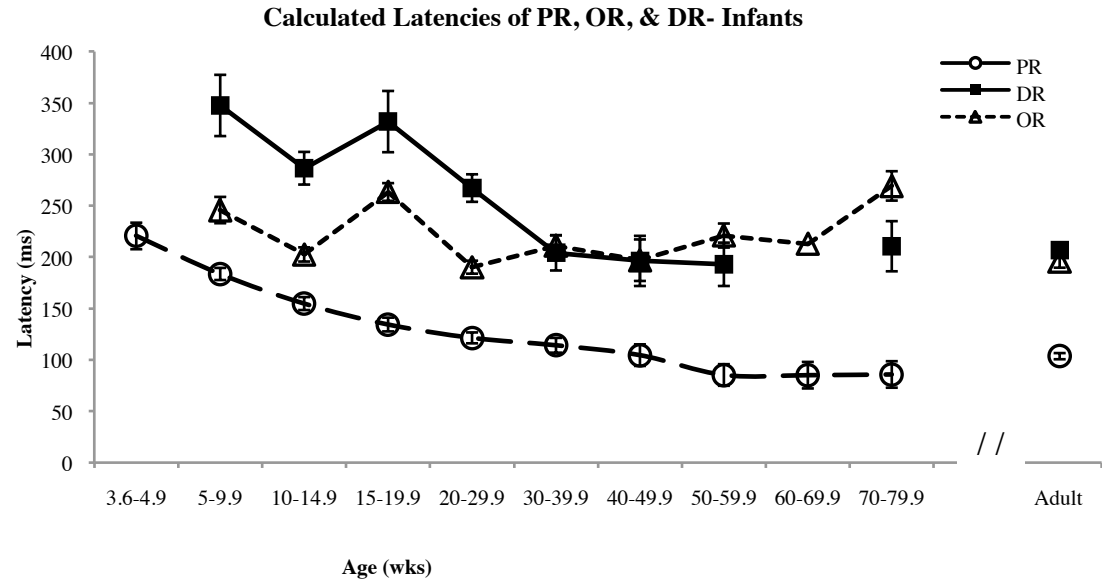
ANOVA (with age as a between-subjects factor) revealed that any infants under 20 weeks of age showed non-significant differences in the transient latencies for all three stimuli ($F(12, 152) = 0.7$, $P = 0.7$). As for the calculated latencies, infants under 30 weeks of age showed non-significant differences in their OR and DR latencies $F(1, 25) = 1.1$, $P = 0.4$. While the latencies of OR and DR began to merge at around 30 weeks of age, both latencies remained significantly higher than the calculated latency of PR for infants under 18 months of age ($F(2, 198) = 101.9$, $P < 0.001$) (Figs. 6.1 & 6.2).

For the 19 infants who had peak latencies from significant components at the reversal frequency for all three stimuli, their transient latencies developmental trajectory mimics that of infants data found in the previous three chapters where there is a linear decrease up to 30 weeks of age followed by an asymptote of 100-135ms for all three stimuli. The pattern is different for the calculated latencies. While the DR latency of the 19 infants is similar to that of previous findings, the OR and PR latencies are less clearly

defined. Nonetheless the overall message remains the same: PR calculated latency is much smaller compared to the OR and DR calculated latencies (Figs. 6.1 & 6.2).



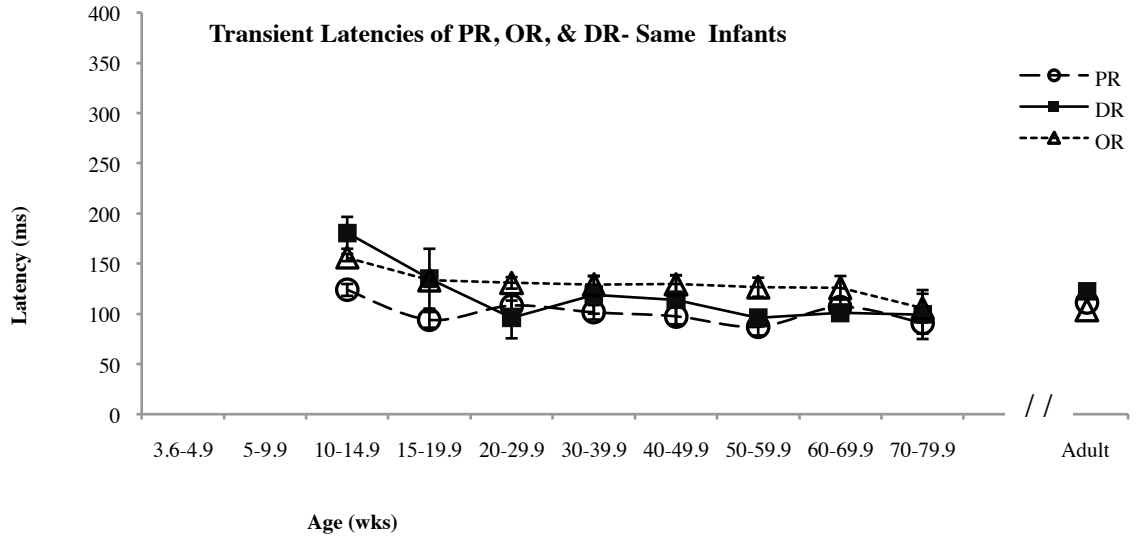
A



B

Fig. 6.1: Comparison among pattern, orientation, and direction-reversal VEP latencies as a function of 10 age groups (mean± SE) for any infants that showed significant (A) transient P1 latencies and (B) phase-based calculated latencies in any of the three stimuli.

The adult values were added for reference. (The data is aggregated from previous three chapters.)



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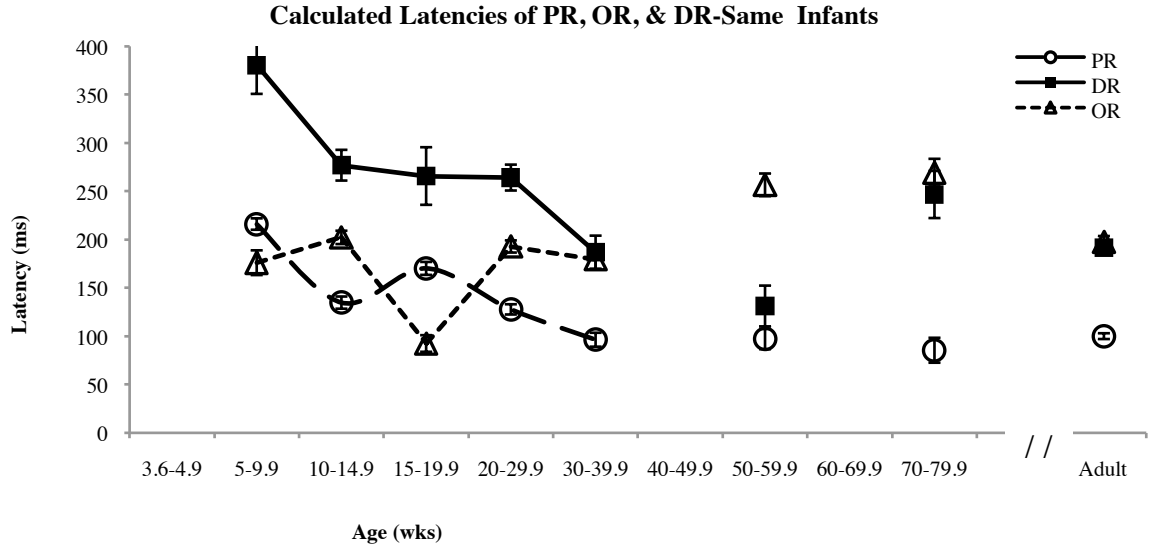


B

Fig. 6.2: Comparison among pattern, orientation, and direction-reversal VEP latencies as a function of 10 age groups (mean± SE) for the 19 infants that showed significant (A) transient P1 latencies and (B) phase-based calculated latencies in all three stimuli. The adult values were added for reference.

6.3.4 Comparison of latencies between adults and infants

Infant transient P1 latencies of the three stimuli reached adult values at different times. While infant peak latency was not significantly different from the adult value after 15 weeks of age in PR, the development in OR transient latency was much more extended and did not reach adult value until after 50 weeks. As for DR, both the early and regular transient latencies were similar to adult values at the onset of DR around 10 weeks (Table 6.3).

For the calculated latency, the calculated latency of OR showed little variation across development and was similar to the adult value by the age of onset at around 4 weeks (Chapter 4; Lee et al., 2012b). For both PR and DR, the calculated latency asymptoted to adult value around 30 weeks of age (Chapters 3 & 5; Lee et al., 2012 a & c; Table 6.3).

	Phase	Orientation	Direction	Direction Early
Transient Latency (weeks)	15	50	10	10
Calculated Latency (weeks)	30	5	30	—

Table 6.3: Age (weeks) at which infants' transient and calculated latencies asymptote to adult value for phase, orientation, and direction reversal VEPs.

6.4 Discussions

6.4.1 Response rate

It was much more difficult to obtain significant DR responses in comparison to PR or OR-VEPs for both the adult and infant participant groups. While PR induced the largest mean amplitudes for both the adults and infants, OR induced smaller amplitudes with DR inducing the smallest voltages.

6.4.2 Transient P1 latency

In adults, the transient P1 latencies of the pattern and orientation reversal VEPs were similar (Chapters 3 & 4; Lee et al., 2012 & 2012b). While the peak latency for DR was 10-20 ms longer than that for both the PR and OR, the early peak latency of DR was 16-37 ms shorter than the other three peaks. For the infants, the peak DR latency was similar to that of OR. The longer DR peak latency compared to contrast and orientation responses maybe due to DR's greater dependency on long-range horizontal connections, which require longer transmission and synchronisation times.

For both adult and infant groups, an additional early peak was found for DR that was not seen in the waveform for PR and OR (Lee et al., 2013b). As proposed in Lee et al (2013a) and discussed in Chapter 5, the early peak may indicate a faster subcortical route directly to V5 for motion processing, bypassing V1.

The more prolonged waveform for DR compared to OR and PR meant that the response to a reversal was not complete by 250 ms. In the 4 r/s recording, therefore, the transient peak was likely to be confounded with the response to the preceding stimulus,

and this reversal rate, unlike for PR and OR, could not be taken as contributing to the estimate of transient latency; instead it has to be treated as a frequency for steady-state analysis (Lee et al., 2013a).

6.4.3 Phase-based calculated latency

For both adults and infants, most participants had calculated latencies for orientation and direction reversal VEPs that were almost double their respective transient latencies. Unlike the peak latency that reflects the timing needed to produce the initial peak between 102-123 ms, the phase-based calculated latency indicated the processing time of the entire VEP waveform. For both adult and infant groups, the calculated latencies of OR were similar to that of DR. While the calculated latency of PR was similar to its peak latency in adults, the calculated latencies of both OR (192 ms) and DR latencies (198 ms) were about double that of PR (100 ms) (Lee et al., 2013b). This difference indicates that separate cortical processes are involved in analyzing the transient versus the calculated phase latencies (Chapters 3, 4 & 5; Lee et al., 2012a, 2012b, & 2013a). DR having the longest calculated latency may serve as another indication of additional processing time contributed by two possible routes: (1) a shortcut from the subcortical area to MT and (2) V1 to MT. The development of recurrent and feedback loops from both routes may also explain the additional overall VEP processing time.

6.4.4 Latency development

6.4.4.1 Transient P1 Latency

Infants had equivalent peak latencies in all three stimuli around 20 weeks or 4.6 months of age. Yet infants reached adult values at different times for the three stimuli. Infant response for motion matured first-around 10 weeks or 2.3 moths, then pattern at 15 weeks or 3.5 months, and finally orientation at about 50 weeks or 11.5 months (Lee et al., 2013b).

The visual cortex has a number of functional changes as it matures. The peak latencies of orientation and motion VEPs were similar in infants but different in adults. This similarity in infants but not in adults was the same for pattern-reversal and the early peak of direction-reversal. Yet the peak latencies of pattern and orientation were different in infants but the same in adults. While the early peak of direction latency remained relatively constant across age, all other transient peak latencies followed a similar decline with age (Lee et al, 2013b). This indicates that the initial detection of contrast, orientation, and direction may stem from similar or parallel processes. The decrease seen with age could largely due to progressive myelination of the optic nerve, tract and radiation (Dubois et al., 2008; Kos-Pietro et al., 1997; Tsuneishi & Casaer, 1997).

6.4.4.2 Phase-based calculated latency

The trend of calculated latencies, however, remained the same for both infants and adults. Infants reached adult pattern and direction latency at similar times around 30 weeks or 6.9 months. At 6.9 months, infants also had similar calculated latencies for OR

and DR stimuli, which was about 2 months later than the age at which all transient peak latencies converge. There is little latency change with the OR calculated latency over age (Lee et al, 2013b).

While OR calculated latency remained relatively unchanged in the first 1.5 years of age, both PR and DR latencies decreased with age. As infant latency for orientation reached its adult value before pattern and direction, internal feedback within V1 may mature earlier than the processes within the extrastriate areas. Nonetheless, although initial detection of motion may mature earlier than form, fine-tuning of the motion pathway is probably delayed compared with the form pathway.

The longer calculated latency seen in both adults and infants indicates processing time beyond the initial detection of direction-reversal (Figs. 5.3A & B), which includes timing needed to generate and process the entire VEP wave. These additional processes may be because of: horizontal connections (Gilbert & Wiesel, 1989; Nauhaus et al., 2009) between the direction-selective cells, recurrent and inhibition loops between V1 and extrastriate visual areas, non-linear transformation between V1 and extrastriate visual areas (Geisler & Albrecht, 1995), and the integration time of spatiotemporal features (Lamme & Roelfsema, 2000).

6.4.5 Limitations

To gain firmer data on the relationship within the same participants, it would be valuable to gather more data, since there are only 8 infants who showed both transient and calculated latency data for all three stimuli. Due to limitations on the participants' attention span, future studies should focus on obtaining both transient and calculated

latency data rather than cramming in as many TF as possible within one sitting. Recording session could be prolonged with sufficient amount of breaks build-in. Nonetheless, transient and calculated latency data from the 8 infants who had significant data in all three stimuli respectively did show overall similar trends to the findings of chapter 3, 4, and 5.

6.5 Summary

In summary, the transient P1 latencies of phase, orientation, and direction VEPs showed similar developmental trends and possible parallel processing routes. Phase based calculated latency, however, suggests that the internal feedback governing orientation in V1 might mature earlier than the processes that determine phase and direction from extrastriate areas. While the dorsal stream governing motion may appear to mature earlier than the ventral stream responsible for form, the complete maturation and fine-tuning of the motion pathway is delayed in comparison with form. However, there is a functional change upon maturity such that the higher visual cortices appear to utilize similar or parallel processing to analyse both form and motion. Deeper understanding of the vision pathways governing phase, orientation, and direction in healthy infants will serve as valuable standardized baseline for at-risk infants with neuro-visual abnormalities.

7 ATYPICAL INFANT DEVELOPMENT

7.1 Background

Cerebral visual impairment (CVI) is often caused by hypoxic-ischemic Encephalopathy (HIE), traumatic brain injury, or periventricular leukomalacia (PVL) in preterm infants. CVI is also associated with cerebral palsy, developmental delays, and impairments in senses, cognition, and attention (Atkinson & Braddick, 2008).

Cerebral Palsy (CP) is a disability arising from a non-progressive brain lesion occurring in early life that affects motor and sensory control (van Nieuwenhuize et al., 1984). CP is also associated with cognitive alteration, mental retardation, epilepsy and hearing deficits (Robinson, 1973). As for vision, CP patients often have oculomotor abnormalities, refractive errors and visual acuity loss (Schenk-Rootlieb et al., 1993). CP is the most common cause of physical dysfunction in childhood, affecting about 3 babies per 1000 live births (Morris, 2007).

Measures of visual function are important factors of the broader neurodevelopmental problems. Common clinical tests for at risk infants include: simultaneous recording of transient pattern ERGs and VEPs providing the retino-cortical time (RCT), and the time difference between the P100 of the VEP and the b-wave of the ERG (Celesia & Kaufman, 1985; Kaufman & Celesia, 1985). Hemi-field pattern VEPs can evaluate the function of the optic radiations and occipital cortex (Aminoff & Goodin, 1994; Celesia, 1985). Pattern reversal VEPs have also been used to study developmental trends in infants with HIE (Mercuri et al., 1997, 1998, & 1999).

VEP is a quick and non-invasive assessment tool that does not require active behavioural responses of its subjects. This makes VEP useful to detect abnormalities or to identify delayed infants at risk for later developing symptoms such as CP. For instance, PR-VEP is often used clinically in preverbal patients with amblyopia, delayed visual maturation, cortical blindness, and lesions of the eye and ocular media or the afferent visual pathway. PR is a preferred VEP stimulus in clinical setting as it has little waveform variability between individuals (de Haan, 2007).

Pattern-reversal (PR) VEPs are present in newborns while orientation-reversal (OR) VEP emerge at age 3-8 weeks (Braddick et al., 1986). PR-VEP latencies are known to decrease rapidly from 250 ms at birth and asymptote to the adult P100 value by 15 weeks in normal neonates.

Because of their motor disability, testing in CP children is difficult and promotes misdiagnosis. The specificity and sensitivity of VEP depends on the individual stimulus and the method of analysis. Any approach needs to be systematically tested if it is to be a reliable source for evaluating infants with perinatal brain damage at risk of cerebral palsy.

The opportunity arose to test the methods developed in this thesis in the 'Dolphin' study conducted in association with the Oxford Department of Paediatrics, examining the development of infants at risk for cerebral palsy and testing a dietary supplement designed to improve their neural development. Visual measures have been found to be enhanced by dietary supplementation of premature infants (Birch et al., 1992 & 2007). Damage to white matter of the brain is common in premature birth as part of the pathway leading to cerebral palsy (Du Plessis & Volpe, 2002). Since myelination is a key

determinant of evoked potential latency, VEP latency is promising as an indicator of the neurological damage associated with these conditions.

We therefore carried out a pilot study of using transient and calculated latency of PR-VEP, and the presence of OR VEP, in infants participating in this project. This study aimed to test whether (1) VEP, in particular VEP latency, can serve as an additional mode of assessment technique for CP infants and (2) the relative value of PR versus OR-VEPs.

7.2 Methods

Please refer to Chapter 2 for detailed descriptions of methods and materials used throughout this thesis. The PR and OR stimulus sequences, the recording, and analysis methods, have been fully described in Chapters 3 and 4. The only difference here is that for the control group, up to seven different temporal frequencies (2 to 16 r/s) were tested for PR and five TF (2-8 r/s) for OR. For the clinical group, only up to four different temporal frequencies at 2, 4, 6, and 8 r/s were tested for both the PR and OR stimuli.

7.2.1 Participants

The 137 healthy full term infants (age 4 - 79 weeks) born within 14 days of their due date recruited for the PR, OR, and DR studies served as the comparison group (Chapters 3, 4, & 5; Lee et al., 2012a, 2012b, & 2013a).

For the clinical group, 50 infants (adjusted age: 0.9 to 129 weeks post-term) with perinatal brain damage were recruited. The clinical group was divided into two groups. In D1 (the neonatal group)infants were born with ≤ 32 weeks of gestation and showed grade 2 or below haemorrhage on ultrasound or MRI scans. If the infants had grade 3 or 4 haemorrhage, there needed to be unequivocal evidence of periventricular leukomalacia for them to be included in the study. The second group - D2 (evolving Cerebral Palsy) includes children aged 6-18 months with a clinical diagnosis of CP. There are also a few exclusion criteria, for example, children with such low vision or hearing that they cannot complete assessment with the Bayley scales; children with progressive neurological degenerative conditions; or children with gastrointestinal disease which significantly impairs absorption. The results presented below combine those from the D1 and D2 groups.

7.3 Results

7.3.1 Response rate

Among the 50 clinical infants tested with post-term ages of 0- 129.9 weeks, 33 infants (66%) yielded transient responses while 27 infants (54%) yielded calculated responses for PR- VEP. For the OR-VEP, a total of 25 infants were tested within the same age range. 10 infants (40%) yielded transient responses while 5 infants (20%) yielded calculated responses (Table 1).

	PR			OR		
Age (wks)	**Tested**	**Transient**	**Calculated**	**Tested**	**Transient**	**Calculated**
0-4.9	10	8	9	1	1	0
5-9.9	2	2	2	1	0	0
10-14.9	5	2	1	1	0	0
15-19.9	2	2	2	0	0	0
20-29.9	7	6	2	3	2	0
30-39.9	2	1	2	1	0	0
40-49.9	6	5	5	4	2	1
50-59.9	2	1	1	2	0	0
60-69.9	4	2	1	7	2	2
70-79.9	3	2	1	2	2	1
80-129.9	7	2	1	3	1	1
Total	50	33	27	25	10	5

Table 7.1: Number of clinical infants in each of the 11 age groups with significant components at the reversal frequency in transient and calculated latencies for PR and OR-VEPs.

In other words, 16 infants (30%) yielded non-significant components at the reversal frequency for PR-VEP while 23 infants (50%) yielded non-significant calculated responses. As for OR-VEP, 15 infants (60%) and 20 infants (80%) yielded non-significant components at the reversal frequency for transient and calculated latencies respectively. The distribution of response based on individual age group is displayed in Figure 7.1. As response to the OR-VEP requires clear functional visual cortices, the mere existence of the OR response signify a subset of infants that may be healthier.

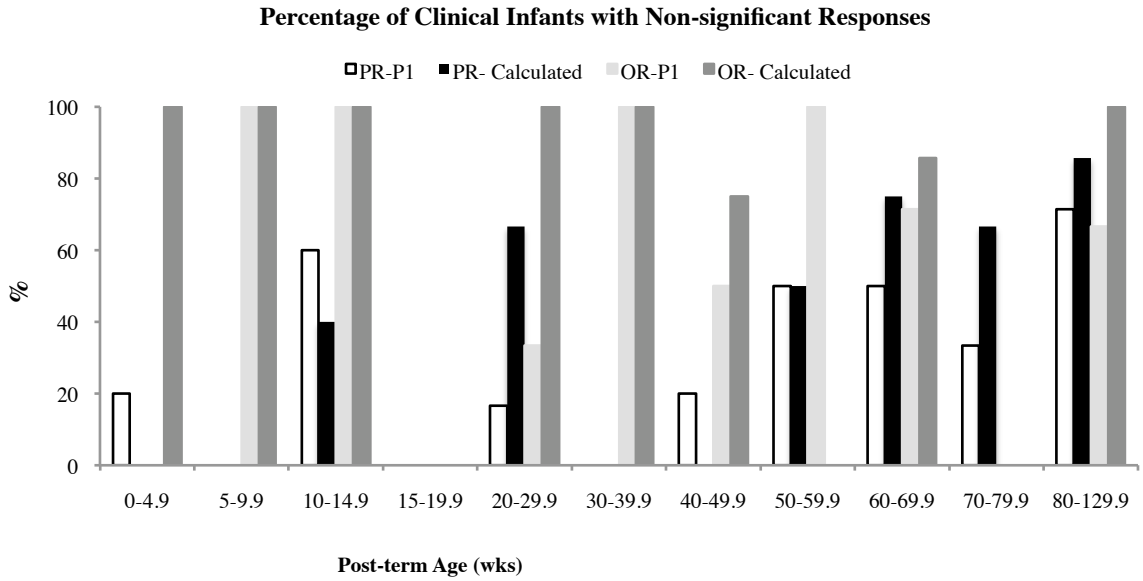
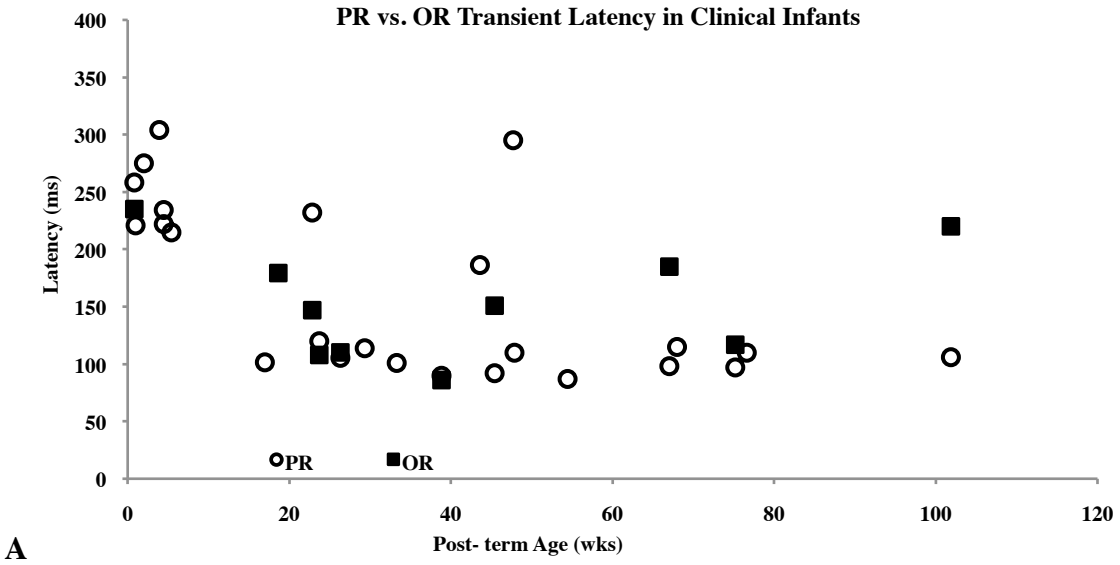


Fig. 7.1: Percentage of clinical infants showing non-significant components at the reversal frequency for PR and OR VEPs as a function of 11 age groups.

7.3.2 Transient P1 latency

For the transient P1 latency for the clinical babies, ANOVA (age group as a between-subjects factor) yielded non-significant latency differences among the low temporal frequencies (2 & 4 r/s) used in the analysis of transient latencies for PR ($F(1, 24) = 0.5$, $P = 0.5$) but these figures were different for OR-VEP ($F(1, 12) = 12$, $P = 0.005$). However, the interaction between the 11 age groups and temporal frequency was also not statistically significant for PR ($F(6, 26) = 0.3$, $P = 0.95$) and OR ($F(9, 5) = 0.8$, $P = 0.6$). For the subsequent analysis, the average of the results at the two temporal frequencies in each infant was defined as the transient latency for both the PR and OR-VEPs.

ANOVA (age as a between-subjects factor) revealed significant mean differences between PR and OR transient latencies in clinical infants: ($F(1, 8) = 5.7$, $P = 0.05$), but insignificant interaction effects between the two latencies and age: ($F(5, 26) = 0.3$, $P = 0.9$). This was in line with the data from typically developing infants (Chapters 3 & 4; Lee et al., 2012a & 2012b).



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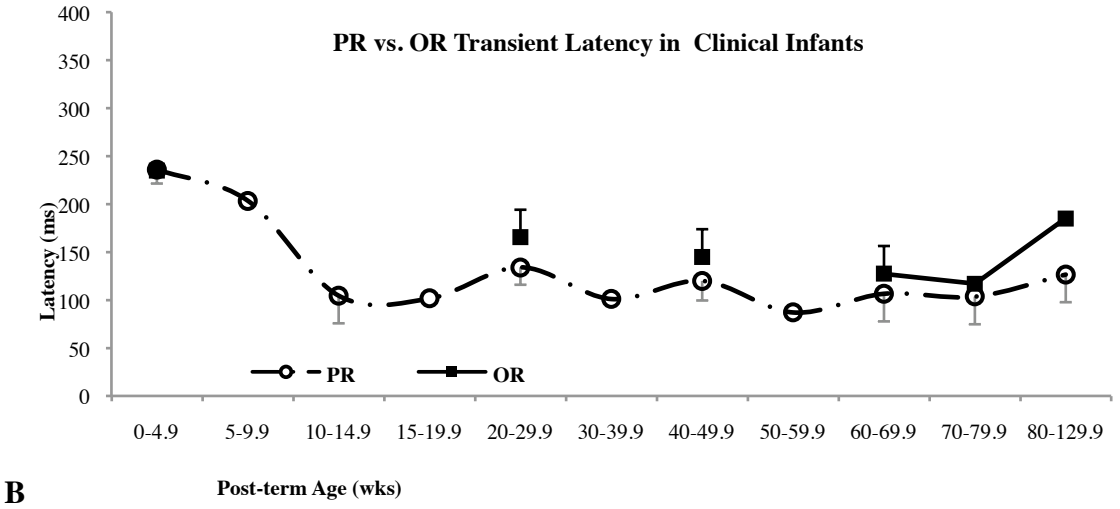


B

Fig. 7.2: PR versus OR transient latency in clinical infants as a function of (A) a continuous age range (all infants) and (B) 11 age groups (mean ± SE).

7.3.3 Phase-based calculated latency

For the calculated latency, both PR and OR showed little variation across development in this clinical group. Using age groups as a between-subjects factor, ANOVA revealed insignificant calculated latency differences between PR and OR ($F(1, 2) = 6.8$, $P = 0.1$) and for the interaction between stimuli and age ($F(2, 18) = 0.6$, $P = 0.6$), reflecting the relative absence of decline in OR compared to PR latency over the age range, as seen in Figure 7.6B. This differs from the data for normal infants where the OR showed statistically longer calculated latencies than PR and significant interaction effects with age (Chapter 4; Lee et al., 2012b).

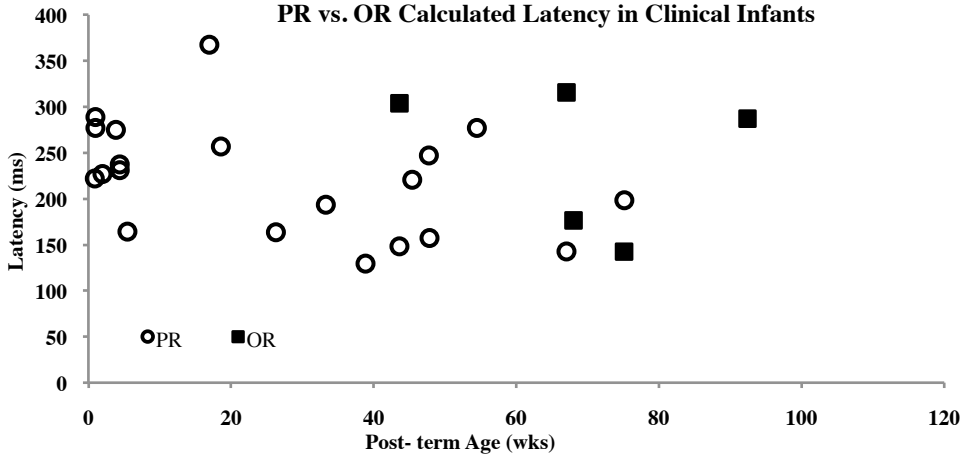


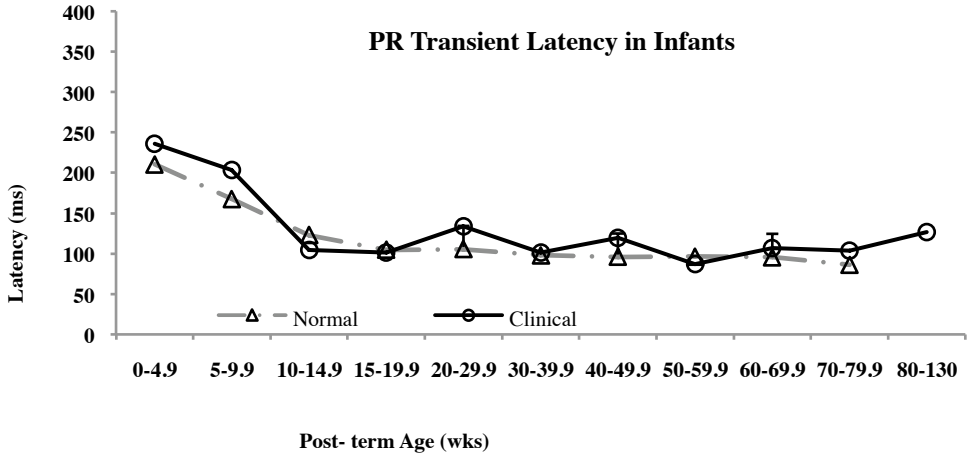
Fig. 7.3: PR vs. OR calculated latency in clinical infants as a function of a continuous age range.

7.3.4 Comparison to typically-developing infants

7.3.4.1 Transient P1 latency

For PR-VEP, ANOVA showed that the difference in P1 latency between the clinical and typically developing groups approached significance (1, 12)= 4.3, P= 0.06) but the interaction effect between the two participant groups and age is not significant: (F (9, 113)= 1.3, P= 0.2) (Fig. 7.4A).

As for the small sample of OR-VEP responses, ANOVA showed the P1 latency of the clinical group is clearly significantly longer than that of the normal groups (F (1, 8)= 78.0, P< 0.001.) but no significant interaction effect between the two participant groups and age: (F (4, 189)= 0.1, P= 0.97) (Fig. 7.4B).



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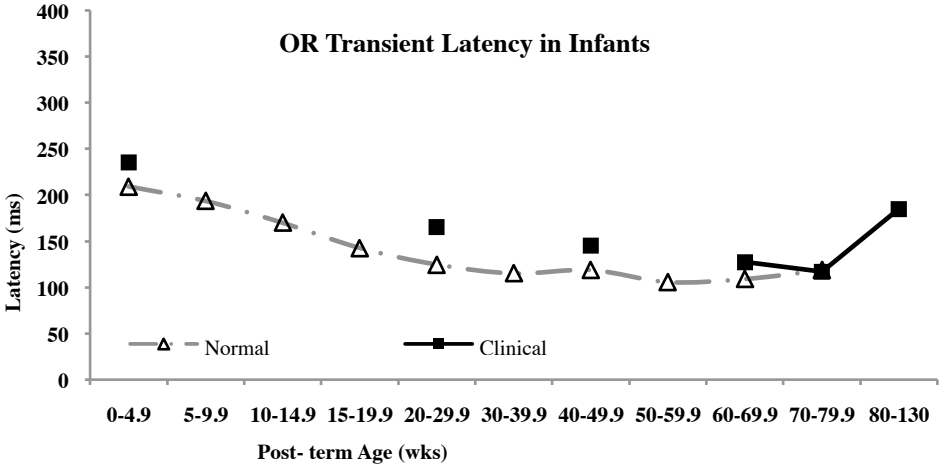


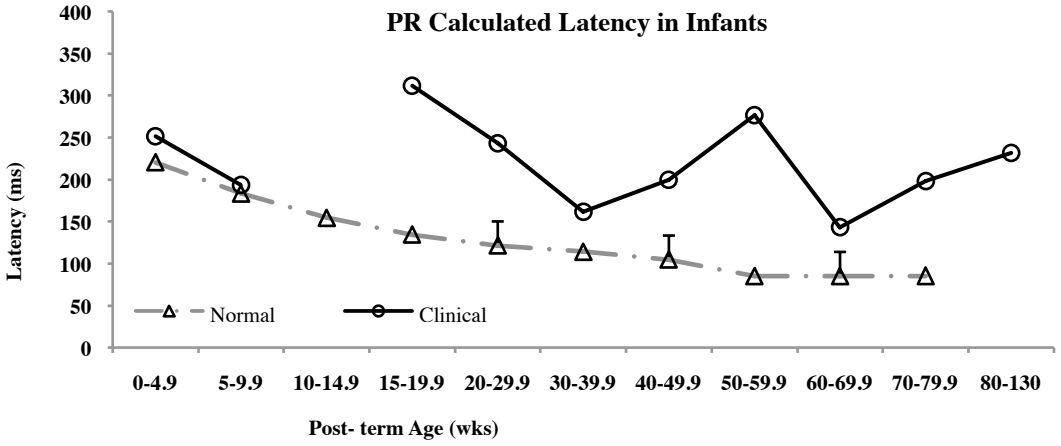
B

Fig. 7.4: Comparison between typically-developing and clinical infants as a function of 10 age groups of (A) PR transient latency and (B) OR transient latency.

7.3.4.2 Phase-based calculated latency

For PR-VEP, ANOVA showed that the mean latency of the clinical group was significantly longer than that of the typically-developing group: ($F(1, 9) = 18.4$, $P = 0.002$). The interaction effect between the two participant groups and age was also significant: ($F(8, 90) = 4.5$, $P < 0.001$) (Fig. 7.5A).

As there were only five data points from the clinical group for the OR calculated latency, ANOVA showed insignificant P1 latency differences between the normal and the clinical groups for the OR-VEP: ($F(1, 2) = 0.3$, $P = 0.6$) and the interaction effect between the two participant groups and age: ($F(2, 69) = 1.6$, $P = 0.2$) (Fig. 7.5B).



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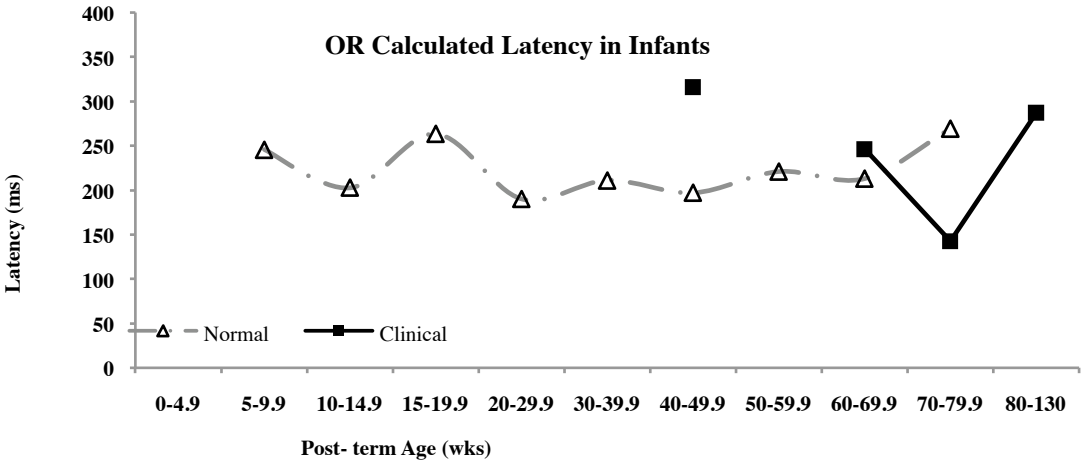

B

Fig. 7.4: Comparison between typically-developing and clinical infants as a function of 10 age groups of (A) PR calculated latency and (B) OR calculated latency.

7.4 Discussion

OR was twice as likely as PR- VEP to show a non-significant response, for both the P1 and calculated latencies. The 60-80% response absence for OR is a strong indicator that OR may be a more sensitive test than PR for clinical infants at risk of CP. This is in line with the finding of Mercuri et al. (1998) finding that OR-VEP was shown to be more sensitive than PR to perinatal brain damage. Mercuri et al. (1999) has also shown OR-VEP is good predictor of neurological outcome in term-born babies and preterms (Atkinson et al., 2008).

7.4.1 Transient P1 latency

Similar to typically developing infants (Chapters 3 & 4; Lee et al., 2012a & 2012b), P1 latencies of the pattern and orientation reversal VEPs were similar for the clinical group when taking age into account. As the latency of the clinical preterm and full term infants were comparable, this suggests that latency is not influenced by early visual stimulation or the absence of the intrauterine environment in later preterm development, a finding consistent with other reports of healthy preterm babies (Hammarrenger et al., 2007; Jando et al., 2012).

7.4.2 Phase-based calculated latency

Both PR and OR showed little calculated latency variation across development for the clinical atypical infants. This differs from the data for normal infants where only the

OR showed insignificant differences with age (Chapter 4; Lee et al., 2012b). The PR latency, on the other hand, had similar developmental trends as its transient latency (Chapter 3; Lee et al., 2012a). This difference could be due to smaller head circumference in the clinical group (Gregori et al., 2006), myelination disturbances, or enhancement in the GABAergic inhibitory neurotransmitter mechanisms (Bale et al., 2005; Robinson et al., 2010).

7.4.3 Comparison with typically- developing infants

For both the control and the clinical groups, the transient P1 latencies for OR seem to follow a similar pattern of development as for PR (Chapter 3; Lee et al., 2012a). Unlike the comparison group, who showed a significant age trend for calculated latency for PR but not OR, the atypical infants showed little change of calculated latency for either stimulus.

In PR the main contribution to latency may be the time needed to generate the first peak. Calculated OR latency, on the other hand, could be dominated by the processing reflected in later response components generatedin V1 and other areas. Because the clinical group is more variable in neurological condition and its group size is much smaller than the normal infants, the same difference found in the normal infants would be much harder to reach statistical significance in the clinical group- practically for the OR response.

7.4.4 Latency development

For the normal-developing infants, while infants' transient P1 latency for PR asymptoted to the adult value at around 15 weeks, infants' OR latency did not reach adult value until about 50 weeks. The infants' response to OR has not only a delayed onset (Braddick et al., 1993) but also a slower developmental course for the peak response compared to the PR latency (Chapter 3; Lee et al., 2012a). As for PR, most of the decrease in OR transient latency occurs within the first 15-20 weeks of life. For calculated latency, however, no distinguishable trend was observed. Shahani et al (2007), using a different transient VEP method, also found a slower developmental time-course for orientation selectivity compared with spatial frequency selectivity.

Unlike the peak latency which measured the timing needed to produce the initial peak between 102-123 ms, the phase-based calculated latency indicated the processing time of the entire VEP waveform. While the transient latency indicates the function of the visual pathways from the eye to the brain, calculated latency signifies cortical brain function for V1 and the extrastriate areas. In this study the significant absence of the OR response (Fig. 7.1), the longer OR transient latencies of the subset group of clinical babies with significant response (Fig. 7.4.B), and longer PR calculated latency (Fig. 7.5A) further confirm that OR-VEP and calculated latency are more sensitive measurements for tracking brain development.

7.4.5 Clinical diagnosis

OR-VEP has a strong clinical value as an indicator of cerebral development. It has been strongly correlated to changes seen in neonatal images of children with focal brain injury (Mercuri et al., 1996) and hypoxic-ischaemic brain damage at term (Mercuri et al.,

1999) and predicts later neuro-developmental outcome of this group when the infants turned two years of age (Mercuri et al., 1999). Using MRI imaging, Mercuri et al. (1997) showed that those very low birth-weight infants (< 1500g) with abnormalities in their basal ganglia had poor visual development, which correlated with either delayed or absent of OR-VEP response. OR is also a better indicator than PR for visual development in prematurely born infants with white matter injuries (Atkinson et al., 2008). The predictive power of the PR and OR-VEPs for CP needs further investigation. It is difficult to find the ideal timing and the frequency for taking measurements in the clinical group.

Clinical use of VEP to measure brain abnormalities is debated. Testing 93 infants of less than 32 weeks of gestation with flash VEPs, Pike and Marlow (2000) found that flash VEP only has a 38% positive predictive power for CP at two years of age. Using PR sine wave gratings at 0.5 and 2.5 c/d and 4 contrast levels (4, 12, 28 & 95%) at 2 r/s, Hammarrenger et al (2007) compared results of 55 preterm infants (born between 24-30 wks) with that of 52 term infants. Similar to the present study, they found no difference in latency in preterm and term infants, suggesting no influence of early visual stimulation. However, in a comprehensive ophthalmological, cognitive, and electrophysiological assessment of 12 pre-terms without neurological disorders and 12 controls, O'Reilly et al (2010) found that preterm infants showed shorter P100 latencies than the controls by 11 ms with no difference in N75 or N125 latency. The authors concluded that the slight latency drop was not attributed to the size of the corpus callosum, difference in white/grey matter from MRI data, neuromotor/ ophthalmological /cognitive tasks, or IQ

level; but rather to the smaller head circumference and white matter damage found in the clinical group.

7.5 Summary

In summary, VEP is a valuable means to assess and monitor visual and brain development for both normal and clinical infants. PR peak latencies reflect the initial cortical response to produce a maximum peak. OR latencies, and calculated PR latencies, reflect the time course of cortical processing and show a slower developmental course. PR latencies may provide an early indicator of visual pathway and wider cerebral damage in children at risk for cerebral palsy. For OR responses, the absence of a significant response may be a better indicator of cerebral impairment than latency. While the calculated latency for PR showed little variation with age in the clinical group, it had a clear downward trend for the normal group.

Preterm birth has long-term, irreversible neurological, cognitive, and educational after-effects. Latency measures potentially provide a key role in monitoring and predicting neurological status of at-risk infants. The values of PR and OR-VEPs in assessing CP progression or treatment efficacy remain to be discovered.

8 FACTORS AFFECTING VEP LATENCIES

8.1 Background

Visual evoked potentials are brainwave responses recorded from the scalp that are time-locked to the visual stimulus. Latency to VEPs depends not only on the participants' physiological makeup but also on the various stimulus parameters in any particular study.

This thesis studied pattern, orientation, and direction-reversal VEPs. While responses to OR and DR arise mostly from orientation specific complex cells, PR responses can be achieved by mostly simple cells in the V1. Complex cells have been shown to receive faster afferents than simple cells in cats (Hoffmann and Stone, 1971) and in monkeys (Bullier & Henry, 1980).

Conduction speed in the visual pathways is influenced by external factors such as temperature, and structural physiological factors such as myelin thickness, axon diameter and length (Waxman, 1980). The latency values investigated in the present study may depend on some or all of the following physiological factors: (1) myelination of pathways to the source, synaptic density, synaptic efficiency, refractory period, and response variability (de Haan, 2007); (2) maturation rate of the classes of neurons that generate SS-VEP and transient VEP signals (Dubois et al., 2008); (3) consistency of the brain's response with age- decreasing variability will decrease peak latency and increase amplitude (Thomas & Crow, 1994); (4) increasing and decreasing the number of neuronal generators and pathways in producing sustained action potential for signal synchronization; (5) the ripple effect of action potential from stimulated neuronal

generators that can travel and be measured at the scalp (Tobimatsu & Celesia, 2006); (6) large scale synchronization-temporally and spatially (Shiegeto et al., 1998); (7) feed-forward connections (Bonmassar et al., 1999; Di Russo et al., 2007); (8) additional delay from neural feedback that includes horizontal connections, inhibition and recurrent loops (Lamme & Roelfema, 2000).

Latency also depends on other factors such as (1) individual features including skull thickness, bone conductance, head circumference (De Haan, 2007); (2) individual performances such as attention (Di Russo & Spinelli, 1999; Di Russo et al., 2002); and (3) stimuli: optimal viewing parameters such as viewing distance and contrast level to drive enhanced feed forward signaling.

To uncover some of the factors that affect VEP latencies, this chapter provides a broader overview of a few of physiological and external factors.

8.2 Possible neural underpinnings

VEP response depends on neuronal spatial and temporal arrangements. Some of the spatial factors include the location of the lead, neuron arrangement, type, spatial area, and geometry. VEP amplitude increases as the recording electrode is closer to the neuronal source. Temporally, VEP latency depends on (1) sustained action potentials, (2) synchronization, (3) feed forward connections, (4) feedback loops, (5) inhibition and recurrent loops by horizontal cells, (6) attention level of the participants (Wood & Allison, 1981). Tovee (1994) suggests that feed forward information for most basic visual recognition will reach the cortex within the first 100 ms, with a 10-15 ms variation between the parallel processing channels. Feedback mechanisms will then modulate

information through lateral inhibition and finally feedback form higher cortical areas. Feedback connections have been shown to amplify and differentiate information from the background noise (Hupe et al., 1998).

8.2.1 Magnocellular vs. parvocellular pathways

Magno and parvo pathways provide distinct inputs to cortical processing. They start their segregation from the retinal ganglion cells, then to the LGN, and finally the cortex. M pathway is the fastest followed by the P pathway and finally the slow konicellular pathway. Directional information is believed to be derived from the magno pathway (Livingstone & Hubel, 1988) while orientation is associated with the parvo stream (Atkinson, 2000). Using single cell recording in macaque monkeys, Kaplan & Shapley (1982) found that signals from P cells usually take 5 ms longer to reach the cerebral cortex than the M-cells. In V1, there is a 20 ms difference between 4Cα (M) and 4Cβ (P) (Nowak et al., 1995). This may explain the additional early transient direction response that is about 20ms earlier than the P1 of the pattern and orientation- reversal VEPs seen in humans (Chapter 3; Lee et al., 2013a). In this thesis, because both the transient and calculated latency measures were derived from overlapping TF ranges, these experiments could not accurately differentiate the contribution of magno / parvo pathways.

The P pathway that feeds into the ventral stream is responsible for orientation and color. The ventral stream may develop earlier compared to the M pathway that is responsible for the dorsal stream that analyses motion and binocular disparity. In development, Moskowitz and Sokol (1980) found that 2 to 6 months old infants were able to achieve adult level temporal tuning at low SF by 3-4 months and at high SF by 5

years. This consistent with earlier development of the magno function that will support high TFs at low SFs (Braddick & Atkinson, 2009). The reason may be that the immature V1 contains about 10 times more P cells compared to the population of M cells (Ahman & Spear, 1993).

Nonetheless the segregation between the M & P pathways is difficult to identify. Zeki & Shipp (1988) proposed that none of the functions are necessarily unique to a specific brain region. First patchy stains from the enzyme horseradish peroxidase in the V1 signified that V1 could be further subdivided into unique functional areas. Not all cells in V1 have direct connections with V5. Second, orientation selectivity is generated in both the P-V4 & M-V3 systems, both involved in form perception. Third, input to V5 from V1 & V2 terminates patchily. Zeki & Shipp (1988) thus suggests that each area is a part of a pathway that involves several cortical areas.

There is also intermixing of the two pathways in LGN and up to the cortical areas (Nealey & Maunsell, 1994). As the population of the P cell is about 10 times more than that of M cells, (Ahman & Spear, 1993) the different population distribution and potential summations creates different SNR ratio and synchronization capabilities, where the P cells may result in earlier peak latency than the more noisy M cells. As neurons shift their individual response onset to result in a synchronized population response, the result is a more reliable and enhanced peak response (Fries et al., 2001). Nakamura & Ohtsuka (1999) proposed that even though P1 is thought to originate from the P pathways, it might also be possible that part of P1 was from neuronal inputs of the M pathway. Latency changes with the size of neuronal population where summation of cell can elicit earlier responses (Mansell et al., 1999). At 28 cd/m^2 luminance (similar to the mean luminance

used in this study- 31 cd/m^2), models from single cell recordings from two anesthetized adult monkeys showed that P cells is much faster in the beginning of a response. M cells innate processing speed only becomes an advantage when there are at least 10 M cells to every 100 P cells. Borg-Graham, Monier, and Fregnac (1998) have also proposed that both on and off response combine their excitatory & inhibitory inputs through strong shunting GABA input to the cortex that are early and nonlinear. Shorter peak latency thus may be reflective of specific cell population summation rather than earlier stage of visual processing.

Lamme and Roelfsema (2000) have also addressed the difficulty in the proper distinction of the dorsal and ventral stream, M and P pathways. That is because of (1) the size of the receptive field increases in higher areas and tuning become more complicated, (2) not all neurons within a given area receive their inputs from shortest routes, (3) a neuron topologically closer to the retina but belong to slower stream may respond later, (4) the internetwork of lateral and feedback interloops.

8.2.2 Other neurological pathways

Visual processing latency depends on inputs from alternative pathways (Coburn et al., 1990), conduction times due to myelination (Buchner et al., 1994), the length of anatomical pathways (Beckers & Zeki, 1995), the hierarchical order of intercortical connections (Bullier et al., 1996), signal-processing times (Wallis & Rolls, 1997), and patterns of convergence (Maunsell et al., 1999). As receptive field structure increases in the higher cortical areas, interactions and tuning also becomes more complex. The significant difference seen between the calculated and transient latencies in infants

reflects that these neuronal populations mature at different rates, and the proportions of different type of neuron contributing to VEP to a particular SF may also change with maturation.

There are many different connectivity loops. Hupe et al., (1998) proposed that feedback connections work in a push-pull action where they amplify the response to the optimal stimulus in the centre of the receptive field but decrease the response to less optimal stimuli. MEG (Tzelepi et al., 2001), fMRI, and multiple dipole analysis (Vanni et al., 2004) have shown that V5 responds 10-20 ms after V1 activation using simple pattern-onset stimulus. Moreover, Bringuier et al (1999) found that the synaptic depolarization of VEP spreads into the vicinity through horizontal networks at a constant velocity like a radial wave, suggesting that the recorded VEP response may be influenced by the previous evoked potential in the cortex few milliseconds prior.

Mountcastle (1998) used single cell recording to show that different hierarchical levels are simultaneously activated by visual stimuli. Similarly using structural connectivity data from CoCOMac database and single-cell recording data of all brain regions, Capalbo et al (2008) also proposed that a revised computational model with fewer levels of connectivity compared to most models and inclusion of a subcortical-cortical route fitted the data best. In Capalbo et al's proposed hierarchy, subcortical areas simultaneously feed into regions V1, V2, V3, MT, MST (medial superior temporal), and FEF (frontal eye fields) which then all feed upward to area V4. However, the model contains few constraints: 1) the conduction velocity difference cannot fully account for the inter-area latency difference; 2) conduction velocities differ between cortical and subcortical pathways; 3) conduction velocity is hard to estimate- as it depends on

myelination and diameter of neurons that differs among cell types and their functional streams. Our data is consistent with others (Capalbo et al., 2008; Mountcastle, 1998) that the visual system carries parallel channels and supports the claim of simultaneous processing.

Further physiological changes occur in development, so that upon reaching maturity, contrast and orientation responses arise from the same level of cortical processing in V1, which is already orientation selective at the time of the peak responses. The overall brainwave response involves temporal integration through a series of spectral filtering operations and the processing of features. For example, orientation requires recurrent processing from top-down feedback loops and/ or long-range horizontal connections (Lund & Levitt, 1996). These pathways develop over a longer period (Burkhalter, 1993; Dubois et al., 2008) and will introduce further processing delays.

8.2.3 Visual development

Changes in transient latency may be influenced by the concurrent synaptic maturation in retina, LGN, and occipital cortex, but the most widely cited factor is the progressive myelination of the visual pathways (Kos-Pietro et al., 1997; Tsuneishi & Casaer, 1997). Dubois et al. (2008) tested 15 infants (5.6-17 weeks) with diffusion tensor imaging of cerebral white matter and VEP to face stimuli. They found that the P1 latency to PR was significantly correlated with infants' age and with structural changes in optic radiation, but not with the global maturation of white matter. Friendly (1993) suggested that the myelination of the LGN pathway was completed by 4 months, which is in accord with our result that adult P1 latency is reached by about 15 weeks of age. Others have

shown continuation of myelin maturation for the first two years of life (Friede & Hu, 1967; Gao et al., 2009). Because myelination varies among different fibers during development (Dubois et al., 2008; Loenneker et al., 2011), this variation will degrade phase coherence of neural transmission to the cortex, and would be expected to result in degraded amplitude and delayed latency in the VEP responses. The inhomogeneity of timing may contribute to the higher latency variance seen in the infant group.

In addition to incomplete myelination, there are many ways in which visual cortical processing is immature during the first 4-6 months (Atkinson, 2000). For local processing, while the onset of form processing appears to precede motion (Braddick et al., 2005), peak latency of motion detection matured before form, in line with other studies (Burkhalter et al., 1993; Huttenlocher & de Courten, 1987). Synaptic density in layer 4B, responsible for motion analysis (Hawken et al. 1988), was found to reach its maximum 4 months earlier than layer 2/ 3 that governs form processing (Huttenlocher & de Courten, 1987). A post mortem infant study by Burkhalter et al. (1993) revealed that the horizontal connections within layer 4B were adult-like by 8 weeks and within layer 2/3 around 16 weeks. This corresponds well to the present study where the transient latency of DR matured around 10 weeks (Chapter 5; Lee et al., 2013a) while pattern did so at about 15 weeks of age (Chapter 3; Lee et al., 2012a). This maturation of horizontal connections may be also related to the extended range of velocities with age found by Wattam-Bell (1991). The onset of global form at about 9-20 weeks, however, was delayed compared to the age of onset of global motion at 7-10 weeks (Braddick et al., 2005; Wattam-Bell, 2010). The faster development of local and global motion coherence may partly explain why its associated dorsal stream is more vulnerable to brain trauma

than the ventral stream that is mainly responsible for form (Braddick et al., 2003). We propose that immaturity of cortical processing, reflected in infants' simpler VEP waveforms, is one of the many explanations for the additional developmental delays seen in the latency calculated from relative phase compared to transient peak latency.

8.3 Stimulus parameters

Peak latency is dependent on the particular visual stimulus parameters such as temporal frequency (TF), SF (Moskowitz & Sokol, 1983; Tobimatsu et al., 1993), luminance, contrast level (Tello et al., 2010; Tyler & Apkarian, 1985), monocular versus binocular stimulation (McCulloch et al., 1991), and the individual's attention (Di Russo and Spinelli, 1999).

Development of latency to contrast changes is strongly dependent on the specific stimuli used. From studying 439 children aged 1 month to 5 years, Moskowitz & Sokol (1983) found that P1 peak latency to PR becomes adult like by 1 year for large checks (30-240'), and beyond 5 years of age for small checks (7.5 and 15'). McCulloch & Skarf (1991) found that infants' peak latency lies within one SD of adult value by 4-5 months for 120' and 60' checks (consistent with our results) but is still not adult-like by 2 years for smaller checks (30', 15', and 7.5'). It would be of interest to extend our studies and examine whether the longer latencies found by the calculated method remain over a longer developmental period at higher spatial frequencies.

8.4 Other factors

The success rate of VEP responses depends on individual attention level (Di Russio et al., 2002). Calculated latency may be more affected by attention than the transient latency. Attention to the spatial frequency of a stimulus has been shown to affect transient VEP components at 150 ms and beyond, but not at 100 ms or earlier (Baas et al., 2002; Fries et al., 2001; Martinez et al., 2001). Kim et al. (2007) suggested that attention increases response by contrast gain, increasing its stimulus contrast, or by activity gain, boosting stimulus driven activity. Attention has been shown to improve orientation detection (Ling & Carrasco, 2006) possibly due to increased synchronization of response activity by increased phase coherence of the neuronal population and boosting the stimulus evoked activity. Attention may introduce feedback connection from higher visual areas to improve the salience of the attended stimuli (Di Russo et al., 2003; Gomez Gonzalez et al., 1994; Martınez et al., 2001). Such attentional effects on later waveform components may contribute to the larger variance seen in the calculated latency.

There are other factors that may increase VEP latency. For example, elder age (Allison et al., 1984), especially those above 65 years (Fiorentini et al., 1996), and increasing head circumference (Zhao & Pan, 2008) has all been correlated with longer transmission time. As males usually have larger head circumference than females, male often have longer P1 latency (Celesia et al. 1987; Tobimatsu et al., 1993a). However, latency increases with decreasing pupillary diameter (Tobimatsu et al., 1988), contrast (Chiappa, 1997; Tello et al., 2010; Tobimatsu et al., 1993a), luminance (Tobimatsu et al., 1988; Tyler & Apkarian, 1985), TF (Tobimatsu et al., 1993), and the individual's attention (Di Russo & Spinelli, 1999).

8.4 VEP limitations

As with all EEG studies, the true meaning of the transient P1 latency and phase-based calculated latency and their respective physiological origins remain unclear. Most studies can only conclude that it stems from the striate cortex (Hashimoto et al., 1999; Nakamura et al., 1997 & 2000; Seki et al., 1996; Shigeto et al., 1998).

Because VEP is only a measurement of activity recorded from the scalp, the underlying neural bases of these VEP responses and their associated developmental changes remains a challenge to understand. To calculate a source from surface potentials, one needs to localize all the dipole sources, inward, and outward trans-membrane currents at the microscopic level. As Wood & Alison (1981) suggested, this would only work if all potentials were assumed to be generated by single point dipole sources. This remains a conundrum as dipoles are known to interfere with each other, and are most likely to do so in distinct ways in different brains - for different brains and skulls have their own physical properties: density, thickness, resistivity, and conductivity. Accurate head modeling will require structural MRI of individual heads– a challenge for infant studies where such imaging is normally done only for clinical purposes. Modeling also depends on tissue properties that may differ between infants and adults – for example, the open fontanel in the cranial bones during the first postnatal months must affect the geometry of current flow in the heads of young infants.

8.5 Summary

Factors that affect VEP latency include physiological neuronal underpinnings and external stimulus parameters. These factors should be taken into consideration when interpreting any VEP or EEG data. Although VEP is postulated to record postsynaptic activity in the input layer, the specific origin of the VEP response remains a mystery. Given all the challenges in determining the true meaning of VEP latency data, interpretation and extrapolation of the data presented in this thesis should be limited to the three specific stimuli and the conditions used.

9 CONCLUSIONS

9.1 Overview

Visual evoked potentials record synaptic activity from neuronal populations that propagates to the scalp surface where the recording is made. It reveals temporal and spatial aspects of the visual system, and results in precise detection of the temporal pattern of neuronal response, with high SNR. This thesis provides a series of systematic studies of the developmental changes in the VEP to different types of stimulus event, specifically in the latency of responses. While the transient P1 latency focuses on the initial cortical response to retinal input, the phase-based calculated latency reflects all the components of the VEP waveform, which better indicate the time course of cortical processes. Studies on adults, infants and clinical groups proved these latency measures to be crucial and reliable indicators of visuocortical development. The primary goal of this research were to establish (a) the efficacy of the two latency methods: transient P1 latency and phase-based calculated latency, (b) the comparison between the two methods, and (c) normative baselines of latency development for both measures, for pattern, orientation, and directional VEPs respectively.

The broader aim of this thesis is to enhance the current scientific understanding of (a) how parallel visual processes develop in infancy, (b) the balance of visual information that infants can access in a key period for their cognitive and spatial development; and (c) to provide means of assessing normal and abnormal development of the visual pathway for clinical evaluations.

9.2 Comparison of pattern, orientation, and direction- reversal VEPs

9.2.1 Participants

VEP latency baselines were established after studying 81 adults (median age 21.4) and 137 healthy full term infants (3.6- 79.0 weeks) in most of the studies in this thesis.

9.2.2 Comparison of all three stimuli

9.2.2.1 Transient P1 latency

VEP waveforms usually develop from a single late positive peak at birth to double peak & trough complex. For both adult and infant groups, DR responses were the most difficult to obtain while orientation ranked second and PR responses were the easiest to record. DR in many subjects was found to have an additional early peak 16-37 ms shorter and a regular P1 latency that was 10-20 ms longer than that of both the PR and OR-VEPs. The early peak may indicate a faster subcortical route directly to V5 for motion processing (Chapter 5; Lee et al., 2013a). The transient P1 latencies for adult PR and OR were similar. Lamme & Roelfsema (2000) suggested that the first spikes may be selective for orientation and optical flow. This is also in line with Tovee (1994)'s prediction that low-level visual processing (contrast, orientation, and motion) should be reflected in the cortex within about 100 ms with 10-15 ms interspike interval differences

Infants had similar peak latencies in all three stimuli by about 20 weeks or 4.6 months of age. The initial response to pattern, orientation, and direction may stem from similar or parallel processes in which all three functions require the initial transmission of visual information from the retina to the cortex. The decrease seen with age could largely

be due to progressive myelination of the optic nerve, tract, and radiations (Dubois et al., 2008; Kos-Pietro et al., 1997; Tsuneishi & Casaer, 1997).

Yet the rate of maturation for infants' responses to the three visual stimuli varies. Infants' latency of the initial peak matured first for motion - around 10 weeks or 2.3 months, then for pattern at 15 weeks or 3.5 months, and finally orientation at about 50 weeks or 11.5 months. This suggests that peak latency of motion (DR) detection matured before form (OR). Results of other studies (not measuring latency) have suggested that while the initial onset of motion responses is later than that for orientation (Braddick et al., 2005), subsequently motion processing develops more rapidly than for form (Braddick et al., 2003; Wattam-Bell et al., 2010).

9.2.2.2 Phase-based calculated latency

Unlike the transient latency that represents the arrival of some visual input at the cortex, calculated latency represent the timing of the whole waveform that leads to delays or temporal shifts across the entire range of temporal frequencies. Our results show that calculating latency from relative phase in SS-VEP can yield usable results even with just two TFs. This is especially helpful for future studies on infants or patients where recording time is limited and sustained attention is poor. For both adults and infants, while the calculated latency of PR responses was similar to their peak latency, the calculated latency of both OR and DR responses (~200 ms) were almost double their respective peak latencies (~100 ms).

In infants, whereas OR calculated latency remained relatively unchanged up to 1.5 years of age (and was little different from adults'), both PR and DR latencies

decreased with age. Infants reached adult orientation values first at about 4 weeks, then adult pattern and direction latencies at about 30 weeks. This difference may be because orientation responses are governed by feedback loops and lateral connections within the primary visual cortex, whereas DR may depend on additional feedback from higher level processing from the extrastriate cortices that develop gradually over the early years of life. However, this would imply the unexpected result that PR responses are like DR rather than OR in this pattern of cortical processing.

Calculated latency must reflect the time taken for cortical processing beyond the initial orientation-selective response, perhaps including processing time arising from horizontal connections between the orientation columns (Gilbert & Wiesel, 1989; Nauhaus et al., 2009), non-linear transformation between the primary and extra-striate visual areas (Geisler & Albrecht, 1995), and/or integration of spatio-temporal features (Lamme & Roelfsema, 2000). Recurrent and inhibition loops between V1 and extra-striate areas could also contribute to late components of the response (Lamme & Roelfsema, 2000).

9.4 Limitations

As VEP responses are recorded from the surface of the scalp, interpretations and explorations of the recordings are limited. First, the distinction between transient VEP and steady-state VEP is a fine line. Heinrich (2010) proposed that a key factor to look for is when the stimulus frequency above which the waveform is essentially sinusoidal. This often occurs around 4-5 r/s for pattern and orientation reversal VEP, but around 3-4 r/s for direction-reversal VEP. Heinrich proposed that the overlapping of stimulus events

may result in constructive or destructive waveform depending on the harmonic frequency or where the peak and troughs of the waveforms are aligned. According to Heinrich (2010), the higher harmonics might stem from the natural oscillatory frequency of certain neuronal groups or a resonance effect of the entire neuronal network, where few harmonics will actually contribute to the SS-VEP responses. Hence interpretations of the results of this thesis should be limited to response arising directly from the stimulus events and not be extrapolated to higher harmonics or higher visual processes.

Furthermore, it is very difficult to determine when the process of latency development ends. Although the physiology may begin to take shape and mature earlier on, the full functionality of the entire pathway or stream is difficult to test. Physiologically, the LGN is morphologically matured by 9 months (Garey & de Courten, 1983). Hickey (1977) suggest that P cell reaches adult size by the end of the first year while the M cells do so by the end of the second year. Synaptic density and cortical volume, however, doesn't reach adult values until 11 years of age (Garey & de Courten, 1983). After finding an age-dependent amplitude decrease in pattern ERG and VEPs, Brecelj et al (2002) suggested that central retina and the visual pathway may continue to mature in children age 7 to 18. Others suggest that contrast and acuity sensitivity continues to develop till late childhood (Ellemberg et al., 1999; Neu & Sireteanu, 1997). Similarly, Gunn et al (2002) suggest that motion seems to have a slower and variable time course for refinement up to age 10 during childhood. One should be careful in making assumptions of brain maturity, especially its end point, when investigating visual development.

In any case, VEP could provide invaluable data on the generators and interactions that form surface recorded responses. Collaboration among VEP, MEG, and fMRI studies would be necessary to solve the inverse problem of response origins. Animal models, in which intracranial recordings can be made including electrodes in specific cortical layers, could provide more information on specific brain regions and functional pathways responsible for the latency differences.

9.5 Implications

VEP stimuli can be carefully designed to reveal distinctive visual pathways. VEP latency, in particular, is an important indicator for attention (Di Russo & Spinelli, 1999 & 2002), binocularity (Tobimatsu & Kato, 1996), visual development (Fiorentini & Trimarchi, 1991; Porciatti, 1984), luminance and colour contrast (Morrone et al., 1996), clinical evaluation (Falsini & Porciatti, 1996; Tobimatsu et al., 1990), spatial frequency (Simon, 1992; Tobimatsu et al., 1993), and ageing (Porciatti et al., 1992).

The transient P1 latencies showed similar developmental trends and possible parallel processing routes for pattern, orientation, and direction processes. Phase-based calculated latency, however, revealed that orientation in V1 might mature later than the processes that determine phase and direction from extrastriate areas. While the dorsal stream governing motion (indicated by DR-VEP) may appear to mature earlier than the ventral stream responsible for form (indicated by OR-VEP), the complete maturation and fine-tuning of the motion pathway was delayed in comparison to form. As the DR calculated latency asymptotes to OR calculated latency at around 50 weeks, there seems

to be functional change upon maturity such that the higher visual cortices appear to utilize similar or parallel processing to analyse both form and motion. In terms of VEP latencies, V1 may mature earlier than extrastriate cortices; yet interactions between the striate and extrastriate areas may become more prominent with age (Alonso et al., 1993; Mignard & Malpeli, 1991).

VEP latency is also a valuable tool in clinical diagnosis and prognosis. It is useful in tracking any visual-neuro developmental changes such as refractive astigmatism, amblyopia (Sokol & Moskowitz, 1980), dementia (Tobimatsuet al., 1994), Parkinson's disease (Bodis-Wollner, 1990), multiple sclerosis (Blumhardt, 1986; Matthews & Small, 1979), and migraines (Mortimer et al., 1990).

Chapter 7 on atypical infants demonstrated that OR-VEP is a better diagnostic tool for at-risk infants than PR-VEP, suggesting that orientation requires cortical processing. OR-VEP is strongly correlated to changes seen on neonatal imaging in children with hypoxic-ischaemic brain injuries at term (Mercuri et al., 1997) and predictor of later outcome at 2 years (Mercuri et al., 1999). Mercuri et al (1998) suggest that higher TF of OR may be more prone to brain injury because high TF requires more precision of neuronal synchronization across time and space. As PR is present at birth, this fundamental process is less prone to perinatal insults, while the postnatal response of OR and maybe DR are susceptible.

Many response components with specific latencies, have been taken as signatures of specific aspects of processing latency responses to date. For example, N60 is sensitive to attention levels (Di Russo & Spinelli, 1999), N95 to low contrast levels, N120 to colour changes (Tobimatsu et al., 1999), and N170 to orientation changes (Rossion et al.,

2000). N170, N290, P400 peaks are all seen as responses to faces (de Haan, 2007).

Does shorter latency imply earlier visual processing in detecting the stimuli, or earlier functionality in development? The answer depends on the neuronal population, the synchronization ability of the neurons, the location of the visual pathways (the distance to the source), and connectivity of the neurons. All of these areas need to be thoroughly investigated before true implications of latency data can be understood.

9.6 Future directions

As this study uses sine waves for PR and OR, investigation into the latency of different gratings could also be interesting. While a sine wave contains only the fundamental spatial frequency component, a square wave contains the fundamental and multiples of its fundamental frequency at higher harmonics that are aligned in the same orientation. Since the primary visual cortex is nonlinear, our hypothesis is that latency will vary based on its harmonic spectrum. Bobak et al (1988) found that although checkerboard and sine wave grating produce similar latencies, latencies of checkerboards are more affected by blur.

It would be interesting to investigate the difference between the latency of different temporal harmonics in the response waveform. The higher frequency components in the response may reflect a higher cortical level that introduces more processing delays. The major response to the onset-offset-onset-offset sequence in pattern reversal consists of symmetrical ON and OFF responses, resulting in the dominance of the second harmonic responses. The calculation of latency from phase values can however be done for higher harmonics as well as for this response at the

reversal frequency. F2 and F4 are found to be independent processes in patients with multiple sclerosis (Ghilardi et al., 1991) and Alzheimer's disease (Celesia et al., 1993). F2 responses had greater binocular inhibition than that of F4 (Tobimatsu & Kato, 1996). F4 latency seems to be unaffected by early age while F2 is (Porciatti et al., 1992).

In addition, it should be possible to extrapolate the current findings and find the latency development of global form and motion. Wattam-Bell (2010) found that the extrastriate area of 5-month-olds could integrate local visual information to detect global organization and generate global form and motion VEP responses. Others (Ellemberg et al., 2003; Kuba & Kubova, 1992) have found N2 (150-200 ms) to be more associated with motion processing while P1 was for pattern processing. Amplitude of N2 not P1 reduces with motion adaptation (Beach & Ullrich, 1994). N2 not P1 is independent of contrast (Beach & Ullrich, 1997). One could examine the changes of N2 peak and calculated latencies against various TF.

In the clinical setting, continued investigation in using orientation-reversal VEP to diagnose and monitor atypical infants would provide further clues into the use of OR-VEP and implications regarding its latency. Another possible suggestion for development is to use high-density arrays that could separate the timing of V1 and extrastriate processing, and perhaps test whether the P1 and the 'early peak' in DR have anatomically separate origins. It would also be of interest to extrapolate the clinical value to DR-VEP to assess higher cortical functions such as motion processing.

As VEP provides only a glimpse of neuronal function, a complete picture of brain development can only be achieved through a collaboration of disciplines, such as studies in animal anatomy, electrophysiology, human imaging, behaviour testing, and

computational models. In the future, there needs to be more integration of electrophysiological and behavioural tests in order to fully comprehend physiological and functional change across the human lifespan. Cooperation among the developmental cognitive, biological, and social neurosciences will be necessary to understand normal infant visual development and assist the understanding and therapy of atypical development.

9.7 Summary

In summary, VEP is useful in studying infant perceptual and brain development because it is a quick analyser of neuronal transduction. VEP peak latency, morphology, and amplitude all change across the life span. This thesis found that transient peak latencies of phase, orientation, and direction VEPs showed similar developmental trends suggesting possible parallel processing routes. Latencies calculated from steady-state phase, however, may reflect the timing of cortical processing beyond the initial response, including cortical feedback effects. While peak latency indicated that initial detection of motion matured before orientation, calculated latency revealed that the fine-tuning of orientation matured before motion processes. There is also a dominant effect of transmission delay in infancy due to immature myelination and cortical processing in terms of synaptic connections. By adulthood, there is a significant contribution of later cortical processing to generate the overall brainwave.

To better understand latency development, the best strategy is to perform longitudinal and systematic electrophysiological studies to track the responses over many

stages of infancy. Future work will need to integrate electrophysiological studies with other behavioural, neuro-imaging approaches and animal studies to fully appreciate the functional significance of the brainwave responses in infant visual development.

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