An exploration of pre-attentive visual discrimination using event-related potentials

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Abstract

The Mismatch Negativity (MMN) has been characterised as a 'pre-attentive' component of an Event-Related Potential (ERP) that is related to discriminatory processes. Although well established in the auditory domain, characteristics of the MMN are less well characterised in the visual domain. The five main studies presented in this thesis examine visual cortical processing using event-related potentials. Novel methodologies have been used to elicit visual detection and discrimination components in the absence of a behavioural task. Developing paradigms in which a behavioural task is not required may have important clinical applications for populations, such as young children, who cannot comply with the demands of an active task. The 'pre-attentive' nature of visual MMN has been investigated by modulating attention. Generators and hemispheric lateralisation of visual MMN have been investigated by using pertinent clinical groups.

A three stimulus visual oddball paradigm was used to explore the elicitation of visual discrimination components to a change in the orientation of stimuli in the absence of a behavioural task. Monochrome stimuli based on pacman figures were employed that differed from each other only in terms of the orientation of their elements. One such stimulus formed an illusory figure in order to capture the participant's attention, either in place of, or alongside, a behavioural task. The elicitation of a P3a to the illusory figure but not to the standard or deviant stimuli provided evidence that the illusory figure captured attention. A visual MMN response was recorded in a paradigm with no task demands. When a behavioural task was incorporated into the paradigm, a P3b component was elicited consistent with the allocation of attentional resources to the task. However, visual discrimination components were attenuated revealing that the illusory figure was unable to command all attentional resources from the standard deviant transition. The results are the first to suggest that the visual MMN is modulated by attention.

Using the same three stimulus oddball paradigm, generators of visual MMN were investigated by recording potentials directly from the cortex of an adolescent undergoing pre-surgical evaluation for resection of a right anterior parietal lesion. To date no other study has explicitly recorded activity related to

the visual MMN intracranially using an oddball paradigm in the absence of a behavioural task. Results indicated that visual N1 and visual MMN could be temporally and spatially separated, with visual MMN being recorded more anteriorly than N1.

The characteristic abnormality in retinal projections in albinism afforded the opportunity to investigate each hemisphere in relative isolation and was used, for the first time, as a model to investigate lateralisation of visual MMN and illusory contour processing. Using the three stimulus oddball paradigm, no visual MMN was elicited in this group, and so no conclusions regarding the lateralisation of visual MMN could be made. Results suggested that both hemispheres were equally capable of processing an illusory figure.

As a method of presenting visual test stimuli without conscious perception, a continuous visual stream paradigm was developed that used a briefly presented checkerboard stimulus combined with masking for exploring stimulus detection below and above subjective levels of perception. A correlate of very early cortical processing at a latency of 60-80 ms (CI) was elicited whether stimuli were reported as seen or unseen. Differences in visual processing were only evident at a latency of 90 ms (CII) implying that this component may represent a correlate of visual consciousness/awareness.

Finally, an oddball sequence was introduced into the visual stream masking paradigm to investigate whether visual MMN responses could be recorded without conscious perception. The stimuli comprised of black and white checkerboard elements differing only in terms of their orientation to form an x or a +. Visual MMN was not recorded when participants were unable to report seeing the stimulus. Results therefore suggest that behavioural identification of the stimuli was required for the elicitation of visual MMN and that visual MMN may require some attentional resources.

On the basis of these studies it is concluded that visual MMN is not entirely independent of attention. Further, the combination of clinical and non-clinical investigations provides a unique opportunity to study the characterisation and localisation of putative mechanisms related to conscious and non-conscious visual processing.

Declaration

The work presented in this thesis is the work of the author.

Table of contents

Abstract..... 1
Declaration..... 3
Table of contents..... 4
List of abbreviations..... 9
List of figures..... 10
List of tables..... 12
List of publications and conferences..... 13
Acknowledgements..... 14
Preface..... 15
1 General introduction..... 16
1.1 Anatomy of the visual pathways..... 17
1.2 Laminar structure of the visual cortex..... 19
1.3 Central visual system..... 20
1.4 Visual association cortex..... 21
1.5 Techniques employed in the investigation of central visual function 22
1.5.1 PET..... 23
1.5.2 fMRI..... 24
1.5.3 MEG..... 24
1.5.4 EEG..... 24
1.6 Principles of event-related potentials..... 25
1.6.1 ERP definition..... 25
1.6.2 Averaging and digital filtering..... 26
1.6.3 Oddball paradigm..... 26
1.7 Visual ERP components..... 27
1.7.1 Exogenous components..... 29
1.7.2 Endogenous components evoked in an oddball paradigm..... 30
1.7.3 N2..... 30
1.7.4 P3..... 31
1.7.5 MMN..... 31
1.8 The auditory MMN..... 32
1.9 Characteristics of the visual Mismatch Negativity..... 34
1.10 Visual event-related potentials in clinical research..... 37

1.11 Aim of this research..... 38
2 Methodology..... 39
2.1 Ethical considerations..... 39
2.2 Instrumentation..... 40
2.3 Methods..... 42
2.3.1 Participants..... 42
2.3.2 Protocol..... 42
2.3.3 Stimuli and stimulus presentation..... 43
2.3.4 Data acquisition..... 44
2.3.5 Filters..... 44
2.3.6 Electrodes..... 44
2.3.6.1 Scalp electrodes..... 45
2.3.6.2 Intracranial electrodes..... 45
2.3.6.3 Reference electrode..... 45
2.3.7 Off line data analysis..... 46
2.3.7.1 ERP construction..... 46
2.3.7.2 Measurement of voltage amplitude and latencies..... 46
2.3.7.3 Subtraction waveforms..... 47
2.3.8 Statistical analysis..... 47
3 Can illusory deviant stimuli be used as attentional distracters to record visual MMN in a passive three stimulus oddball paradigm?..... 49
3.1 Aim..... 49
3.2 Introduction..... 49
3.2.1 Rationale and predictions..... 51
3.3 Methods for Experiments 3.1 and 3.2..... 52
3.3.1 Participants..... 52
3.3.2 Stimuli and procedure..... 52
3.3.2.1 Experiment 3.1..... 52
3.3.2.2 Experiment 3.2..... 53
3.3.3 EEG recording and analysis..... 53
3.3.4 Results..... 54
3.3.4.1 Experiment 3.1..... 54
3.3.4.2 Experiment 3.2..... 58
3.4 Discussion..... 61

4 Intracranial recording of visual evoked potentials..... 64
4.1 Aim..... 64
4.2 Introduction..... 64
4.2.1 The inverse problem..... 64
4.2.2 Intracranial recordings..... 65
4.2.3 Intracranial studies of visual discrimination..... 66
4.3 Methods..... 68
4.3.1 Participant..... 68
4.3.2 Stimuli and procedure..... 69
4.3.3 Subdural electrode implantation and electrodes..... 69
4.3.4 EEG recording and data analysis..... 72
4.4 Results..... 72
4.5 Discussion..... 76
5 Exploration of hemispheric lateralisation of visual MMN and perception of illusory contours..... 79
5.1 Aim..... 79
5.2 Introduction..... 79
5.2.1 Hemispheric specialisation..... 81
5.2.2 Importance of the right hemisphere for visual MMN..... 81
5.2.3 The right hemisphere and illusory contour processing..... 82
5.2.4 Rationale..... 84
5.3 Methods for Experiment 5.1 and Experiment 5.2..... 85
5.3.1 Participants..... 85
5.3.2 Procedure..... 87
5.3.3 EEG recording..... 87
5.4 Experiment 5.1: Procedure to confirm primary optic pathway misrouting..... 88
5.4.1 Stimuli..... 88
5.4.2 VEP data analysis..... 88
5.4.3 Results..... 89
5.4.4 Discussion..... 92
5.5 Experiment 5.2 visual oddball paradigm..... 93
5.5.1 Participants..... 93
5.5.2 Stimuli..... 93

5.5.3 VEP data analysis..... 93
5.5.4 Results..... 94
5.5.4.1 VEP results..... 94
5.5.4.2 Statistical analysis of illusory deviant latency data..... 96
5.5.4.3 Statistical analysis of illusory deviant amplitude data..... 99
5.6 Discussion..... 102
6 Investigation of early visual processing responses in the pattern onset evoked potential and conscious visual perception..... 105
6.1 Aim..... 105
6.2 Introduction 105
6.2.1 The significance of the checkerboard stimulus in probing the visual system..... 107
6.3 Methods for Experiments 6.1 and 6.2..... 109
6.3.1 Participants..... 109
6.3.2 Stimuli and procedure..... 109
6.3.2.1 Experiment 6.1..... 109
6.3.2.2 Experiment 6.2..... 110
6.3.3 EEG recording and data analysis..... 111
6.3.4 Statistical analyses..... 112
6.4 Results..... 112
6.4.1 Experiment 6.1..... 112
6.4.1.1 Subtraction waveforms - pattern appearance/disappearance VEPs subtracted from a mask stimulus..... 112
6.4.2 Experiment 6.2..... 114
6.4.2.1 Comparison of pattern appearance / disappearance responses between Experiment 6.1 and 6.2 (masked versus unmasked conditions)..... 115
6.5 Discussion..... 120
7 Visual mismatch negativity to masked stimuli presented at very brief presentation rates..... 124
7.1 Aim..... 124
7.2 Introduction..... 124
7.2.1 Subliminal ERPs to neutral stimuli..... 125
7.3 Rationale and aim..... 127

7.4 Methods Experiment 7.1 128
7.4.1 Participants 128
7.4.2 Stimuli and procedure 128
7.4.3 EEG data recording 130
7.4.4 VEP data analysis 130
7.5 Results 131
7.5.1 VEP data analysis 131
7.5.2 Statistical analysis of amplitude data 133
7.5.2.1 Time window 155-185 ms 133
7.5.2.2 Time window 305-335 ms 134
7.6 Discussion 135
8 General discussion 139
8.1 Introduction 139
8.2 Summary of experiments 140
8.3 Visual MMN as a pre-attentive mechanism 142
8.4 Neuronal mechanisms underlying visual MMN 146
8.5 Generators of the visual MMN and hemispheric lateralisation 150
8.6 Development of visual diagnostic tests and future directions 152
8.7 Conclusion 153
References 154
APPENDIX I 177
APPENDIX II 178
APPENDIX III 179
APPENDIX IV 180

List of abbreviations

Ag/AgCl	Silver Silver-Chloride
ANOVA	Analysis of Variance
Auditory MMN	Auditory Mismatch Negativity
BA	Brodmann Area
BESA	Brain Electrical Source Analysis
BOLD	Blood Oxygenation Level-Dependent
cd/m²	Candela per Square Metre
CRT	Cathode Ray Tube
EEG	Electroencephalograph
ERPs	Event-Related Potentials
EPs	Evoked Potentials
fMRI	Functional Magnetic Resonance Imaging
GOSH	Great Ormond Street Hospital for Children
Hz	Hertz
iEEG	Intracranial Electroencephalograph
IGS	Image Guidance System
ISI	Interstimulus Interval
ISCEV	International Society for Clinical Electrophysiology of Vision
LGN	Lateral Geniculate Nucleus
MEG	Magnetoencephalography
MMN	Mismatch Negativity
MMNm	Magnetoencephalographic Mismatch Negativity
MOG	Middle Occipital Gyrus
ms	Millisecond
µV	Microvolt
PET	Positron Emission Tomography
PCA	Principle Components Analysis
SCD	Scalp Density Analysis
SD	Standard Deviation
sLORETA	Standardised Low-Resolution Brain Electromagnetic Tomography
SOA	Stimulus Onset Asynchrony
Visual MMN	Visual Mismatch Negativity

List of figures

Figure 1.1 Structure of the eye....17
Figure 1.2 Visual pathways to the brain....19
Figure 1.3 Brodmann architectural map, after Brodmann, K. 1909.....21
Figure 1.4 Functional neuroimaging methods and their temporal and spatial resolution. 23
Figure 1.5 Schematic of a generic visual waveform time-locked to stimulus event with labelled components....28
Figure 2.1 Schematic of an EEG laboratory set up....41
Figure 3.1 Stimuli presented in an oddball paradigm....53
Figure 3.2 Grand average waveforms referenced to Fz at electrodes O1 and O2. 55
Figure 3.3 Grand average waveforms for standard, deviant and illusory deviant stimuli at Fz, Cz, O1, Oz and O2 referenced to averaged mastoids. 58
Figure 3.4 A: Grand average waveforms referenced to Fz for standard, deviant and illusory deviant stimuli at electrodes O1 and O2. 59
Figure 4.1 3D MRI reconstruction and co-registered subdural electrodes, highlighted pink area denotes surface visible lesion. 71
Figure 4.2 Photograph of exposed cortex and 32 contact subdural electrode array in place 71
Figure 4.3 Standard, deviant and subtraction waveforms from the six strip contacts 73
Figure 4.4 Grand average ERPs to grid contacts.....75
Figure 5.1 Normal and albino visual pathways 80
Figure 5.2 Pattern onset stimuli - left half field (stimuli 5, 4), right half field (stimuli 2,3) 88
Figure 5.3 Individual participant grand average and subtraction waveforms. ...90
Figure 5.4 Group grand average waveforms for each of the stimuli for the left eye (A) and the right eye (B) at electrode O1 and electrode O2. 91
Figure 5.5 Grand average waveforms for standard, deviant and illusory deviant stimuli at occipital electrodes. 95
Figure 5.6 Grand average waveforms for the illusory deviant for left and right eye viewing 96

Figure 6.1 Typical pattern onset response (positive upwards) 108
Figure 6.2 Schematic representation of single simulation cycle in the experimental protocol 110
Figure 6.3 Schematic representation of single stimulation cycle in the control protocol 110
Figure 6.4 Subtraction and ERP waveforms when the pattern appearance/ disappearance VEP was subtracted from a masked background or emerged a grey background 113
Figure 6.5 Mean peak-to-peak amplitudes (μV) of CI to CII at stimulus durations of 7, 14 and 21 ms when the pattern appearance/disappearance VEP emerged either from a grey background or was subtracted from a masked background 117
Figure 6.6 Mean peak-to-peak amplitudes (μV) of CII to CIII at stimulus durations of 7, 14 and 21 ms when the pattern appearance/disappearance VEP emerged either from a grey background or was subtracted from a masked background. 118
Figure 7.1 Schematic representation of single stimulation cycle presented in the oddball paradigm 130
Figure 7.2 Grand average waveforms referenced to Fz (negative upwards) at electrodes O1 and O2 132
Figure 7.3 Mean amplitude (μV) of component waveforms at bilateral occipital electrodes in the 155-185 ms time window as a function of stimulus type and stimulus duration (ms) 134

List of tables

Table 2.1 Overview of experiments and number of participants 39
Table 3.1 Mean amplitude (μV) and standard deviation (SD) for each stimulus type at electrode sites for the 170-190ms time window for the passive task (*n*=14) 56
Table 3.2 Mean amplitude (μV) and standard deviation for each stimulus type at electrode sites at 150-170ms for the active task (*n*=13) 60
Table 5.1 Clinical characteristics of test sample (F=female, M=male), *n*=9 86
Table 5.2 Mean latency (ms) and standard deviation for illusory deviant stimulus by of of presentation and electrode site for component onset.....97
Table 5.3 Mean peak to peak amplitude (μV) and standard deviation for the illusory deviant stimulus by eye of presentation and electrode site, *n*=6.....100
Table 6.1 Mean latency (ms) and standard deviation (SD) of pattern appearance/disappearance VEP responses subtracted from the masking reversal stimuli.....113
Table 6.2 Mean peak-to-peak amplitude (μV) of pattern onset responses subtracted from the masking reversal stimuli.....114
Table 6.3 Mean latency (ms) and standard deviation (SD) of pattern onset VEPs to checkerboard appearing from a grey background.....114
Table 6.4 Mean peak-to-peak amplitude (μV) and standard deviation (SD) of pattern onset VEPs to checkerboard appearing from a grey background.....115
Table 7.1 Mean amplitude (μV) and standard deviation (SD) for each stimulus type at occipital electrode sites for the 155-185 ms and 305-335 time windows for the stimuli presented at 7 ms and 14 ms (*n* = 15).....133

List of Publications and Conferences

Flynn, M., Liasis, A., Gardner, M., Boyd, S. and Towell, A. (2009). Can illusory deviant stimuli be used as attentional distractors to record vMMN in a passive three stimulus oddball paradigm? *Experimental Brain Research*, 197(2), 153-161

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I would like to dedicate this piece of work to my parents who I know would have been very proud and probably very surprised!

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Preface

The electrophysiological component known as the auditory Mismatch Negativity (aMMN), reflective of a pre-attentive change detection mechanism, has provided an objective marker for central auditory processing. As such, it is proving a useful tool for research and clinical investigations, offering insight into brain functioning and clinical diagnostics. At the start of this research, an analogous component was claimed to be identified in the visual system, the visual Mismatch Negativity (visual MMN) and indeed also in the somatosensory system. A research focus was to ascertain whether visual MMN exhibits similar properties to auditory MMN, namely independence of attention, endogeneity and sensory memory.

When my research started there were two main issues relating to the visual MMN: whether recordings were reflective of sensory memory or due to the refractory state of neurons, and whether visual MMN could be recorded in the absence of focused attention (shown to reflect a pre-attentive process). The research presented in this thesis has mainly focused on recording a visual MMN in the absence of focused attention rather than investigating correspondence with the sensory memory trace. However, the accumulation of research now suggests that the visual MMN does exist in an analogous way to auditory MMN and there have been developments in paradigms for eliciting visual MMN. Therefore, the research in earlier chapters will be presented in a manner faithful to the original objectives. In the discussion chapter, findings will be reinterpreted in the light of newer research and theoretical models.

1 General introduction

For humans to survive we need to be able to adapt our behaviour to a dynamically changing environment. In order to do this we need to assimilate information rapidly from the environment, process it and produce appropriate behaviour. We gain information about the complex world in which we live through our sense organs. This information is then transduced into neural signals and, through cortical networks in the brain, transformed into what we perceive as experience. A primary source of environmental information is gained from visual input. The perception of the visual world is based more on our brain's construction rather than an exact image of the complex world of which we strive to make sense. The rich array of stimuli entering our eyes has to be filtered and information that is relevant brought into the focus of attention. The point at which visual information enters consciousness and the mechanisms by which this occurs are still matters of debate.

The fact that certain clinical visual tests produce, within a normal population, electrophysiological responses that have little variability in terms of morphology, polarity and latency means that electrophysiological methods can provide unique insights into brain functioning in relation to visual discrimination and this, in turn, can lead to the development of clinical tests for the diagnosis of abnormal brain function. The research presented in this thesis is an investigation of the early cognitive processes underlying the detection of change in visual perception and memory in the absence of focused attention with a particular emphasis on the development and application of electrophysiological methods for clinical visual testing for populations who cannot respond to the demands of an active task.

Current clinical visual electrophysiological tests when carried out within the correct parameters can assess the functioning of the visual pathways to the cortex. However, at the level of the cortex new tools are required. To understand the requirements of any clinical or experimental test it is necessary to have an understanding of the anatomy and physiology of the system under investigation. Therefore, firstly the visual system will be described.

1.1 Anatomy of the visual pathways

Before visual information can be processed, it has to be converted from electromagnetic radiation arriving at the eye and encoded by a number of neuronal events. Light enters the eye through the pupil where it is focused by the cornea and the lens, travelling through the vitreous humor, to the retina at the back of the eye. The retina is lined with visual photoreceptors, approximately 125 million - rods and cones, (Bear, 2007) and it is here that transduction of light occurs.

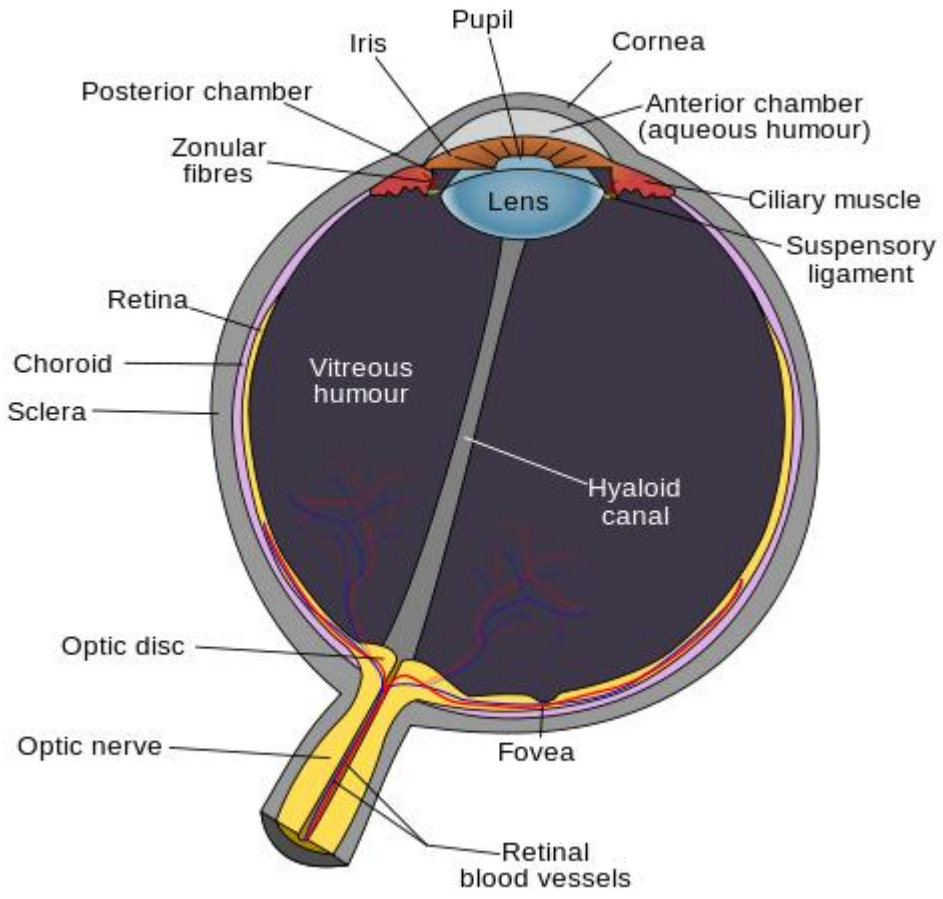

Figure 1.1 Structure of the eye

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Differences in rod and cone structure and their distribution lead to functional differences between the peripheral and macula retina. Rods outnumber cones 20 to 1 in the human retina (Bear, 2007). Rods are longer than cones, with more membranous disks containing a higher concentration of light sensitive photopigments. The higher proportion of rods to cones and photoreceptors to ganglion cells in the peripheral retina means, that functionally, the peripheral retina is specialised for vision in low light. The thinnest part of the retina and the central area of the macula, the fovea, contains only cones. There are three types of cone, each containing a photopigment maximally sensitive to different wavelengths of light. At the fovea there is also an overrepresentation of the central few degrees of visual space. This is because relatively few photoreceptors feed each ganglion cell (Zeki, 1993). The fovea is therefore specialised for colour and detailed vision.

Once the action potential is generated in the rods and cones of the retina, the impulse travels to bipolar neurons closer to the centre of the eye and then to ganglion cells whose axons form the optic nerve. The optic nerves from each eye join together at the base of the brain to form the optic chiasm. In the normal mammal with binocular vision there is a partial decussation - the axons from the nasal retina projecting contralaterally and the axons from the temporal retina projecting ipsilaterally. The majority of these retinal ganglion cells ascend via the optic tract to form synaptic connections with the cells of the lateral geniculate nucleus (LGN) located in the dorsal thalamus. The majority of geniculate neuron axons then project via the optic radiation where they synapse with the primary visual cortex. Thus, all of the information from the left visual hemifield goes to the right hemisphere of the brain and all of the information from the right visual hemifield goes to the left side hemisphere of the brain (see Figure 1.2).

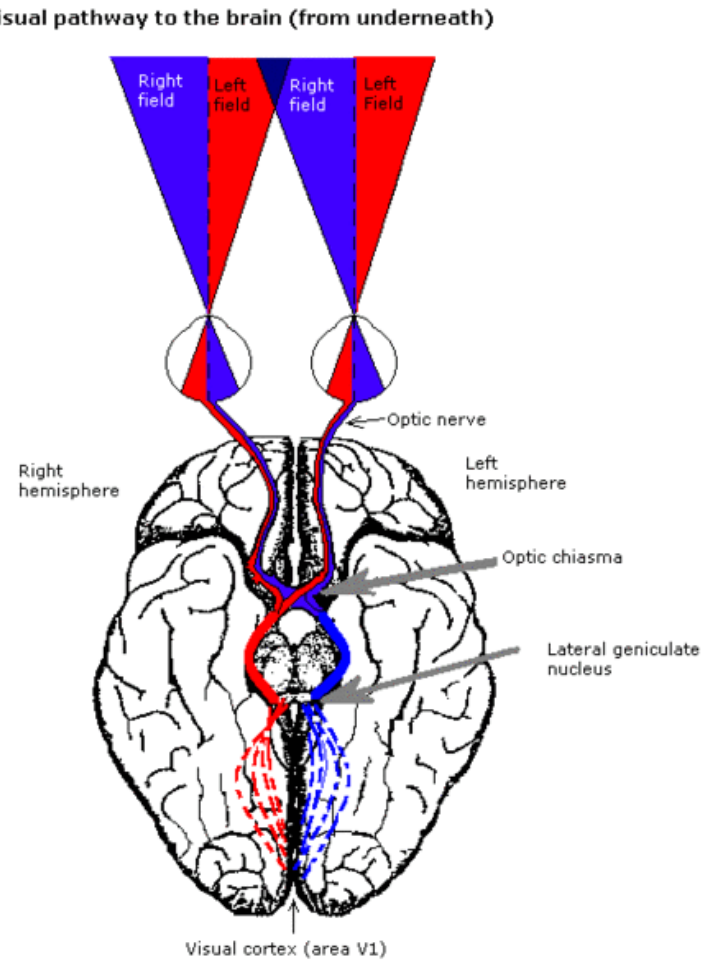

Figure 1.2 Visual pathways to the brain

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1.2 Laminar structure of the visual cortex

Like other areas of the cerebral cortex, the visual system is characterised by a laminar structure. The ganglion cells in the retina, project via the optic tract to the six layers of the LGN. The four upper layers of the LGN contain parvocellular or P-type ganglion cells and the two lower layers contain magnocellular or M-type ganglion cells. The optic nerve fibres from each eye are segregated in each LGN with projections from the ipsilateral eye synapsing in layers 5, 3 and 2, projections from the contralateral eye synapsing in layers 6, 4 and 1. The parvocellular cells in the retina project to the parvocellular layers in the LGN and the magnocellular cells

in the retina project to the magnocellular layers in the LGN. The ganglion cells from the LGN synapse on the striate cortex, which has approximately six layers I-VI, when using Brodmann's convention (Rompelman & Ros, 1986). There is a point to point projection from the retina, to the LGN, and to the striate cortex. This is thought to lead to differential processing: the parvocellular cells in the LGN feed information into the parvocellular layers in the striate cortex whilst the magnocellular cells feed information into the magnocellular layers of the striate cortex.

1.3 Central visual system

In humans, the primary visual cortex, also known as the striate cortex, V1 and Brodmann's area (BA) 17, is found in the occipital lobe and surrounds the calcarine fissure (see Figure 1.4). Initial cortical processing of all visual information required for visual perception occurs in the striate cortex and loss of vision in the contralesional hemifield occurs when it is damaged (Dragoi, 1997). The striate cortex is surrounded mostly by the secondary or extrastriate cortex (V2, V3, V4, V5). Extrastriate areas are also known as Brodmann's areas 18 and 19. Damage to the extrastriate cortex results in deficits in complex visual perception tasks, attention and learning/memory (Dragoi, 1997).

There are two main ways in which information is organised within the striate cortex. Firstly, like other areas of the cerebral cortex, the striate cortex is organised in functional columns. Secondly, like the retina, the striate cortex is organised retinotopically, this means that neighbouring cells in the retina feed information to neighbouring places in the LGN and then the striate cortex. It is thought there are 20 to 40 distinct areas in the extrastriate cortex in humans (Bear, 2007). Information from the visual cortex is integrated and associated with information arising from other modalities in cortical association areas.

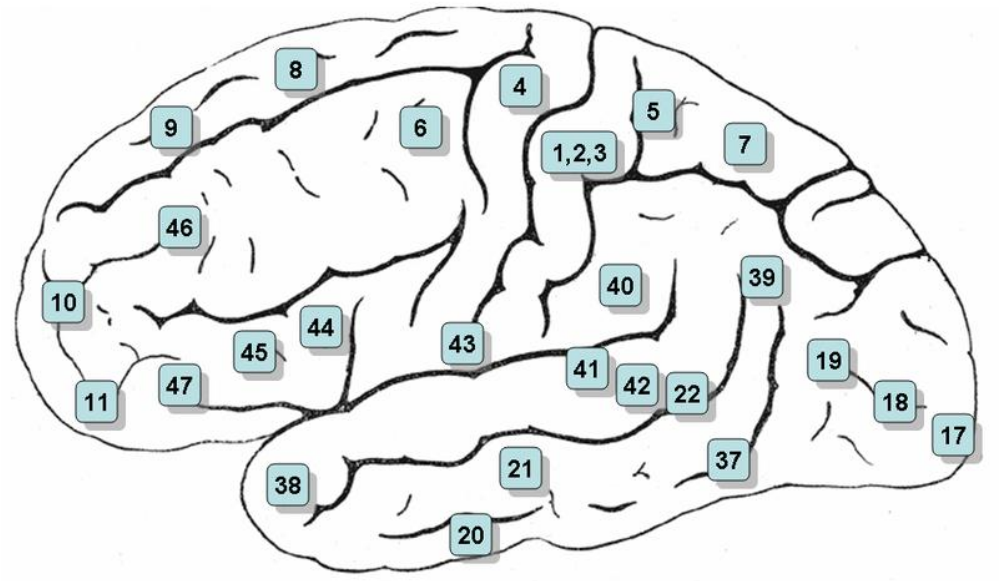

Figure 1.3 Brodmann architectural map, after Brodmann, K. 1909.

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Note areas 17 refers to the striate cortex and 18 and 19 to the extrastriate cortex.

1.4 Visual association cortex

Mapping of association cortex has largely been derived from primate models where it has been possible to use invasive methods to lesion and trace the interconnections between the various cortical visual structures and areas they project to (Felleman & Van Essen, 1991). Newer methods such as magnetic stimulation, which essentially induces a reversible functional lesion, have allowed testing of the cortical organisation of visual functions in humans and have helped clarify some of the anatomical processes revealed through primate research (Pascual-Leone & Walsh, 2001)

From the retina to the striate cortex there are two main streams of visual information processing the parvocellular pathway which is specialised for colour vision and detail, and the magnocellular pathway which is specialised for motion.

This separation of the visual processing continues as the main pathways feed from the striate cortex to other areas of the association cortex, a dorsal stream runs between the occipital, parietal and frontal lobes (BA 7, BA 20 and the superior part of BA 39) and is responsible for location and movement processing. A ventral stream comprises the pathway between the occipital lobes and the temporal lobes (BA 20, the inferior part of BA 37 & BA 39) and is responsible for object and colour identification (Goodale & Milner, 1992; Komatsu & Goda, 2009).

1.5 Techniques employed in the investigation of central visual function

Activation of the visual cortex is dependent on the functional integrity of central visual pathways at all levels, including the eye, retina, the optic nerve, optic radiations and occipital cortex (Odom et al., 2010). Cognitive processes including those relating to central visual function and visual discrimination can be explored through the application of a number of methodologies that allow investigation of brain function and organisation. The methodologies enable the measurement of changes in activity in blood, oxygen metabolism or neurons under defined conditions, and are of two distinct groups, hemodynamic and electromagnetic.

Hemodynamic techniques are best used for the localisation of function and include Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). fMRI offers excellent spatial resolution. The assumption underlying the use of hemodynamic techniques is that increases in local oxygen metabolism and blood flow relate to task induced neuronal activity. However, due to the speed of the circulatory system their temporal resolution is poor in comparison to electromagnetic techniques, in the order of seconds. Electromagnetic techniques include magnetoencephalography (MEG) and electroencephalography (EEG). Due to their excellent temporal resolution they are best used for exploring the time course of cerebral events including those relating to visual discrimination processes. Neuronal transmission is almost instantaneous and as these methods measure the magnetic or electric fields generated by neuronal activity, the temporal resolution is in the order of milliseconds. However, the spatial resolution of these techniques is poor compared to imaging techniques as there is no unique

or universally agreed mathematical solution to working out what is known as the 'inverse problem' – that is attempting to predict internal neural generators of cognitive processes from scalp voltage distributions when there are multiple dipoles from which activity can be generated. Figure 1.5 illustrates the temporal and spatial resolution of functional neuroimaging methods and these are outlined in more detail below.

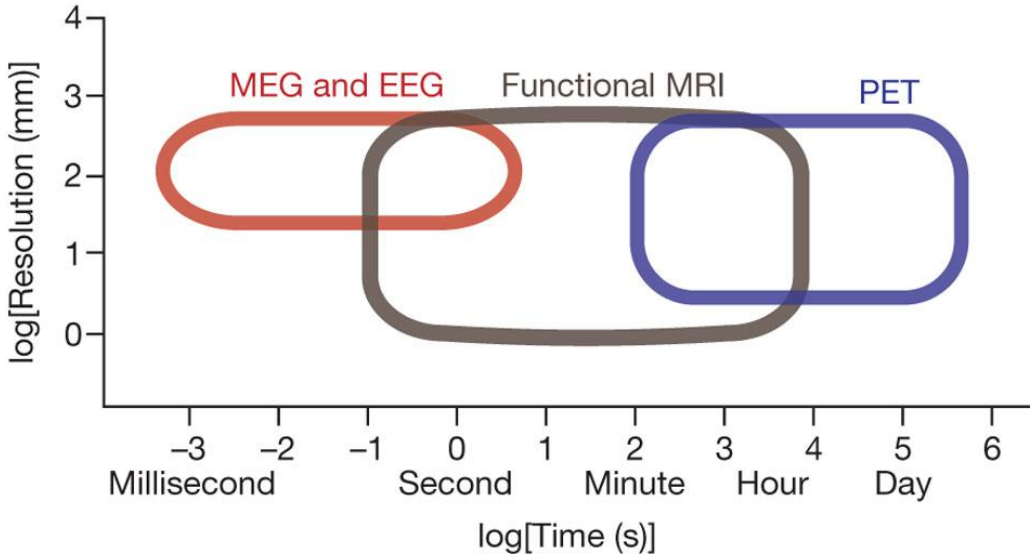


Figure 1.4 Functional neuroimaging methods and their temporal and spatial resolution.

Reproduced exactly from Meyer-Lindenberg (2010) with permission. However, this is schematic as, for example, when the y axis resolution shown is 3= log (resolution mm), then actual resolution = 10 mm³ = 1000 mm.

1.5.1 PET

By introducing into the body a radioactive tracer, functional processing can be imaged by the measurement of changes in regional cerebral blood flow through the decay of radioactive ligands. Comparison of blood flow images under different experimental manipulations can reveal the brain regions implicated in task performance. Imaging takes place in a scanner and this invasive technique, has a spatial resolution in the order of 4 mm and a temporal resolution of 30-40 seconds (Levin & Hoffman, 1999).

1.5.2 fMRI

An imaging technique that is widely used to explore neuronal localisation of cognitive processes is fMRI (Belliveau et al., 1991). fMRI is based on the measurement of changes in blood oxygenation and flow in the brain using Blood Oxygenation Level-Dependent (BOLD) responses. It has a relatively high spatial resolution ($3mm^3$) (Bear, 2007) and this provides anatomical information by enabling the location of cognitive processing in the brain based on increased blood flow levels under different experimental conditions, however, temporal resolution is poor, in the order of seconds.

1.5.3 MEG

MEG is based on the measurement of the magnetic fields produced during cortical activation. This technique has a high temporal resolution in the order of milliseconds and a better spatial resolution than EEG in the order of 2-3 mm for cerebral cortex sources (Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993), although depending on the experiment spatial resolution may be in the order of seconds. Like EEG, the spatial resolution of MEG is inferior to hemodynamic techniques.

1.5.4 EEG

EEG is based on the measurement of electrical fields produced by neuronal activity. Due to the columnular organisation of the cortex electrical potentials propagate to the scalp where their differences can be measured (D. A. Kaiser, 2005). Compared to other techniques, EEG has a number of advantages, it is non-invasive, unless it is being used to record directly from the cortex as, for example, in pre-surgical evaluation of epilepsy. It also has excellent temporal resolution, in the order of milliseconds and is comparatively inexpensive to use. However, spatial resolution is poor in comparison to fMRI, PET and MEG and this means that it is difficult to localise underlying neural generators with this method - although, the use of mathematical source modelling techniques such as standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) and Principal Component Analysis (PCA) can be used. Historically, one of the

main advantages of EEG is that it can be time locked with an external or internal signal (e.g. a muscle movement or perception of a visual stimulus) to study cortical processing to a discrete event. The resulting recording is known an event-related potential (ERP) or an Evoked Potential (EP) and relies on averaging tens to hundreds of EEG epochs related to the onset of the event or signal. The use of ERPs has been chosen for this study due to its high temporal resolution and its ability to illuminate the stages of cognitive processing.

1.6 Principles of event-related potentials

This section introduces the principles of event-related potentials and how they are used to explore cognitive function in relation to discrimination processes. This technique offers the opportunity to study early brain processes associated with the presentation of stimuli.

1.6.1 ERP definition

ERPs are small changes in the electrical activity of the brain that are recorded from the scalp, or directly from the cortical surface and are time-locked to some sensory, motor or mental event. The ERP signal that is recorded reflects activity in the neuronal networks of the brain and is thought to be the spatial and temporal summation of a large number of cortical excitatory and inhibitory post-synaptic (dendritic) potentials (Allison, Wood, & McCarthy, 1986). This electrical activity is transient and has a spatially extended field (Luck, 2005).

ERPs are time-locked voltage change responses to specific stimuli. These signals are small in amplitude, 3-25µV, compared to the ongoing cortical activity in which they are embedded which can vary between -100 and +100µV. To evaluate cortical response to stimulation, the ERP can to be separated from the continuous EEG by means of averaging and digital filtering. ERPs therefore allow the non-invasive evaluation of brain function and organization during cognitive processing.

ERP components are defined by the polarity of their deflections (positive or negative), latency, scalp distribution and relationship to experimental variables. The time course of cognitive processing is reflected in the order and latency of

ERP components. This can be recorded with millisecond temporal resolution and from multiple locations. The allocation of neural resources to specific cognitive processes is reflected in component amplitude (Duncan et al., 2009).

1.6.2 Averaging and digital filtering

The most common method of extracting the ERP 'signal' from the ongoing EEG 'noise' is the use of time domain averaging techniques (Picton, Bentin, et al., 2000; Picton, Lins, & & Scherg, 1995). By defining an epoch within an EEG that is locked to the stimulus and having repeated presentations it is assumed that the response to a stimulus will have a constant and known relationship, whereas, background activity will be unrelated. Averaging therefore results in a reduction of the noise relative to the signal and is proportional to $\sqrt{n}$, where n is the number of responses (Rompelman & Ros, 1986).

The application of digital filters during EEG data acquisition is a simple method to improve signal to noise ratio as filters can be set to a pertinent bandwith in order to decrease the amount of electrical activity unrelated to the measurement of interest (Picton, Bentin, et al., 2000). In addition, the data can be subjected to further offline filtering following acquisition (Picton et al., 1995).

1.6.3 Oddball paradigm

The oddball paradigm developed out of a literature based on target detection and vigilance studies embedded in information processing models such as Triesman's feature-integration theory of attention (Treisman, 1991; Treisman & Gelade, 1980). This involves the presentation of a sequence of frequent or 'standard' stimuli (p=0.90), interspersed with the presentation of an infrequent or 'deviant' stimulus (p=0.10) that differs in some physical attribute from the standard stimulus. The detection of an infrequent stimulus in a train of frequent stimuli, provides an experimental paradigm whereby the attributes of the ERP can be correlated with processes of detection, discrimination and the evaluation of probability. The oddball paradigm is a widely used technique due to its success in evoking reliable markers of cognitive function related to discrimination processes. In conjunction with ERPs, the oddball paradigm can provide insights into the time course of

events related to visual discrimination. Oddball experiments can take place in either an active or a passive condition. During an active paradigm, the participants are asked to attend to the stimuli and respond in some predefined way to a target stimulus – this could be by pressing a button every time the target stimulus appears or by mentally counting the number of target stimuli. The behavioural task is often unrelated to the variables of interest. In a passive condition, the participants are either asked to ignore the stimuli or given no instructions beyond perhaps focusing at a fixation point on the screen where the stimuli are presented. A distinction between these conditions is that a passive oddball paradigm can be used in populations who cannot meet the demands of an active task such as young children or children who have motor deficits.

1.7 Visual ERP components

This section introduces the ERP components commonly associated with visual detection and discrimination tasks. The visual cortex responds to a wide variety of different visual stimuli and the pattern visual ERP is representative of the visual cortex's response to stimuli presented in the middle of the visual field. The main components of a visual ERP are the CI, P1, N1, P2, N2. See Figure 1.6 for a schematic representation of visual components time-locked to a stimulus event.

Of specific interest to this thesis are the P3 and the MMN whose elicitation is dependent on the experimental paradigm and which are slow potential wave complexes related to visual discrimination processes.

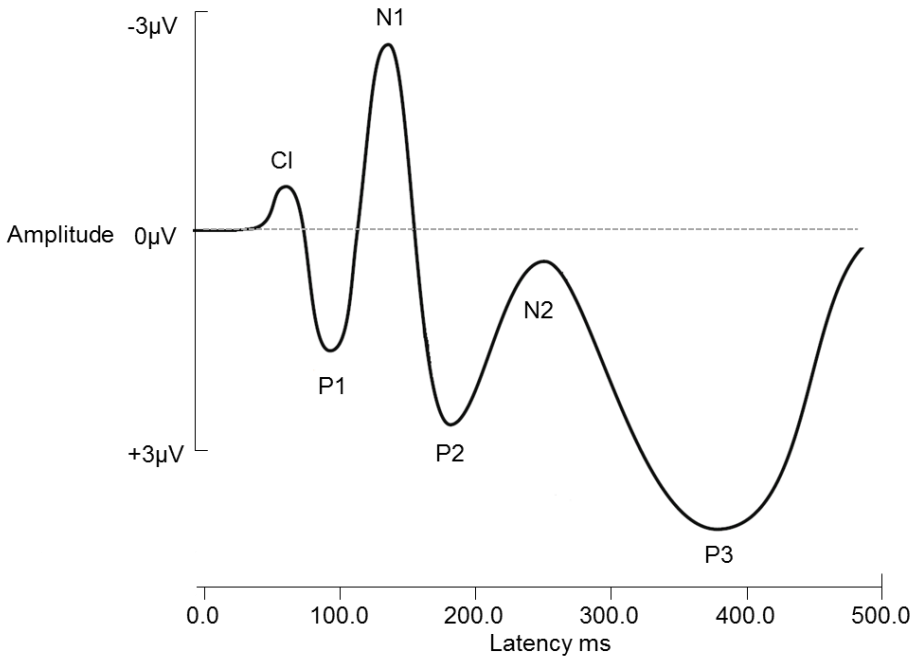


Figure 1.5 Schematic of a generic visual waveform time-locked to stimulus event with labelled components

Adapted from Woodman (2010).

ERPs that are specific to sensory perception or processing and whose component characteristics are reliant on the physical characteristics of the stimuli are called 'exogenous' or 'sensory-evoked potentials' or, in the case of the visual modality, Visual Evoked Potentials (VEPs) (Coles, 1995). Although largely independent of the participant's cognitive state, attentional manipulations can influence these feature-based stimulus elements. The ERP components that are reliant on the participant's interaction with the stimulus are known as 'endogenous' components and these usually occur following sensory processing. Endogenous components are sensitive to task difficulty and manipulations of attention. However, these distinctions are not absolute, evoked potentials can be exogenous, endogenous or both (Picton, Bentin, et al., 2000). Exogenous components can be modulated by cognitive aspects of a stimulus and endogenous components can be modulated by the physical properties of a stimulus. Exogenous components and the endogenous components evoked by an oddball paradigm of particular relevance to this thesis shall be outlined in the sections below.

1.7.1 Exogenous components

The earliest elicited sensory component to pattern onset stimuli is the C1 (also referred to as the 'NP80') which peaks between 60-80 ms. The unique aspect of the C1 component compared to other visual ERPs is that depending on whether the visual stimuli are presented to the upper or lower visual field the polarity of the scalp recorded voltage reverses – lower visual field presentation leads to a positive waveform and upper visual field presentation leads to a negative waveform (Di Russo et al., 2005; Jeffreys & Axford, 1972a). This polarity reversal has enabled the localisation of this component to the striate cortex (Clark, Fan, & Hillyard, 1995; Jeffreys & Axford, 1972a). The striate cortex principally covers the calcarine fissure and receptive field from upper-field visual stimuli map onto the lower banks of the calcarine fissure; and receptive fields from lower-field visual stimuli map to the upper banks of the calcarine fissure. The prevailing view for many years was that C1 was not thought to be influenced by attentional modulations (Martinez, Di Russo, Anllo-Vento, & Hillyard, 2001). However, more recent studies reveal that the C1 can be influenced by attentional manipulations (Proverbio, Del Zotto, & Zani, 2010), for a review of studies see (Rauss, Schwartz, & Pourtois, 2011).

The **'**P1' (also referred to as 'P100') is usually the first positive component observed in visual tasks and peaks between 80-130 ms with a maximal amplitude over occipital electrodes (Mangun, 1995). In a dipole modelling study using a combination of multichannel scalp recordings, MRI and fMRI, the generators of the early and late phase of the P1 have been localised to sources in the dorsal extrastriate cortex of the middle occipital gyrus and the ventral extrastriate cortex of the fusiform gyrus respectively (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002).

The P1 is followed by the N1 (also referred to as 'N100') which is the first negative component and peaks between 140-190ms after stimulus onset with a maximal amplitude over occipital-parietal scalp sites (Mangun, Hillyard, & Luck, 1993). Generator sources for the N1 have proved more difficult to identify, due to the widespread activation across occipito-temporal and parietal regions, although Di Russo et al. (2002) identified generators of subcomponents of N1 to the dorsal

extrastriate cortex of the middle occipital gyrus and to generator sources located deep in the parietal lobe.

Both P1 and N1 can be modulated by attention (Hillyard, Vogel, & Luck, 1998; Martinez et al., 1999). There is debate as to whether the modulation of P1 is related to consciousness or to a preconscious selection process that influences what does enter consciousness. For a review, see Railo, Koivisto, and Revonsuo (2011). The N1 component is correlated with discrimination processes within the focus of attention. Studies have shown that the N1 component amplitude is increased in visual discrimination compared to detection tasks (Hopf, Vogel, Woodman, Heinze, & Luck, 2002; Vogel & Luck, 2000).

It is worth noting that there is some confusion in the literature as to the nomenclature of early pattern onset components. Early work demonstrated differing polarities of the CI component and a positive CII component (Jeffreys & Axford, 1972a, 1972b). However, other authors refer to Jeffreys and Axford's CII as a P1 (Di Russo et al., 2002). Further, Di Russo et al. (2005) describe pattern onset components as C1, P1, N1 These discrepancies are described in more detail in Section 6.5.

1.7.2 Endogenous components evoked in an oddball paradigm

A wide range of research, in auditory, somatosensory and visual modalities, has shown that a number of ERP components specifically related to stimulus discrimination processes can be evoked by using an oddball paradigm. These include the N2, P3a, P3b and Mismatch Negativity (MMN).

1.7.3 N2

The N2 component in the visual modality is the second negative peak observed in visual tasks and peaks typically 200-400 ms after stimulus onset and is maximal over occipital electrode sites (Simson, Vaughan, & Ritter, 1977). It has been associated with automatic and controlled evaluation and stimulus classification processes (Folstein & Van Petten, 2008). The N2 component can also

demonstrate sensitivity to tasks involving manipulations of spatial attention (Woodman & Luck, 1999).

1.7.4 P3

A consistent finding in ERP research is that the P3 wave (also known as P300), a positive deflection occurring from 280 to 400ms post-stimulus indicates attentional processing (see Hagen, Gatherwright, Lopez, & Polich, 2006; Hruby & Marsalek, 2003; Polich, 2003). The P3 is not modality specific and it can further be divided into the subcomponents P3a and P3b. P3a originates from frontal attention mechanisms to task novelty and/or distractors whilst the P3b is generated in more temporal/parietal regions and is associated with context updating and memory storage operations (Polich, 2007). The P3a has an earlier and more frontal peak latency and a smaller amplitude than the P3b. The P3a is usually evoked in experiments associated with novelty and is thought to represent a reorienting mechanism. Whereas, the P3b can be evoked in experiments where the subject is required to attend actively to a target stimulus (Polich, 2003). The P3 is often preceded by the smaller N2b which occurs around 200 to 350ms post stimulus.

1.7.5 MMN

The component of an ERP that is thought to represent a detection of change mechanism or a violation of regularity is known as the mismatch negativity (Näätänen, Gaillard, & Mantysalo, 1978; Näätänen et al., 2012). It has been proposed that the functional significance of the MMN generator is to initiate an attention switch to the eliciting stimulus change (Näätänen, 1990a, 1992) and as such it should be present in all sensory systems. Although this process has been clearly evidenced in the auditory system where the majority of work has been carried out (Näätänen, 1990a, 1992; Näätänen, Jacobsen, & Winkler, 2005; Picton, Ritter, Achim, Alain, & Otten, 2000) and to an extent in the somatosensory system (Näätänen, 2009; D. Restuccia et al., 2009; Spackman, Boyd, & Towell, 2007; Spackman, Towell, & Boyd, 2010) it is only recently that the cumulative research is providing evidence for its existence in the visual system (for a review of the evidence see Kimura, Schroger, & Czigler, 2011). Establishment of the existence of MMN in the visual system has been predicated on the characteristics and

functional significance of the auditory MMN, therefore the literature and characteristics of the auditory mismatch negativity are reviewed below.

1.8 The auditory MMN

The auditory MMN is a component of an ERP that is reflective of task-irrelevant processing of 'deviant' sounds presented in a series of repetitive 'standard' sounds that is best observed in the absence of attention, for reviews see, Näätänen (1992); Näätänen et al. (2012); Näätänen, Kujala, and Winkler (2011); Näätänen, Paavilainen, Rinne, and Alho (2007). The auditory MMN appears as a negative deflection at approximately 100-250ms after stimulus onset and is thought to reflect the pre-attentive detection of acoustic changes (Näätänen, 1990a).The auditory MMN overlaps other change components that are elicited in auditory oddball sequences such as the N2b (Näätänen, 1988) and it is delineated by subtracting the ERP to standard sounds from the ERP to deviant sounds (for a review of methodology for delineating MMN see Kujala, Tervaniemi, & Schroger, 2007).

Evidence that the auditory MMN represents a sensory memory trace rather than a response generated by refractoriness of neural populations is provided by a number of studies (for a review see Näätänen et al., 2005). The auditory MMN is not elicited by deviant stimuli when they are presented without the intervening standards or when inter-stimulus intervals are long (Sams, Paavilainen, Alho, & Näätänen, 1985). It is not evoked by the first stimulus in a sequence (Cowan, Winkler, Teder, & Näätänen, 1993). Therefore the auditory MMN is not elicited by any stimulus, without a number of preceding repetitions of a different stimulus (the standard) preceding this stimulus. This is indicative of a relationship between the present stimulus and the representation of the preceding stimulus. The auditory MMN can also be elicited by stimulus omission in a stimulus sequence (Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997).

The auditory MMN is recorded with largest amplitudes over the fronto-scalp areas. Modelling of generator sources explains the fronto-central scalp distribution by the summation of bilaterally generated activity in the supratemporal cortices (Giard et al., 1995; Rinne et al., 1999). In addition, magnetoencephalograhic (MEG)

equivalent ‘MMNm’ recordings (Hari et al., 1984; Levanen, Ahonen, Hari, McEvoy, & Sams, 1996) support this interpretation. Intracranial recordings in humans (Halgren et al., 1995; Halgren, Marinkovic, & Chauvel, 1998; Liasis, Towell, & Boyd, 1999, 2000) indicate auditory MMN generation in the auditory cortices. In addition to the bilateral supratemporal cortices, evidence has been provided for frontal-lobe involvement in auditory MMN generation from scalp density analysis (SCD) (Deouell, Bentin, & Giard, 1998), from source-current modelling studies (Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000) and from intracranial studies (Liasis, Towell, Alho, & Boyd, 2001; Rosburg et al., 2005).

It has been suggested that the functional significance of the MMN generation process is to initiate an automatic attention switch to the eliciting stimulus change (Näätänen, 1990a, 1992; Näätänen et al., 2011)and that the frontal lobe involvement in the generation of MMN is due to the attention call process (Näätänen et al., 2011). Further evidence for frontal lobe involvement in auditory MMN generation is demonstrated by results that show lesions of dorsolateral prefrontal cortex result in attenuated MMN amplitudes (Alain, Woods, & Knight, 1998). Current interpretations of the auditory MMN generation process emphasise the active role of the memory trace assumed to be used in MMN generation.

> ‘*The MMN is elicited by a mismatch between auditory input and the predictions formed on the basis of trends or rules that are automatically detected in the recent auditory stimulation*’ (Näätänen et al., 2011, p. 6).

The value of the auditory MMN as a research tool for exploring brain function relating to auditory discrimination processes and its value for investigating central auditory processing has been widely documented (Näätänen, 2003). In addition, attenuation of the auditory MMN and prolonged peak latency is implicated in a number of neuropsychiatric, neurological and neurodevelopmental disorders and cognitive decline due to the normal ageing process (for a review see Näätänen et al., 2012). An important feature of the auditory MMN is that it can be elicited in the absence of focused attention - in fact attention leads to the overlap of other attention related ERP components. This has clear benefits for use with clinical populations who cannot meet the demands of a behavioural task.

1.9 Characteristics of the visual Mismatch Negativity

The visual Mismatch Negativity (visual MMN) is a negative ERP deflection that usually peaks around 150-400ms post stimulus change. The component has been most frequently elicited using an oddball paradigm where the response elicited to the infrequent or deviant stimulus is observed, see (Czigler, 2007; Kimura et al., 2011; Pazo-Alvarez, Cadaveira, & Amenedo, 2003). The emergence of the visual MMN is maximal over posterior electrode locations and generators have been localised to visual extrastriate areas and prefrontal areas (Kimura, Ohira, & Schroger, 2010; Urakawa, Inui, Yamashiro, & Kakigi, 2010)

Visual MMNs have been reported in 'match' and 'non match' tasks where the stimuli are presented with equiprobability to control for the effects of global stimulus presentation (Fu, Fan, & Chen, 2003; Maekawa, Tobimatsu, Ogata, Onitsuka, & Kanba, 2009), for changes in orientation and spatial frequency (Kimura, Katayama, Ohira, & Schroger, 2009; Kimura, Murohashi, & Katayama, 2006). Visual MMNs have also been reported within an oddball paradigm whereby a variety of other dimensions of the visual stimulus known to be important in early visual processing are manipulated. These include changes in spatial frequency (Maekawa et al., 2005), motion (Kremlacek, Kuba, Kubova, & Langrova, 2006), colour (Czigler, Balázs, & Pató, 2004; Czigler, Balázs, & Winkler, 2002), form (Berti & Schroger, 2004; Besle, Fort, & Giard, 2005; Stagg, Hindley, Tales, & Butler, 2004) and orientation (Astikainen, Korhonen, Ruusuvirta, & Wikgren, 2004; Astikainen, Lillstrang, & Ruusuvirta, 2008; Czigler & Csibra, 1992; Flynn, Liasis, Gardner, Boyd, & Towell, 2009).

Although a number of studies have identified the visual MMN there has been debate as to whether an authentic visual MMN has been recorded (Czigler, 2007; Pazo-Alvarez et al., 2003). This is mainly due to methodological limitations including a failure to control attentional, exogenous and refractory effects. It has been argued that to be considered a true analogue to the auditory MMN, visual MMN must have the same characteristics including: independence of attention, endogeneity, sensory memory, sensory discrimination (Pazo-Alvarez et al., 2003). These characteristics are outlined below.

The criterion of endogeneity requires that the changes observed in the waveform are not due to changes in the physical characteristics of the stimuli but to the interaction of the participant with the stimulus. To do this, stimulus characteristics must be carefully controlled. The first reported visual MMN studies did not control for this fully. Maekawa et al. (2005) controlled for endogeneity by alternating, standard, deviant or target stimuli. Others have attempted to standardise the adaption state of receptors and neurons in the visual fields exposed to the deviant and standard stimuli (Czigler et al., 2002; Stagg et al., 2004).

MMN is best observed when the participant's attention is directed away from the stimulus, as the overlap of other negative components at the same latency range (e.g. N2b) is thus avoided. In order to differentiate between MMN and other ERP change components, such as the N2 and the P3, the participant's attention is usually drawn away from the test stimuli using a variety of behavioural tasks. A typical MMN paradigm is a selective attention task, where the participant is asked to focus on one aspect of the environment whilst ignoring another; the stimulus sequence is usually presented as task-irrelevant or unattended. For example, in a typical auditory MMN experiment, participants are presented with a visual task, such as reading a book or playing a computer game, whilst a regular train of auditory 'standard' stimuli is presented interspersed with an occasional 'deviant' stimulus that differs in some physical aspect such as frequency or duration. By varying the demands of the visual task, it has been shown that attention to the auditory tones can be withdrawn. In a typical visual MMN experiment, the participant is presented with a visual display that can contain a target stimulus amongst a variable number of distractor stimuli to which the participant is asked to respond, or a number of task irrelevant stimuli are presented peripherally whilst the participant is asked to focus their attention on a task in the middle of the visual field. In both the auditory and visual MMN the experimenter is interested in the processing of the rejected stimuli and the MMN is elicited even when the eliciting stimuli are unrelated to the ongoing task.

Neumann, Vanderheijden, and Allport (1986) in their discussion on the attentional requirements in vision and hearing highlighted that sound is usually only produced

when something happens in the environment, or as noted by Czigler (2007) apart from in music or speech only rarely guides behaviour continuously. Whereas, in a lighted environment, visual information is continuously available and therefore continuously guides behaviour. These differences in characteristics of the auditory and visual attentional systems mean that developing an 'ignore' condition in the visual domain is more difficult than in the auditory domain. Although visual MMN studies have tried to control for attention, for example, (Astikainen et al., 2004; Stagg et al., 2004; Tales, Newton, Troscianko, & Butler, 1999) it is unclear whether focal attention was controlled.

A number of competing theories have been put forward to explain the MMN neural mechanisms and its functional significance. The 'adaptation or refractory hypothesis' suggests that the change in neural activity between the standard and deviant transition represented by the MMN is due to habituation of afferent neurons to the features of the standard stimulus and activation of fresh populations of neurons to the features of the deviant stimuli.(Berti & Schroger, 2004; Mazza, Turatto, & Sarlo, 2005). A number of studies in the auditory domain have shown that the MMN is not due to the refractoriness of the neurons (Näätänen et al., 2005). The 'memory trace hypothesis' (Näätänen, 1990a) posits that MMN reflects a comparison process whereby the 'deviant' stimulus is found to be incongruous with the sensory memory trace that has been established by the repetitive presentation of the standard stimulus and is thought to represent a change detection mechanism. Similar to the auditory MMN the visual MMN is thought to reflect the memory based detection of deviant stimuli rather than refractoriness (see Czigler, 2007 for a detailed discussion). However, not all of the results from visual MMN studies can be explained by the memory trace hypothesis (Berti & Schroger, 2004; Kenemans, Jong, & Verbaten, 2003; Mazza et al., 2005) and recently, the memory trace hypothesis has been extended so that MMN is explained within a hierarchical predictive coding framework (Baldeweg, 2007; Friston, 2005, 2010) as a specific form of visual sensory memory 'unintentional temporal-context-based prediction in vision' (Kimura et al., 2011, p. 671). Within this framework evidence has shown that the visual MMN response reported in a number of studies has been shown to comprise of two separable components: an

N1 which represents the refractoriness of neurons, and a later mismatch - which is based on a memory comparison process or a predictive coding response (Kimura et al., 2009). These theories shall be discussed in more detail and in relation to the experiments presented in this thesis in Section 8.4

One of the problems for recording a 'true' MMN within the visual system is that both the relevant and irrelevant 'to be ignored' stimuli are usually presented within the visual system (Czigler, 2007). This differs to studies of the auditory MMN, which in order to draw focal attention away from the task irrelevant stimuli usually have a behavioural task engaging the visual system. This 'unimodal' presentation and the requirement for an absence of attention is particularly difficult in passive paradigms in which no behavioural task is required.

1.10 Visual event-related potentials in clinical research

Clinical electrophysiological tests have been devised that allow assessment of the functional integrity of the visual system. In combination with clinical presentation and psychophysical findings, an understanding of each test, and what they reveal about the functioning of the visual system, can assist in the diagnosis of a number of diseases. Furthermore, electrophysiological examination when related to cognitive processes can provide an insight into the cognitive processing of visual stimuli.

A number of tests have been standardised for use in clinics by the International Society for the Clinical Electrophysiology of Vision (ISCEV) including those for Visual Evoked Potentials (Odom et al., 2010). These include the standardisation of testing conditions and the stimuli presented. These tests can tell us about visual functioning in a normal population as some tests, for example the pattern reversal, hardly differ within an individual or differ relatively little between individuals with normal visual functioning. Visual tests currently available can help to assess the integrity of the visual pathways from the retina to the visual cortex. However, once the information gets to the visual cortex, assessment is less clear. It is not the purpose of this thesis to describe the full armoury of visual tests used in clinical diagnosis and evaluation but rather to acknowledge the existence of tests to

pattern onset, reversal and offset that provide markers of specific aspects of visual processing (Odom et al., 2010). The visual MMN may provide the opportunity to develop visual diagnostic tools that can provide an assessment of visual functioning at the level of the cortex reflecting the integration of visual processes required for discrimination.

In addition, as the MMN can be recorded in the absence of attention, it offers the potential to address one of the challenges in paediatric visual electrophysiology, namely to assess visual function while the child's attention is otherwise occupied. It would constitute a major breakthrough if the tests could take place whilst, for example, watching a video playing. With this in mind one of the aims of this study was to try to develop electrophysiological methods for clinical assessment whereby stimuli were presented below and above subjective thresholds of detection in a continuous visual stream.

1.11 Aim of this research

The research reported in this thesis explores the development of visual diagnostic techniques using novel methodologies in which active participation on the part of the participant is not required. This was done by investigating electrophysiological correlates of pre-attentive visual processing using ERPs to measure brain activity when controlled changes in visual stimulation occur. Specifically the oddball paradigm was used to elicit visual MMN components and visual detection/discrimination components when stimuli are presented either away from the focus of attention or below and above subjective levels of perception. In addition, by recording EEG from two specific populations – namely a child undergoing pre-surgical evaluation for epilepsy (which enabled recording directly from the surface of the cortex thus improving spatial resolution) and children with albinism (who have optic misrouting such that asymmetrical VEP responses with a contralateral hemisphere dominance are observed) - the generator sources of visual pre-attentive processes and hemispheric specialisation were investigated.

2 Methodology

Five studies are reported in this thesis, see Table 2.1 for an overview of experiments. The stimuli and recording paradigms varied between experiments in order to control focal attention and to explore different aspects of visual discrimination. All experiments, with the exception of Experiments 5.1, 6.1 and 6.2 were based on an oddball paradigm in which there was a change of stimulus orientation. The experiments reported in this thesis, with the exception of Experiment 3.2, were designed to elicit VEPs in the absence of a behavioural task.

Table 2.1 Overview of experiments and number of participants

Experiment number	Experiment overview	Number of participants
3.1	Passive visual MMN paradigm	14
3.2	Active visual MMN paradigm	13
4.1	Intracranial recording to explore VEP generators	1 of 3 analysed
5.1	Assessment of optic pathway misrouting for participants with albinism	9
5.2	Exploration of hemispheric lateralisation	6 of 9 analysed
6.1	Visual detection paradigm with masking	16
6.2	Visual detection control study	7
7.1	Visual MMN paradigm with masking	15

2.1 Ethical considerations

The research reported in this thesis has been given ethical approval. Ethical approval studies on non-clinical populations (Experiments 3.2, 3.2, 6.1, 6.2, 7.1) was obtained from the University of Westminster and participants completed a consent form after reading a description of the research (see Appendices I-III for examples of participant information sheets and consent forms). The studies with patient groups (Experiments 4.1, 5.1 and 5.2) were reviewed by the Great Ormond

Street Hospital for Children (GOSH) NHS Trust/Institute of Child Health Research Ethics Committee and given ethical approval. The intracranial recording was carried out as part of a pre-surgical assessment with parental consent. The parents of the children with albinism completed a consent form after reading a description of the research. The author was given an honorary contract at GOSH and decisions about patient groups were covered by the relevant clinical lead at the hospital. GOSH has a strong tradition of evidence based clinical investigation and parents were willing to participate in clinical research that may contribute in some way to understanding their child's condition. As a matter of ethical principal and good practice staff were sensitive to the wishes of the child and where co-operation was not forthcoming the experimental protocols would be stopped. As in all experimental clinical studies if any data revealed any facts relevant to the child's condition/ diagnosis/ prognosis the matter would be dealt with by the lead clinician or their nominee.

2.2 Instrumentation

The recording equipment consisted of two synchronised systems, the EEG data acquisition/analysis system Neuroscan SCAN version 4.3 (Compumedics USA Ltd., Charlotte, North Carolina, USA) and a visual presentation system. For the studies exploring unmasked visual stimuli (Experiments 3.1, 3.2, 4, 5.1 and 5.2) the visual presentation system was Stim² (Compumedics USA Ltd., Charlotte, North Carolina, USA) and for the studies exploring stimuli presented at very brief presentation rates, masked (Experiments 6.1,7.1), unmasked (Experiment 6.2) the visual presentation system was E-Prime version 2.0 (Psychology Software Tools, Sharpsburg, Pennsylvania, USA). SCAN 4.3 was used to acquire and analyse the data, while 64 channel SynAmps² amplifiers (Compumedics USA Ltd., Charlotte, North Carolina, USA) were employed to amplify and digitise the cortical electrical signals obtained through the use of electrodes (see figure 2.1 for a schematic EEG laboratory set up).

For the studies exploring cortical responses to unmasked visual stimuli, the stimuli were presented on a 15” computer screen (Experiments 3.1, 3.2 and 4.1). For the children with albinism (Experiments 5.1 and 5.2) the unmasked stimuli were presented on a 50 inch plasma screen (Pioneer PD50). For the studies where masked visual stimuli were presented at very brief presentation rates (Experiments 6.1, 6.2 and 7.1) the stimuli were presented on a 21 inch cathode ray tube (CRT) monitor (Samsung SyncMaster) with an NVIDIA GeForce 8800GT 320MB graphics card, running with a screen refresh rate of 160Hz. Particular details of the instrumentation used will be given in the relevant methods section for each of the studies.

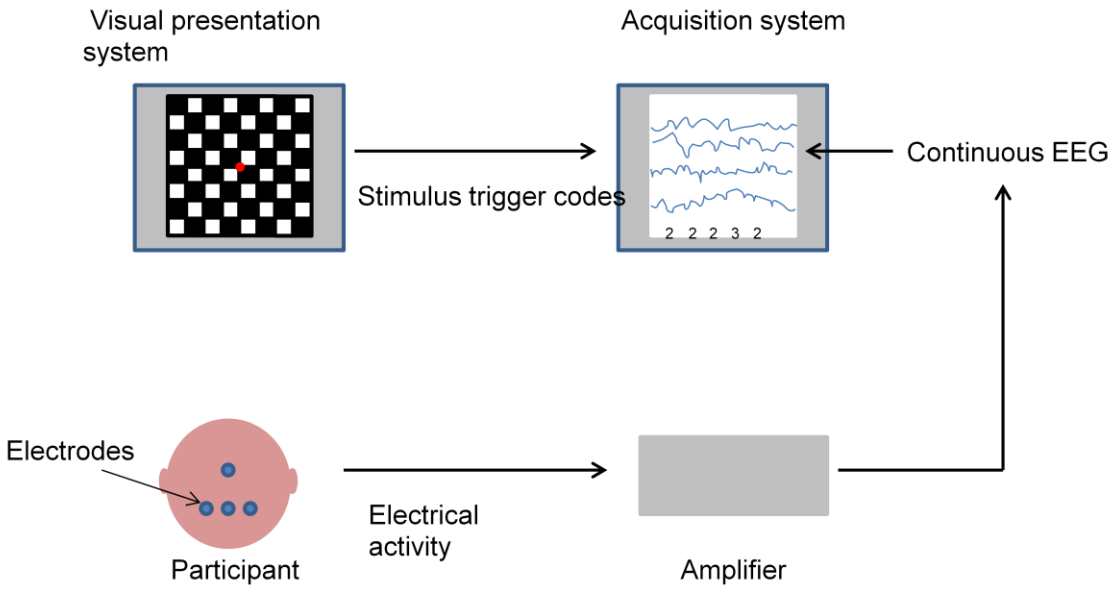


Figure 2.1 Schematic of an EEG laboratory set up

2.3 Methods

2.3.1 Participants

Participants for non-clinical studies were recruited from friends and colleagues for Experiments 3.1, 3.2, 6.1 and 6.2 and students from the University of Westminster were recruited through a departmental research participation scheme for Experiment 7.1. Clinical participants were recruited at GOSH. The participant undergoing surgical resection for epilepsy (Experiment 4.1) was recruited from the Department of Clinical Neurophysiology and the children with albinism (Experiments 5.1 and 5.2) had been referred to a clinic at the Department of Ophthalmology. Further details of the participant populations are given in the relevant chapter in the methods section.

2.3.2 Protocol

During all recordings with the exception of the intracranial recording (Experiment 4.1), participants were seated comfortably in a darkened room 1 m in front of the presentation screen and requested to fixate on a small dot that was present throughout recordings in the centre of the display. The participant was presented with a sequence of visual stimuli whilst ERPs were recorded non-invasively through scalp electrodes. Throughout this time the participants were asked to relax as much as possible but to remain alert. During the recording from the participant undergoing pre-surgical evaluation for epilepsy (Experiment 4.1), the recording was taken in his hospital room with the participant sitting up in bed and the ERPs were recorded from invasive subdural electrodes. Experiment 3.2 was the only experiment to incorporate a behavioural task, participants were asked to respond by pressing a button when a particular stimulus was presented. In Experiments 5.1 and 5.2, stimulus presentation was monocular, stimuli were presented to one eye, whilst the other eye was covered with a patch and then vice-versa. Further details of the particular experimental protocols are given in the relevant chapters in the methods section.

2.3.3 Stimuli and stimulus presentation

Experiments 3.1, 3.2, 4.1 and 5.2 used the same three stimuli based on pacman figures which differed from each other only in terms of the orientation of their elements. These stimuli were generated employing Stim² software (Compumedics USA Ltd., Charlotte, North Carolina, USA) and were presented in an oddball paradigm (see Section 1.6.3). Details and a figure for these stimuli are outlined in the first study chapter in which these stimuli were used (Experiment 3.1, Section 3.3.2.1). Details of stimuli for Experiment 5.1 are outlined in Section 5.4.1.

Visual masks were used in Experiments 6.1 and 7.1. Details and a figure showing the mask stimuli are provided in the first study chapter in which these stimuli are used (Experiment 6.1, Section 6.3.2.1). Experiments 6.1 and 6.2 did not use an oddball paradigm but presented a train of identical checkerboard stimuli under two conditions, either masked (Experiment 6.1) or emerging from a grey background (Experiment 6.2). The checkerboard stimuli were generated using Stim² software (Compumedics USA Ltd., Charlotte, North Carolina, USA). The mask stimuli were generated using Adobe Photoshop. In Experiment 7.1 stimuli that differed in orientation were used to explore the visual MMN. The stimuli were created in Microsoft Powerpoint and then in Adobe Photoshop. Details and a figure of the stimuli are shown in Section 7.4.2.

For the experiments employing an oddball paradigm (Experiments 3.1, 3.2, 4.1, 5.2, 7.1) pseudorandom sequences were used in the experiments to ensure that the sequence could be structured so that no two deviants were presented one after the other, which would contaminate the VEPs by evoking a visual MMN but in addition would reinforce a memory trace of the standard stimulus. In addition, to strengthen the memory trace order was constrained so that the first ten stimuli presented in the sequence were standards. On analysis of the data, these first ten standards were excluded.

For the experiments employing an oddball paradigm (Experiments 3.1, 7.1), as recommended by Kraus, Sharma, McGee, and Carrell (1995), additional deviant and illusory deviant 'alone' conditions were presented. The 'alone' condition acts as a control for stimulus differences and involves presentation of the deviant / illusory deviant stimulus as the only stimulus in a repetitive sequence. The evoked response to the deviant stimulus in context was compared to the evoked response to the same stimulus presented alone. If an MMN is present, a relative negativity will be apparent only in the evoked response elicited in the context of the oddball paradigm and will not be present when the deviant is presented alone.

2.3.4 Data acquisition

In all five studies the amplifier settings were identical. EEG was acquired continuously with a sampling rate of 1000 Hz and amplified (x1500) before conversion into a digital format and saved to the computer hard drive for offline analysis. The continuous EEG record was marked digitally each time a stimulus was presented by the visual presentation computer. The markers that were sent to the amplifier's digital ports via a parallel port to the acquisition computer were different for each type of stimulus and identified the onset of all the stimuli presented to the participant. These markers enabled the isolation and grouping of epochs that are time-locked to the same types of stimuli.

2.3.5 Filters

During all recordings low pass filters were set to 100Hz and high pass filters were set to 0.05Hz. Offline filters were set to a 1-30Hz bandpass. In addition, all offline filtering in this thesis was performed using digital filters set to prevent phase-shifting of frequencies which can distort waveform morphology (Picton, Bentin, et al., 2000).

2.3.6 Electrodes

Electrodes were used to make the connection between the conducting fluid of the tissue in which the electrical activity is generated and the input to the amplifiers (Cooper, Osselton, & Shaw, 1969).

2.3.6.1 Scalp electrodes

Prior to the placement of the electrodes, the skin on the scalp was abraded using Neuroprep (Nihon Kohden Ltd.) to reduce electrode impedance (Picton et al., 1995) and the electrodes were attached to the scalp using Elefix conductive gel (Nihon Kohden Ltd). The conductive gel reduces the amount of resistance created between the conductive fluid of the tissue and electrode. The electrode locations were based on the International 10-20 system of electrode placement (Jasper, 1958). This system is based on specific measurements from skeletal structures designed to ensure that the electrodes are place over the same cortical areas irrespective of variations in head size. In accordance with the International 10-20 system head measurements were taken with a tape measure and electrodes placed over pertinent cortical areas. Grasse silver-silver chloride (Ag/AgCl) electrodes were used to record all data from the scalp and the impedance of the electrodes during the recordings was maintained below 10KOhms. The EEG was recorded using electrode montages that varied from one study to another. All montages used, had numbers of electrodes that met or exceeded the minimum recommended by ISCEV (Odom et al., 2010).

2.3.6.2 Intracranial electrodes

Implantation of a subdural electrode array (SEA) and a strip enabled recordings directly from the cortex. The SEA and strip consisted of platinum electrodes embedded in a one and a half millimetre thick flexible plastic sheet. Centre-to-centre distances between electrodes were ten millimetres. Many metals cause inflammatory reactions when implanted in the brain tissue for periods of longer than one to two days. Silver, silver-chloride, copper, tungsten, gold and platinum electrodes will all evoke reactions (Cooper & Crow 1966) but tungsten, gold and platinum are the most innocuous. Please refer to Section 4.3.3 for more details.

2.3.6.3 Reference electrode

Measurement of the EEG is dependent on the calculation of the electrical potential difference between two electrode locations. EEG recordings are the result of the difference in voltage between the reference electrodes and each active scalp

electrode. The reference electrode is often placed at a neutral site such as the nose, earlobes or mastoids in order to minimise activity from the reference (Luck, 2005). Current EEG data acquisition systems such as Neuroscan enable the re-referencing of the data following acquisition. In the experiments reported in this thesis, the reference and ground electrode were placed at the right and left mastoid respectively Following acquisition, data was referenced to either Fz – which is customary to resolve activity generated in the posterior visual areas (Tales et al., 1999), or to averaged mastoids which is a commonly used as a reference electrode to explore P3 activity (Stagg et al., 2004) .

2.3.7 Off line data analysis

2.3.7.1 ERP construction

The EEG was segmented into epochs from -100 ms before stimulus presentation to +500 ms post stimulus presentation unless otherwise stated. The data was artifact rejected using an automated procedure that rejected epochs with data from any channel exceeding an amplitude of ±100 μV. After artifact rejection the epochs were averaged into different groups. Averages were constructed of all standards before deviants and deviant/illusory deviant epochs. In addition, averages of all deviants presented in an 'alone' condition were constructed. During experiments a minimum of 100 deviants were presented, This ensured that even after artifact rejection, averages were constructed from a minimum of 65 epochs. In the experiments with clinical populations (Experiment 4.1 and 5.2) a minimum of 30 deviants were presented. Before measurement of the VEP component amplitudes and latencies all channels were baseline corrected employing an average of a 100 ms pre-stimulus baseline as zero.

2.3.7.2 Measurement of voltage amplitudes and latencies

Two measures of voltage amplitudes and latencies were used in this thesis. In the studies in which the latency of the components was of particular interest, peak latency and peak-to-peak amplitude was calculated (Experiment 5.2, Experiment 6.1 and 6.2). The peak latency of components was identified by manual analysis of the waveforms, the amplitude of components was measured from the peak-to-peak

of sequential components. In Experiments 3.1, 3.2, 4.1 and 7.1 a temporal window was defined based on expected component latency, location and on the grand average waveforms. The mean amplitude for these time windows was then calculated.

2.3.7.3 Subtraction waveforms

Visual MMN was delineated by subtracting the ERP to the standard stimulus from the ERP to the deviant stimulus and the ERP to the standard stimulus from the ERP to the deviant illusory stimulus. The emergence of visual MMN was assessed by *t*-tests as the deviance from zero on the difference potential in the time window ranges centred on the grand average peak latency at electrodes O1 and O2. In addition, the deviant/illusory deviant 'alone' ERP was subtracted from the deviant/illusory deviant ERP when the stimulus was presented in a sequence of standard stimuli. The 'alone' condition acts as a control condition as observation of the MMN by subtracting the response to the standard from the response to the deviant may be confounded by pure stimulus differences (see Section 2.3.3).

2.3.8 Statistical analysis

Repeated measures Analysis of Variance (ANOVA) was used to analyse latency and amplitude data. When assumptions of sphericity were not met by the data and Mauchley's test of sphericity was significant, Greenhouse Geisser corrections were applied. When significant main effects and/or interactions were observed paired *t*-tests were used to compare means. In most instances Bonferroni corrections were applied when multiple *t*-tests were used. However, in more exploratory experiments such as those reported in Chapter 7 Bonferroni corrections were not applied. All exploratory analyses using uncorrected multiple *t*-tests are flagged at the appropriate point. When sample sizes were small Partial Eta Squared is reported. The ANOVA models used are outlined in the methods section of the relevant chapters.

In supplementary analyses the presence of MMN was assessed by computing *t*-scores at each point on the subtraction waveform. This point-by-point approach is commonly used in the literature (Kraus et al., 1995). Using the *t*-test function in

Neuroscan Edit point-by-point algorithms (based on Student's *t*) were applied to the subtraction waveform data (both deviant minus standard and illusory deviant minus standard). This enabled the comparison over time of each point on the difference waveforms for each electrode, comparing the relative negativity in the waveforms with the baseline. Significant *t* scores indicated a statistically reliable negativity in the difference waveform. As spurious significant values may occur across short time intervals (Guthrie & Buchwald, 1991) suggest that a waveform is significantly different from baseline only if obtained across an interval of at least 12 sampling points. In the current study intervals of 20 or 30 sampling points were used.

In order to control for pure stimulus differences point-by-point *t*-tests were also used to compare the discrimination waveform to the deviant stimulus with the discrimination waveform when that same stimulus was presented alone i.e. out of context and not in an oddball paradigm.

3 Can illusory deviant stimuli be used as attentional distracters to record visual MMN in a passive three stimulus oddball paradigm?

3.1 Aim

The experiments reported in this chapter aimed to evaluate an experimental paradigm designed to elicit, in the absence of an active task, visual discrimination ERP components to a change in orientation. Attentionally salient Kanizsa square stimuli were employed both in place of (Experiment 3.1), and alongside (Experiment 3.2), an active task. Illusory figures such as the Kanizsa square (Kanizsa, 1976) have been shown to 'pop-out' of visual displays when presented in the context of a visual search task and, when used as visual cues, automatically capture spatial attention (Senkowski, Rottger, Grimm, Foxe, & Herrmann, 2005). To date, no other study has used an illusory figure in a passive paradigm in an attempt to control for the effects of attention in a visual MMN study. The comparison between Experiments 3.1 and 3.2 served to assess whether the illusory figure diverted attention away from the standard-deviant transition.

3.2 Introduction

In comparison to other ERP change components, such as N1, N2 and P3, the MMN can be elicited in the absence of attention (Pazo-Alvarez et al., 2003). Therefore, in order to differentiate between MMN and other ERP change components the participant's attention is typically drawn away from the test stimuli, employing a variety of behavioural tasks. For example, in studies to elicit a visual MMN, Stagg et al. (2004) and Tales et al. (1999) required participants to press a button in response to target stimuli. Astikainen et al. (2004) used an auditory distraction task whereby participants were required to focus their attention on counting the number of words in a story whilst being presented with visual stimuli.

One of the features of the auditory MMN is that it can be recorded even when the participants are not attending to the auditory stimulation. This means that it is not contaminated by task related processing (Schroger, 1998). The auditory MMN is regarded as an automatic or pre-attentive process in that is not reliant on the

participant's explicit intention to detect deviants and can be elicited in the absence of attention. In keeping with this view, auditory MMN has been elicited in coma patients (Kane et al., 1996) and in sleeping newborn babies (Cheourluhtanen et al., 1995). In addition, to assess whether the auditory MMN is contingent upon attention, studies have employed a highly demanding primary task, such as visual tracking, to divert the attention of the participants from the auditory input. Although auditory MMN elicitation is rarely affected by attention, this approach has on occasion yielded conflicting results with studies showing that MMN to changes in frequency is not modulated by primary task complexity (Alho, Woods, & Algazi, 1994) while complexity of visual tracking task does modulate and attenuate MMN in relation to changes in pitch (Yucel, Petty, McCarthy, & Belger, 2005). It is still a matter of debate whether the N1/N2 waves elicited by visual stimulus change reveal the same degree of automaticity as in the auditory MMN (Garrido, Kilner, Stephan, & Friston, 2009).

Kanizsa figures are ambiguous figures in which the illusion of a square or triangle is perceived in the middle of inducers, such as pacmen in the absence of real contours. When illusory figures are presented in the context of a visual search task and when used as visual cues, they automatically capture spatial attention (Senkowski et al., 2005). The binding process that leads to the perception of an illusory figure, such as a square or a triangle, causes the figure to 'pop-out' from a visual display and thus, when presented in the midst of distractor stimuli, illusory figures capture attention (Davis & Driver, 1994).

It has generally been understood that a concurrent active task is mandatory in eliciting visual MMN to control for the effects of attention so that resources are allocated away from the standard-deviant discrimination towards the active task (Czigler, 2007; Heslenfeld, 2003). However, not all patient populations can meet the demands of an active task. Therefore, in the present study a three-stimulus passive oddball paradigm was developed. Stimuli differed with regard to orientation of local endline type pacman figures and their information/entropy content (see Figure 3.1). So in addition to standard and deviant stimuli, an infrequent illusory deviant stimulus was introduced in order to assess the effects of an attentionally

salient stimulus on change detection components. The illusory deviant stimulus was a Kanizsa figure (Kanizsa, 1976) which formed an illusory square, a salient event thought to demand attention to reconstruct contours that are absent from visual images (J. Kaiser, Bühler, & Lutzenberger, 2004).

The P3 component served as an indicator of the effect of the illusory deviant stimulus on the allocation of attention. As described in Section 1.7.4 a consistent finding in ERP research is that the P3 wave, a positive deflection occurring from 280-400 ms post stimulus indicates attentional processing (for reviews see Hagen et al., 2006; Hruby & Marsalek, 2003; Polich & Comerchero, 2003). The P3 can be further divided into the subcomponents P3a and P3b. P3a is thought to originate from frontal attention mechanisms to task novelty and/or distractors whilst the P3b is thought to be generated in more temporal/parietal regions and is associated with context updating and memory storage operations (Polich, 2007).

3.2.1 Rationale and predictions

Two experiments were carried out to validate the use of an illusory deviant stimulus, a Kanizsa square, in orienting attention. Experiment 3.1 was a passive visual oddball paradigm with no behavioural task. It was predicted that discrimination components possibly reflecting visual MMN would be evoked by both the deviant and illusory deviant stimuli whilst a P3a component would be evident only to illusory deviant stimuli that captured attention. Experiment 3.2 introduced a behavioural task, it was predicted that a P3b to the task stimulus would be evoked reflecting participant engagement with the task. If the illusory deviant was sufficient to occupy attention it was expected that there would be no effect of the task on the visual discrimination components. However, if the illusory deviant was not sufficient to occupy attention an effect of task may occur.

3.3 Methods for Experiments 3.1 and 3.2

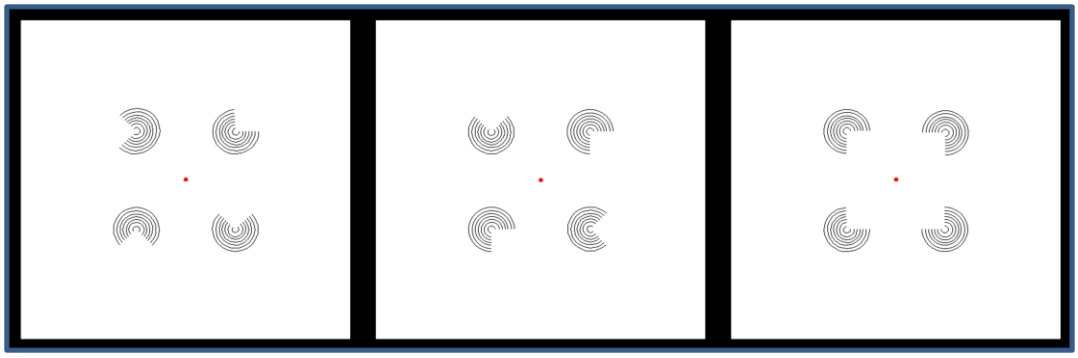
3.3.1 Participants

With ethical approval and informed consent 14 healthy adults mean age 34.5 years ± 8.6 (10 females) were recruited for Experiment 3.1 and 13 healthy adults mean age 29.23 ± 8.8 years (11 females) were recruited for Experiment 3.2. Participants reported no history of neurological disease and had normal or corrected-to-normal visual acuity.

3.3.2 Stimuli and procedure

3.3.2.1 Experiment 3.1

Three monochrome endline type stimuli based on pacman figures were employed in a behaviourally silent oddball paradigm where the ratio of standards to deviants and illusory deviants was 8:1:1. The stimuli (see Figure 3.1) differed from each other only in terms of the orientation of elements, which were oriented unsystematically around their axes for the standard and deviant stimuli and formed an illusory Kanizsa figure for the illusory deviant stimulus. The stimuli appeared on a computer screen for 400 ms with an inter-stimulus interval of 600 ms, the stimuli subtended 4 degrees. In Experiment 3.1 the stimuli were presented in five blocks of 225 stimuli with up to a minute break between blocks. At the end of the oddball recording, blocks of 64 deviants and illusory deviants ‘alone’ were presented. For further details of the stimuli and protocol please refer to Sections 2.3.2 and 2.3.3.



a) b) c)

Figure 3.1 Stimuli presented in an oddball paradigm

Pseudorandom sequences of 8:1:1 respectively a) standard, b) deviant and c) illusory deviant forming a Kanizsa square

3.3.2.2 Experiment 3.2

The same stimuli and procedure as in Experiment 3.1 were utilised with the exception that an active attention task was embedded in the 3 stimulus oddball paradigm. Within the blocks of 225 stimuli, during the inter-stimulus interval (ISI), a small red square replaced the small red fixation dot on 22 trials chosen at random. The red square appeared at the start of the 600 ms ISI and stayed on the screen for 200 ms. Participants were instructed to focus their attention on the red fixation dot and press the right hand button of a mouse as quickly as possible whenever the red square appeared. Inclusion criteria were based on participants correctly detecting the target on 90% or more trials.

3.3.3 EEG recording and analysis

For both experiments, nineteen Ag/AgCl electrodes were used to record the EEG activity and were positioned at sites in accordance with the International 10-20 system (Fz, F3, F4, Cz, C3, C4, T3, T4, Pz, P3, P4, Oz, O1, O2, T5, T6, VEOG, M1, M2). The reference electrode and the ground electrode were placed at the right and left mastoid respectively. An electrode was placed above the left eye to enable online artifact rejection of eye blinks. Continuous EEG was collected using

Neuroscan-SCAN version 4.3at a sampling rate of 1000Hz, with a low pass of 100Hz and a high pass of 0.05Hz and stored on a computer for offline analysis.

Continuous EEG data were epoched offline -100 ms pre-stimulus to +500 ms post-stimulus. The epochs were digitally filtered with a band pass 1-30Hz and baseline corrected. Epochs containing transients greater than ± 100μV were excluded from further analysis. For each participant, ERPs were averaged separately for standard, deviant and illusory deviant stimuli employing Fz as a reference and grand average waveforms were constructed. Additional ERPs were constructed in Experiment 3.2 for the red fixation dot and for the red square that replaced the fixation dot on a number of trials. ERPs to standard stimuli were constructed from epochs that preceded deviant stimuli. As in previous studies (Stagg et al., 2004; Tales et al., 1999), averaged mastoids were employed as a reference to investigate P3 activity.

From the grand average waveforms MMN-like differences were identified on the basis of known negative polarity, known emergence over posterior electrode positions and typical latency range (100-250ms post stimulus: Pazo-Alvarez et al., 2003). In each study, the maximal difference between ERPs to standards and deviants was identified at occipital sites and a 20 ms time window was centred at this latency for electrodes P3, P4, O1, O2, T5, T6 (Astikainen et al., 2008). Mean amplitudes for the time windows were calculated relative to the mean voltage of a 100 ms pre stimulus baseline for each participant for the standard, deviant and illusory deviant stimuli. The mean amplitudes were analysed using Analysis of Variance (ANOVA). In addition, subtraction waveforms were constructed of deviant minus standard and illusory deviant minus standard for Experiment 3.1.

3.3.4 Results

3.3.4.1 Experiment 3.1

A visual response was recorded in all participants consisting of a P1-N1-P2 waveform. Grand average waveforms were constructed for the standard, deviant and illusory deviant stimuli (see Figure 3.2 for waveforms at electrodes O1 and O2). The maximal difference between ERPs to standards and deviants was at

approximately 180 ms post-stimulus at occipital electrodes. Mean amplitudes and standard deviations for the standard, deviant and illusory deviant in the 170 – 190 ms time window are shown in Table 3.1.

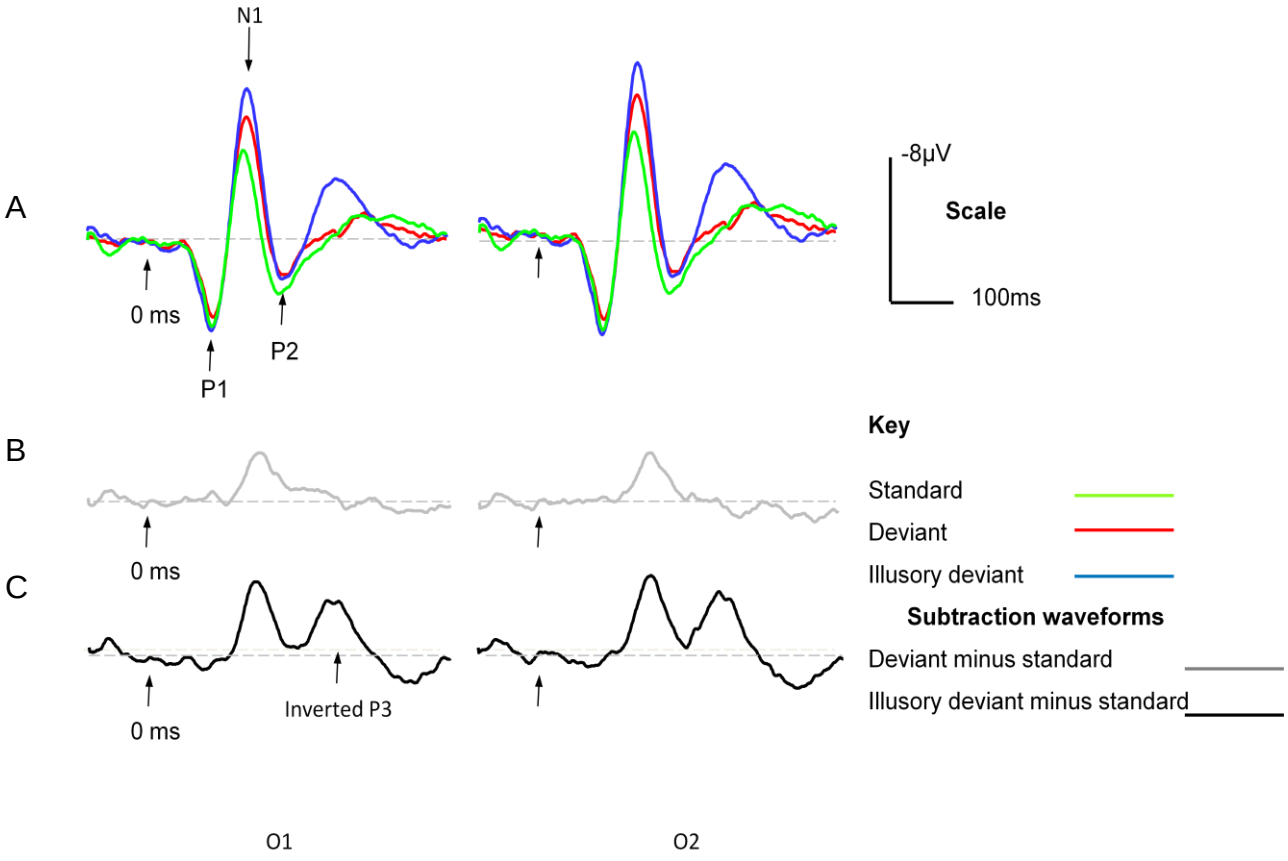


Figure 3.2 Grand average waveforms referenced to Fz at electrodes O1 and O2.

A: Standard, deviant and illusory deviant stimuli B: Deviant minus standard subtraction waveforms, C: Illusory deviant minus standard subtraction waveforms. Note the discrimination responses in B and C with an additional negative component in C corresponding to an inverted P3 (Negative upwards).

Table 3.1 Mean amplitude (μV) and standard deviation (SD) for each stimulus type at electrode sites for the 170-190ms time window for the passive task (*n*=14)

Electrode Site	Mean amplitude (μV) and Standard Deviation (±SD)		
	Stimulus		
	Standard	**Deviant**	**Illusory Deviant**
O1	2.98 ± 2.32	5.67 ± 3.36	7.10 ± 4.10
O2	3.11 ± 2.73	5.66 ± 3.38	7.33 ± 4.38
P3	1.99 ± 1.68	3.75 ± 2.85	5.03 ± 3.49
P4	1.90 ± 1.91	3.43 ± 2.27	5.08 ± 3.12
T5	2.36 ± 2.03	4.59 ± 2.75	5.42 ± 3.07
T6	2.62 ± 1.83	4.70 ± 2.24	5.13 ± 2.75

A three-way within subjects ANOVA was used to analyse these mean amplitude data. Pair-wise comparison of means was carried out using bonferroni corrected *t*-tests. Factors were location (occipital, parietal, temporal), hemisphere (left, right) and stimulus (standard, deviant and illusory deviant). The amplitude differed significantly with location ($F(2,26)= 11.880$ $p <0.001$) and stimulus type ($F(2,26)= 15.886$; $p <0.001$) but not with hemisphere ($F(1,13)= 0.233$; $p = 0.794$). There was a statistically significant interaction between location and stimulus ($F(4.52)= 6.503$; $p = 0.001$ $p <0.001$), indicating that the amplitude of the deviant stimulus was greater than the standard stimulus at occipital ($t = 4.004$; df = 13; p = 0.002) and temporal electrodes ($t = 4.552$; df = 13; p = 0.001) and that the amplitude of the illusory deviant was greater than the standard at occipital ($t = 4.507$; df = 13; p = 0.001), temporal ($t = 4.552$; df = 13; p = 0.001) and parietal electrodes ($t = 4.276$; df = 13; p = 0.001).

Difference waveforms of deviant minus standard and illusory deviant minus standard both revealed visual MMN components (Figure. 3.2B and C respectively). When comparing the deviant to the standard ERP, using the point-by-point *t*-test

algorithm ($p < 0.05$; one-tailed), against baseline there were significant differences at O1 between 173-217ms (181-203 ms; $p < 0.01$) and at O2 between 178-208 ms (185-196 ms); $p < 0.01$). Comparing the illusory deviant to the standard ERP against baseline, there were significant differences ($p < 0.05$; one-tailed) at O1 between 164-212 ms (175-203 ms; $p < 0.01$) and at O2 between 169-212 ms (181-199 ms; $p < 0.01$).

Illusory deviant stimuli evoked an additional late negative component at 234 ms at Oz. To examine whether this component corresponded to an inverted P3 component the waveforms were re-referenced to averaged mastoids. This revealed a positive component over the fronto-central electrode sites corresponding to P3a. At Fz this component had an onset latency of 244 ms, SD=13 ms and a peak latency of 290ms, SD=27 ms with a peak amplitude of 4.19µV, SD=2.06 µV (see Figure 3.3).

As a method of control, to examine whether the differences observed in the subtraction waveforms were confounded by pure stimulus differences, the discrimination waveform to the deviant stimulus was compared to the discrimination waveform when that same stimulus was presented alone i.e. out of context and not in an oddball paradigm. Point-by-point *t*-tests revealed no significant differences between the deviant-standard and deviant - deviant alone waveforms suggesting that when the deviant stimulus was presented alone and out of context it behaved in a similar way to the standard stimulus even though it was physically different. The same procedure was used to compare the illusory deviant stimulus in the context of an oddball paradigm with the illusory deviant stimulus presented alone. Similarly, there were no significant differences between the illusory deviant-standard and illusory deviant alone-illusory deviant waveforms.

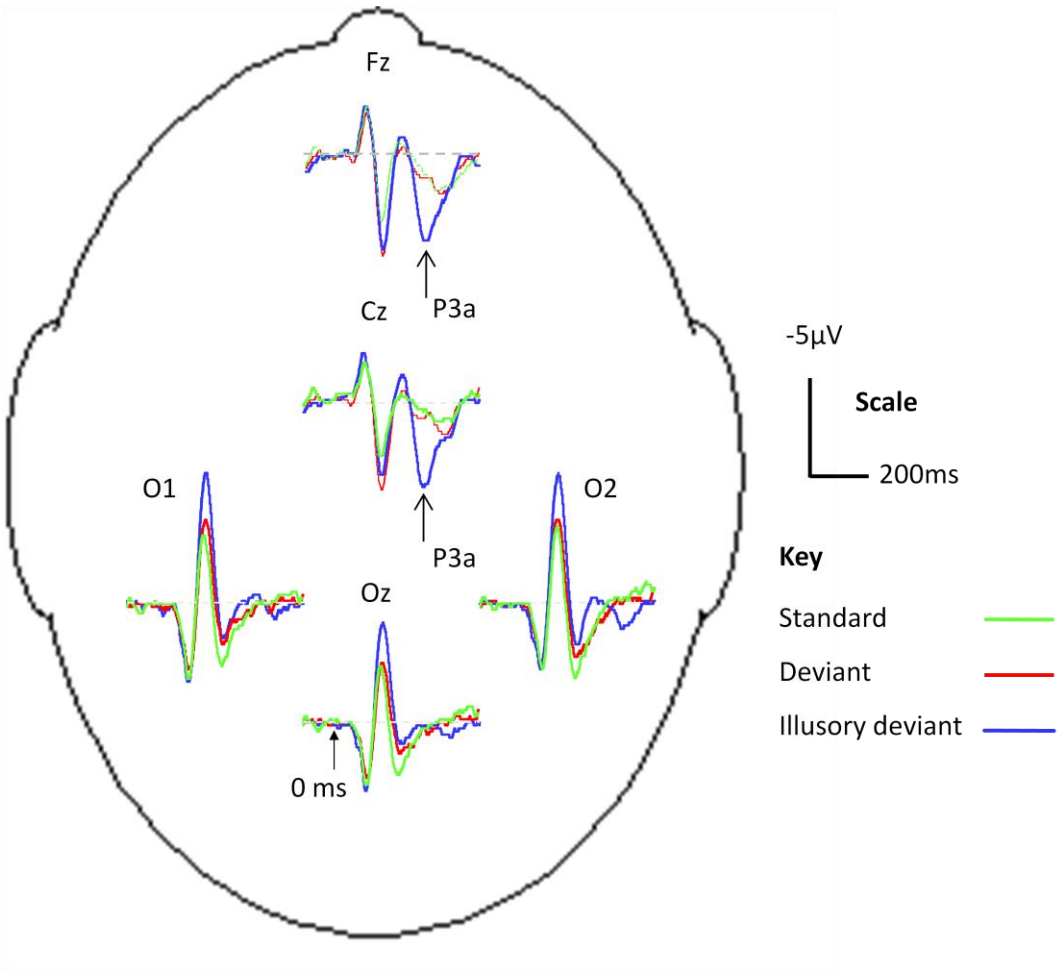


Figure 3.3 Grand average waveforms for standard, deviant and illusory deviant stimuli at Fz, Cz, O1, Oz and O2 referenced to averaged mastoids.

Note the P3a component seen only to illusory deviant stimuli at Fz and Cz (Negative upwards).

3.3.4.2 Experiment 3.2

As in Experiment 3.1, a visual response was recorded for all participants consisting of a P1-N1-P2 waveform. Grand average waveforms were constructed for the standard, deviant and illusory deviant stimuli (see Figure 3.4 for waveforms at electrodes O1 and O2). The maximal difference between ERPs to standards and deviants was at approximately 160ms post-stimulus at occipital sites. Mean amplitudes and standard deviations for the standard, deviant and illusory deviant in the 150-170 ms time window are shown in Table 3.2.

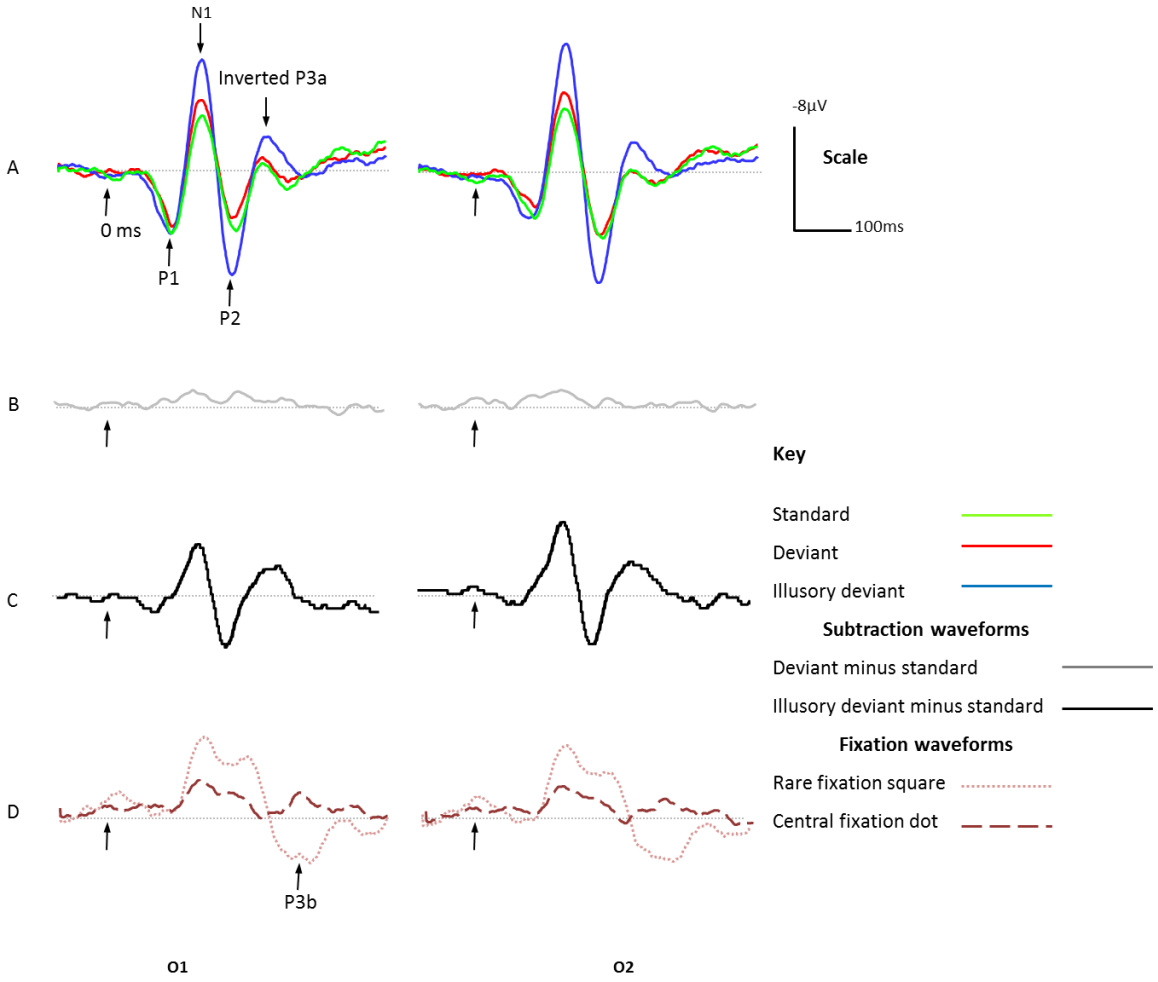


Figure 3.4 A: Grand average waveforms referenced to Fz for standard, deviant and illusory deviant stimuli at electrodes O1 and O2.

Note the P3a component seen only to illusory deviant stimuli, B: deviant minus standard subtraction waveforms, C: illusory deviant minus standard subtraction waveforms, D: grand average waveforms for the rarely occurring red fixation square and for the central fixation dot. Note the attenuated visual MMN in B and the P3b wave to the task in D (Negative upwards).

Table 3.2 Mean amplitude (μV) and standard deviation for each stimulus type at electrode sites at 150-170ms for the active task (*n*=13)

Electrode Site	Mean amplitude (μV) and Standard Deviation (±SD)		
	Stimulus		
	Standard	**Deviant**	**Illusory Deviant**
O1	4.12 ± 2.22	5.12 ± 2.10	7.24 ± 2.79
O2	5.20 ± 3.40	6.25 ± 3.43	9.27 ± 5.20
P3	2.32 ± 1.76	2.79 ± 1.83	3.51 ± 2.22
P4	3.50 ± 2.33	4.07 ± 2.01	5.56 ± 3.28
T5	3.23 ± 1.75	4.18 ± 1.82	5.20 ± 2.00
T6	4.90 ± 2.35	5.64 ± 2.36	7.48 ± 3.92

A three-way within subjects ANOVA was used to analyse these mean amplitude data**.** Pair-wise comparison of means was carried out using bonferroni corrected *t*-tests. Factors were location (occipital, parietal, temporal), hemisphere (left, right) and stimulus (standard, deviant and illusory deviant). The amplitude differed significantly with location ($F(2,24)= 16.874$; $p <0.001$), hemisphere ($F(2,24)= 7.059$; $p =0.021$) and stimulus type ($F(2,24)= 14.254$; $p <0.001$). There was a significant interaction between location and stimulus ($F(4.48)= 10.636$; $p < 0.001$) indicating that the amplitude of the deviant stimulus was greater than the standard stimulus at occipital ($t = 3.796$; df = 12; $p = 0.003$) and temporal ($t = 3.147$; df = 12; $p = 0.008$) electrodes. The amplitude of the illusory deviant stimulus was greater than the standard stimulus at occipital ($t = 4.494$; df = 12; $p = 0.001$), temporal ($t = 4.425$; df = 12; $p = 0.001$) and parietal ($t = 4.105$; df = 12; $p = 0.001$) electrodes. There was a significant interaction between hemisphere and stimulus ($F(2,24)= 3.402$; $p =0.050$) indicating that in the left hemisphere the mean amplitude was greater for the deviant ($t = 4.194$; df = 12; $p = 0.001$) and illusory deviant ($t = 5.536$; df = 12; $p < 0.001$) than for the standard. In the right hemisphere the mean

amplitude of the illusory deviant (t = 5.944; df = 12; p < 0.001) was greater than the standard as was the deviant but to a lesser extent (t = 2.952; df = 12; p = 0.012).

Difference waveforms of deviant minus standard and illusory deviant minus standard both revealed attenuated visual MMN components (Figure. 3.4 B and C respectively). When comparing the deviant to the standard ERP, using the point-by-point *t*-test algorithm (p< 0.05; one-tailed) against baseline, there were significant differences at O1 between 138 and 176 ms but no significant differences were apparent at O2, in keeping with the interaction between hemisphere and stimulus found for the amplitude data. When comparing the illusory deviant to the standard ERP against baseline, there were significant differences (p< 0.05; one-tailed) at O1 between 142 and 178ms and at O2 between 147 and 177ms.

Illusory deviant stimuli evoked an additional late negative component at occipital electrodes. When re-referenced to averaged mastoids this component was positive over the fronto-central electrode sites corresponding to P3a. At Fz this had an onset latency of 223 ms, SD=18 ms and a peak latency of 282 ms, SD=22 ms with a peak amplitude of 5.17µV, SD=2.72 µV.

All participants completed the active task (pressing the mouse when the red fixation dot was replaced with a red fixation square) within the limits of the inclusion criteria. As expected, the active task evoked a P3b component consistent with the allocation of attentional resources to this task (see Figure 3.4D).

3.4 Discussion

The main result from this study is that visual discrimination responses including visual MMN components have been recorded in a behaviourally silent oddball paradigm to a change in orientation. The stimuli utilised in this study evoked a response that was more negative to the deviant stimuli than to the standard stimuli in the period 150 – 200 ms after stimulus onset. Physical differences between the stimuli can contribute to such a finding, as demonstrated by the larger amplitude for standard - illusory deviant comparison relative to that for standard – deviant in both experiments. However, the employment of ‘deviant alone’ and ‘illusory deviant alone’ conditions served as controls (see Section 2.3.3). Subtraction

waveforms using the method suggested by Kraus et al. (1995) for delineating the MMN reveal that the difference in negativity was attributable not to physical differences in the stimuli themselves, but by the context in which the stimuli were presented. The latency of the responses in the current experiments are consistent within the general window for visual MMN responses of between 100-250 ms (Pazo-Alvarez et al., 2003) although it is known that latency and duration of visual MMN will differ according to stimulus characteristics and task complexity with less salient changes and more complex rules resulting in longer latency and less phasic visual MMN responses (Czigler, Weisz, & Winkler, 2006).

The presence of a P3a over frontal/central electrodes for the illusory deviant grand average waveform but not for the standard or deviant grand average waveforms in Experiments 3.1 and 3.2, suggests that the Kanizsa square captured attention. This finding is consistent with research by Senkowski et al. (2005) who found that Kanizsa figures automatically capture spatial attention when used as visual cues and Wallach and Slaughter (1988) who reported that familiarity of the illusory shape increases the likelihood that the shape will be perceived. The enhanced visual N1 amplitude component at the lateral occipital electrodes that was observed in both Experiment 3.1 and 3.2 is also consistent with the illusory deviant stimulus having captured attention (Vogel & Luck, 2000).

As with several other studies (e.g. Clery, Andersson, Fonlupt, & Gomot, 2013; Czigler & Pato, 2009; Tales et al., 1999) an active control task was incorporated in Experiment 3.2. Participants were required to press a button at the occurrence of a change in shape of the central fixation dot. The understanding here is that attentional resources are drawn from the standard-deviant discrimination to the active task. The elicitation of a P3b in Experiment 3.2 reflected engagement with the task. Under these conditions the existence of visual MMN responses was confirmed although they were significantly reduced in amplitude. The attenuation of the visual MMN responses when an active task was incorporated in the paradigm reveal that visual MMN elicitation is to some degree modulated by attention. Without the control task this would imply that the enhanced negativity exhibited by the deviant compared to the standard in Experiment 3.1 may not depend on

attention. *Extra* deviant stimuli conceptulised as distractor stimuli have also been used in the auditory modality to manipulate attention. For instance, Schröger, Giard, and Wolff (2000); Schröger and Wolff (1998) in an auditory duration discrimination task found that task irrelevant distractors in the form of small changes in frequency prolonged reaction times and elicited MMN and P3a components, reflecting orientation towards the distractor.

Some previous studies on visual MMN have tended to engage active tasks embedded in more peripheral areas of the visual field than the current experiments and one study specifically set out to assess the contribution of the magnocellular system (Kremlacek et al., 2006). This pathway forms the dorsal stream and is not sensitive to colour or detail but is thought to be responsible for pre-attentive detection of motion stimuli. Whilst in the present study we cannot exclude the contribution of the magnocellular system, our findings of a visual MMN in the macular field at 4 degrees visual angle also reveals the contribution of the parvocellular system and ventral stream in detecting differences in the sequence of unattended central stimuli. The parvocellular system is particularly adapted to colour and high contrast black and white detailed information. Thus, the present findings are consistent with earlier work using an active task to show a visual MMN at a visual angle of 2 degrees (Besle et al., 2005).

In conclusion, it is suggested that visual discrimination potentials containing visual MMN components can be elicited using a paradigm with no task demands. The existence of attenuated visual MMN when participants engaged in an active distractor task supports the contention that the illusory square was unable to command all resources away from the standard-deviant comparison. This suggests that visual MMN elicitation was modulated by attention. The presence of these discrimination responses in a clinical group may provide useful information on the functioning of the visual cortex.

4 Intracranial recording of visual evoked potentials

4.1 Aim

A 15 year old male with focal epilepsy undergoing pre-surgical evaluation for resection of a right anterior parietal lesion provided the opportunity to examine whether there was a dissociation of detection and discrimination components of the visual ERP. The aim of the experiment was to investigate whether visual N1 and visual MMN could be recorded directly from the cortex in a child and if they could be separated temporally and/or spatially to delineate different cortical areas involved in visual discrimination. To date, no other study has explicitly recorded activity related to the visual MMN intracranially in a passive oddball paradigm.

4.2 Introduction

Understanding the automatic detection of change in an ever changing environment is an important topic in the neuroscience literature. EEG research has investigated the automatic detection of change through the use of the MMN. Discovering the source of the underlying cognitive activity related to discrimination processes is important because the localisation of electrophysiological correlates cannot be verified until it is supported by finding its local generator (Roman, Brazdil, Jurak, Rektor, & Kukleta, 2005) (see Sections 4.2.1 and 4.2.2). In addition, in a number of clinical conditions such as schizophrenia (Rosburg et al., 2005) there is a reduction in MMN generation (for a review see Näätänen et al., 2012). Therefore, identification of the anatomical correlates of this reduction may provide insights into clinical conditions.

4.2.1 The inverse problem

Establishing the location of underlying neural generators from neural activity recorded by scalp electrodes is a difficult issue to solve. This issue is an example of an ‘inverse problem’. In this context, the inverse problem arises from attempting to predict the neural generators of cognitive processes from voltage distributions recorded at the scalp. However, the activity recorded from the scalp may result from an infinite number of generator sources. A number of computational methods

have been devised to address this issue and a number of source location packages are available that all use some form of factor analysis/principal component analysis (PCA) to estimate the contribution of an underlying source to surface activity e.g. brain electrical source analysis software (BESA) and standardized low resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002). These enable estimation of dipole sources and source waveforms of components. However, none of these algorithms can provide a unique solution, instead providing computational evidence for what may be an underlying source. For a review of solutions to the inverse problem in EEG source analysis see Grech et al. (2008).

The source of the neural generators of deviant related negativity has been investigated using a number of methods including EEG, intracranial EEG (iEEg), fMRi, and MEG. In the auditory modality, evidence from topographical (Scherg, Vajsar, & Picton, 1989), brain lesion (Knight, Hillyard, Woods, & Neville, 1980), intracranial studies in animals (Csepe, Karmos, & Molnar, 1987), intracranial studies in adults (Halgren et al., 1995) and children (Liasis et al., 2000) indicate the primary involvement of the bilateral temporal generators and the frontal generators (Liasis et al., 2001). The neural correlates of the underlying cognitive activity relating to the visual MMN, is less well understood, although current understanding suggests that neural generators for the visual MMN are located in the visual extrastriate areas (Urakawa, Inui, Yamashiro, & Kakigi, 2010) and the prefrontal areas (Kimura et al., 2010), typically limited or lateralised to the right hemisphere, for a review of studies see (Kimura, 2012).

4.2.2 Intracranial recordings

The placement of electrode arrays under the dura directly on the surface of the cortex and/or depth electrodes implanted within the cortex enable recording directly from the brain. This procedure is typically performed clinically in order for epileptogenic zones to be identified for surgical removal for the treatment of severe intractable epilepsy. These intracranial recordings have proved a useful tool in providing a window into the neural mechanisms underlying visual (Clarke, Halgren,

& Chauvel, 1999a), auditory (Liasis et al., 2001; Liasis et al., 1999) and somatosensory (Spackman et al., 2010) discrimination.

It is difficult to establish the source of the neural generators of electrophysiological correlates of cognitive processes from scalp electrodes - although temporal resolution is excellent, spatial resolution is poor compared to other methods. One of the problems with the use of scalp electrodes is that they are recording activity that is the result of a number of overlapping sources and they pass through tissue and bone of varying conductance. This varied conductance of potentials leads to the EEG being recorded over wide areas of scalp and also leads to a reduction in amplitude (Hashiguchi et al., 2007). Intracranial recordings are not impeded by barriers in conduction from the scalp and the skull and they have a higher signal-to noise ratio as there are no muscle movement and eye artifacts (Cooper et al., 1969). Responses recorded intracranially are sometimes inverted in comparison to those recorded using scalp electrodes. Intracranial recordings offer the excellent temporal resolution of the EEG, in the order of milliseconds, but offer improved spatial resolution compared to scalp electrodes by recording directly from the cortex of the brain, closer to the generator sources, which is limited only by the electrode size and spacing (Cooper, Winter, Crow, & Walter, 1965; Roman et al., 2005). However, this methodology is limited in that subdural and depth recordings cannot be taken from a normal population and may therefore not necessarily record a normal response. Furthermore, in a practical sense, the location of the electrodes is limited and based on clinical need, rather than research priorities.

4.2.3 Intracranial studies of visual discrimination

A number of studies have used intracranial recordings to infer the neural generator sources of visual discrimination processes (Baudena, Halgren, Heit, & Clarke, 1995; Brázdil, Dufek, Jurák, Rektor, & Daniel, 2001; Clarke et al., 1999a; Clarke, Halgren, & Chauvel, 1999b; Halgren et al., 1995; Kukleta, Brazdil, Roman, & Jurak, 2003; Roman et al., 2005). The visual oddball paradigm, where an infrequent or ‘deviant’ stimulus is presented in a pseudo random sequence of frequent or ‘standard’ stimuli, or a ‘target’ stimulus is presented at lower probability than a ‘non-target’ stimulus, has been utilised in a number of intracranial studies to

explore the underlying neural generators of visual discrimination processes that can be recorded from scalp electrodes. Many of these studies have involved an active task whereby a target stimulus has to be identified by the participant, by either pressing a response button or by mentally counting the targets.

Clarke et al. (1999b) recorded intracranial ERPs from 13 patients undergoing pre-surgical evaluation for intractable epilepsy. A lateralised visual oddball task was used to evoke P3 activity. Participants had to respond manually to a target stimulus which was presented on 25% of the trials and ignore the standard stimulus which was presented on 75% of the trials. The stimuli, an X and an O, were presented in a pseudo-random sequence. Whilst the patients carried out the task, ERP recordings were taken from intracranial depth electrodes that, across the group, were at temporal, parietal and frontal lobe sites. ERPs to target stimuli showed enhanced amplitudes and distinct N2-like and P3-like components, with the P3-like components being larger in amplitude in ventrolateral prefrontal and hippocampal areas than in the lateral temporal lobes, suggesting different cognitive generators. Although a lateralised task was used, there were no lateralised ERP effects, implying that inter-hemispheric integration was more important than hemispheric lateralisation for this type of task.

Brazdil et al. (1999) used depth electrodes located in frontal and temporal lobes and a scalp electrode at CPz in twelve intractable epilepsy patients to record ERPs in a visual oddball paradigm using an X as a rarely presented target stimulus and an O as the frequently presented standard stimulus. Participants were asked to respond to the target stimulus by pressing a button, while silently counting the number of targets. Their findings indicated generators in the frontal lobe sites - orbitofrontal, dorsolateral prefrontal and anterior cingulate, for a triphasic negative positive negative waveform (N2-P3-SW). The positive wave, peaking at about 300-400 ms, they identified as corresponding to a P3a novelty orienting response. Further, a broad positivity at 400-600ms probably corresponding to the scalp recorded P3b was observed. The generators for this component were localised to medial temporal structures.

Roman et al. (2005) took intracerebral recordings using depth electrodes from 17 participants with intractable epilepsy whilst they carried out a task. Participants were presented with X (target) and O (standard) stimuli in a random sequence within a visual oddball task, and had to respond to the target stimulus by pressing a button and also to count silently the target stimuli. Patterns of intracerebral activation included triphasic N2a-P3a-SW and a P3b. Intracerebral P3 was recorded to visual stimulation, to motor responses, and a P3 was recorded that was not locked to either the stimulus or to the required motor response. The P3s were diffusely distributed in the brain and the authors concluded that it was unclear how the intracerebral P3 generators contribute to the scalp recorded potentials.

The above studies add confirmatory evidence of the temporal and spatial distribution of some attentional components. The depth studies indicate that there are subcortical sources to these scalp or subdural recorded potentials. This is the first study to examine pre-attentive visual discrimination intracranially. Further, to my knowledge there is no study to date that has used an oddball paradigm with no behavioural task to elicit visual MMN components. The aim of the current study was to explore whether there was a dissociation of detection and discrimination components of the visual ERP in a single participant. It was predicted that there would be dissociations.

4.3 Methods

4.3.1 Participant

With hospital ethical approval and parental consent, data were collected from a child with a 16 mm hyperintense lesion within the surface of the right parietal lobe, close to the motor region, identified as a Dysembryoplastic Neuroepithelial Tumour and resultant medically intractable symptomatic focal epilepsy. Prior to a focal cortical resection, the child was undergoing pre-surgical invasive monitoring. A temporary subdural electrode array (SEA) and strip electrodes were implanted to localise seizure foci (see Section 4.3.3 below). Areas of functional cortex were also studied. The patient was a 15 year old male with seizure onset at 12 years of age. Development up to the age of 12 was normal and initial assessments found

the child within the normal range of intellectual ability, with no behavioural difficulties. However, increased seizures had impacted on intellectual ability and moderate learning difficulties were diagnosed prior to surgery, with specific impairments in processing speed and visual memory. In addition, by the time of admission for surgery, attentional and behavioural problems had developed. The child was having 12-16 seizures clusters a month with both tonic and clonic phases, characterised by becoming unresponsive and rigid and all four limbs jerking. The seizures usually lasted about a minute and occurred in clusters of 20 or more. In addition, episodes of peri-ictal mental state changes occurred, which include altered perception and a degree of agitation.

4.3.2 Stimuli and procedure

The stimuli used were the three monochrome endline type stimuli based on pac-men figures that were employed in Experiment 3.1 (see Section 3.3.2.1). The stimuli appeared on the screen for 400 ms with an inter-stimulus interval of 600 ms and the patient was asked to focus on the red fixation dot in the centre of the screen. Beyond this request there were no task demands. The recording session lasted less than half an hour and was performed on the telemetry ward, with the patient sitting up in bed viewing a monitor which was placed 1 m in front of him. Due to the difficulties of recording in a clinical environment such as this, only two blocks of the 225 stimuli were presented. The recording was paused when the patient's attention to the screen wandered, as assessed by observation. No ictal events occurred during the recording.

4.3.3 Subdural electrode implantation and electrodes

Before surgical implantation of the electrodes, an MRI was taken and used to construct a three-dimensional (3D) image of the patient's skull and cortex. During surgical implantation of the electrode array, the 3D image was co-registered to the patient's head by taking a number of scalp co-ordinates and using the Image Guidance System (IGS) (see Figure 4.1). Once co-registered, the surgeon could use the IGS software to navigate around the virtual brain locating structures visible to MRI but not to the naked eye. The SEA and strip were implanted under general

anaesthesia through a craniotomy. A photograph of the cortex pre and post electrode implantation allowed individual SEA contacts to be mapped to fissures and blood vessels (see Figure 4.2). Following insertion of the electrodes, the bone flap was replaced and the electrical wires brought through the scalp and connected to the telemetry machine for monitoring of electrical activity. Monitoring of the patient using telemetry and video to observe epileptogenic activity took place over five days prior to surgery.

Based on clinical need to demarcate the area of cortical abnormality, a 32-contact subdural platinum grid was implanted, straddling the parietal and pre-motor gyri, along with a 6-contact strip extending posteriorly over the inferior parietal cortex such that the most distal contact (**S1**) overlay the right occipital cortex (Figure 4.1). The SEA and strip consisted of platinum electrodes embedded in a one and a half millimetre thick flexible sheet. Centre to centre distances between electrodes were ten millimetres. The clinical need for the strip electrodes is that when testing the hypothesis that the seizures are arising from a particular locus, it is common practice to have at least some contacts distal from the area of the lesion to assess, as far as is practicable, whether seizure onset is confined to the area close to the lesion.

Following electrode placement, functional stimulation was carried out by Dr Stewart Boyd, Consultant Clinical Neurophysiologist as part of the clinical assessment of the patient. The stimulation aids in the functional mapping of cortical anatomy. Functional stimulation of electrode G28 highlighted in green in Figure 4.1 evoked movement in the fingers, stimulation of electrode G26, highlighted in brown, evoked movement in the left lower jaw and stimulation of electrodes G17 and G18 (highlighted in blue) evoked movement of the left lower face. The 6 contact strip extends across the lower portion of the parietal lobe and occipital lobes but does not reach the occipital pole. Reconstruction of the electrode placement with the surface-rendered scan suggests that the strip lies below the angular gyrus (BA39) and traverses the caudal portion of the supramarginal gyrus (BA40) onto V2 (BA19) and V3 (BA18) (see Section 1.3).

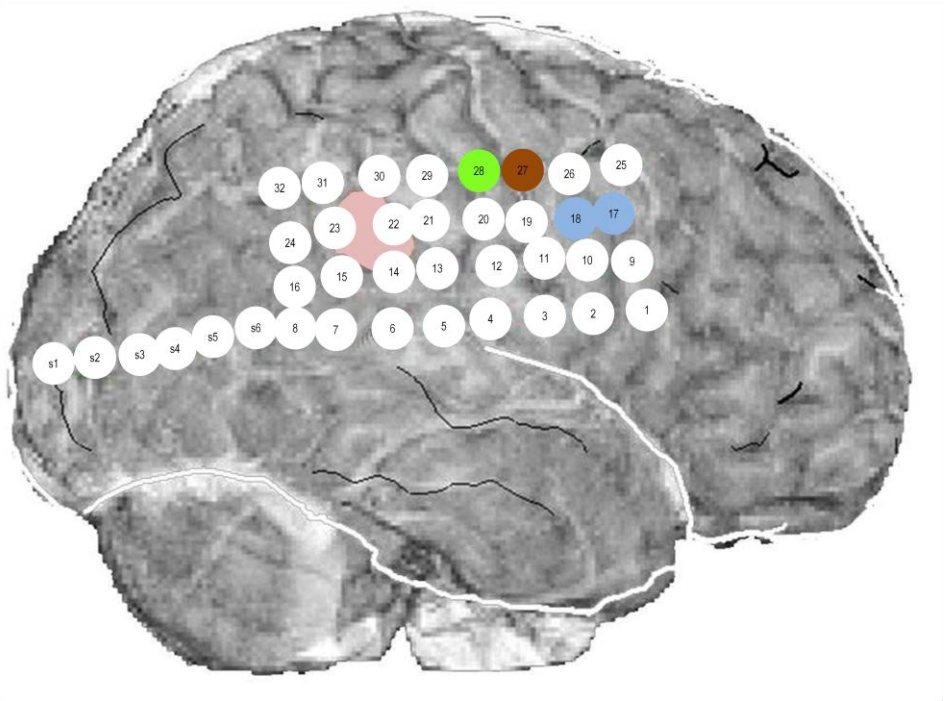


Figure 4.1 3D MRI reconstruction and co-registered subdural electrodes, highlighted pink area denotes surface visible lesion.

Functional stimulation of: electrode G28 (highlighted in green) evoked movement in fingers; G27 (highlighted in brown) evoked movement in mouth; G17 and G18 (highlighted in blue) evoked movement of the lower jaw.

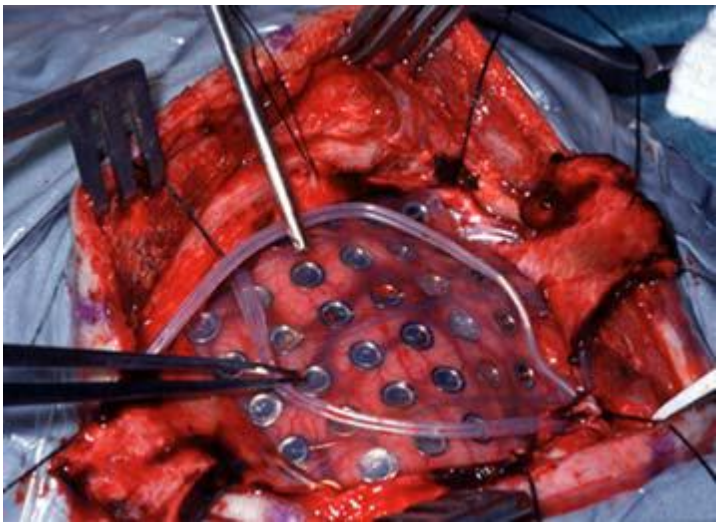


Figure 4.2 Photograph of exposed cortex and 32 contact subdural electrode array in place

4.3.4 EEG recording and data analysis

The intracranial reference electrodes G1 and G2 were selected for the intracranial recording as they were distal from locus of the epileptogenic activity. Continuous EEG was collected using Neuroscan-SCAN version 4.3 (see Section 2.2). Continuous EEG data were processed offline into epochs from -100 ms pre-stimulus to +500 ms post-stimulus. The epochs were digitally filtered with a band pass 1-30Hz and baseline corrected. Due to limited data, no artifact rejection settings were applied. ERPs were averaged separately for standard, deviant and illusory deviant stimuli employing G25 and G26 as an averaged reference, as these electrodes were distal from the epileptogenic activity and from the electrodes over the occipital areas. Average waveforms were constructed from 36 epochs for each of the stimuli. ERPs to standard stimuli were constructed from epochs that preceded deviant stimuli – these were randomly selected. Subtraction waveforms were constructed by subtracting the standard from the deviant waveform.

4.4 Results

As expected, greater amplitudes were recorded using intracranial electrodes in comparison to those typically recorded from scalp electrodes, and responses were inverted. A negative positive negative complex was recorded to all stimuli at the most posterior electrode sites **(S1, S2 and S3)** (Fig 4.3A) indicating visual stimulus detection. The latency and amplitude of the first major negative component (N1) was similar for standard, deviant and illusory deviant stimuli (153ms and -32.39uV, 153ms and -48.54uV, and 162ms and -45.50uV, respectively). Responses to stimulus discrimination (visual mismatch) were recorded more anteriorly at (**S3**) and (**S4**) and were characterised by enhanced positivities at about 90ms (42.32uV) and 219ms (87.21uV) for **S3** and enhanced positivities at 88ms (28.55uV) and 237ms (45.93uV) for **S4**, either side of the major negative component (Figure 4.3A). Subtraction waveforms (deviant-standard) revealed a discrimination response with positive peaks at 86ms and 219ms for electrode **S3** and 93ms and 233ms at electrode **S4** (Figure 4.3B).

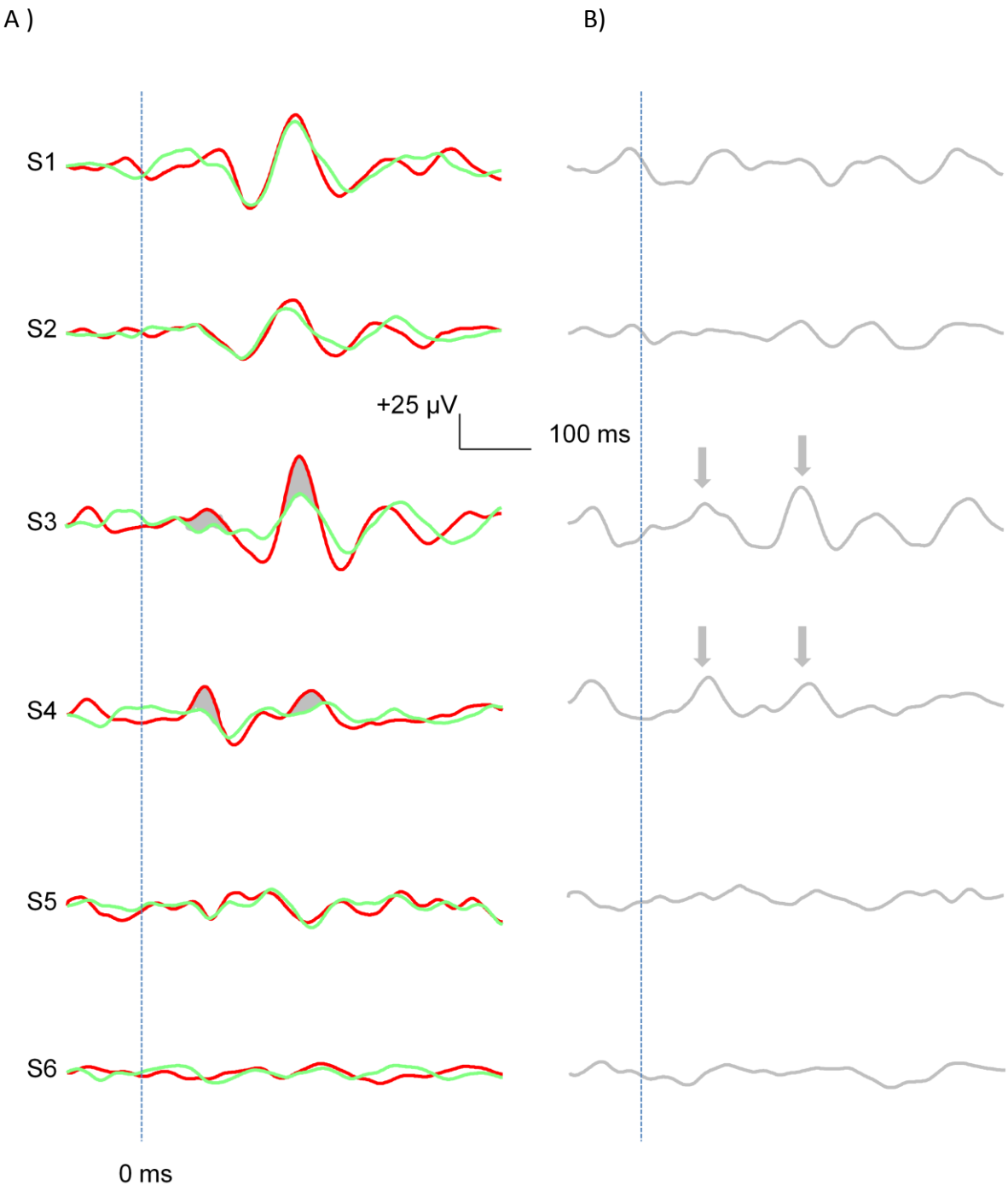


Figure 4.3 Standard, deviant and subtraction waveforms from the six strip contacts

A) Standard (green line) and deviant (red line) waveforms from the six strip contracts. At S1 and S2 the illusory deviant waveform did not differ from the deviant or standard and no consistent changes were seen at S3 and S4. For reasons of clarity the illusory deviant waveform is not shown. Peak amplitude at N1 and inverted discrimination components shown by the grey shaded area. B) Deviant minus standard subtraction waveforms (grey lines). Note the discrimination responses highlighted with grey arrows. (Positive upwards).

Figure 4.4 shows grand average ERPs to all the grid contacts. Responses over the surface visible lesion and the seizure onset zone were not interpreted as it would be expected that they were non-normal. Functional stimulation of fingers, hand and face assist in the anatomical localisation of responses. Of interest to the current experiment, a later positive response to the illusory deviant stimulus was seen at around 386ms over pre-motor regions corresponding to Brodmann's area 6 (electrodes **G9, G17 and G18**), suggesting activation of a frontal system to stimulus novelty and/or target detection (see shaded upper panel, and the lower panel of Figure 4.4).

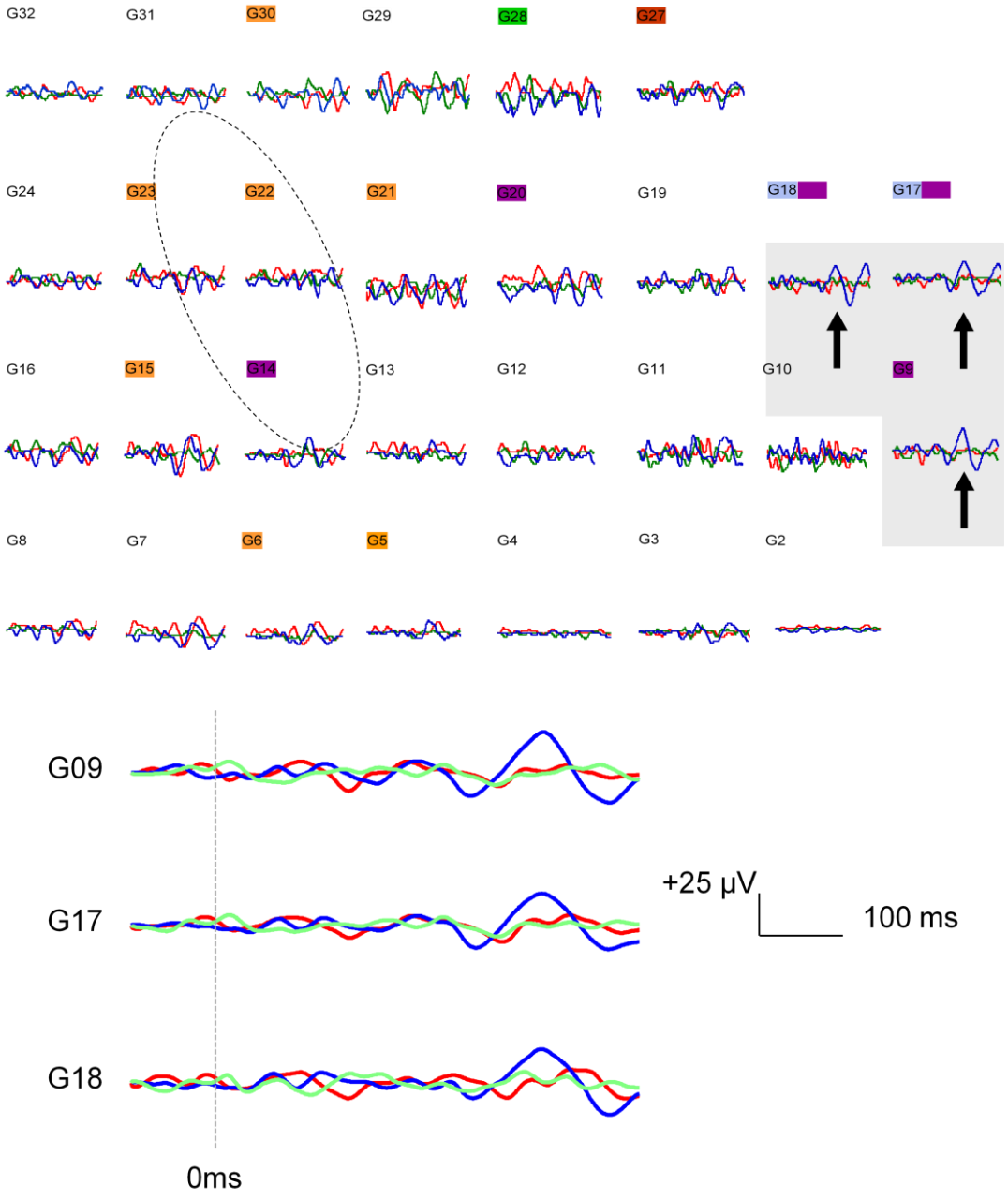


Figure 4.4 Grand average ERPs to grid contacts.

The upper panel shows grand average ERPs to all the grid contacts (standard green waveform, deviant red waveform and illusory deviant blue waveform). The dotted ellipse denotes the surface visible lesion, the seizure onset zone is highlighted in orange (G5, G6, G15, G21, G22). Somatosensory localised responses to functional stimulation of fingers are highlighted in green (G28), of hand are highlighted in light blue (G18, G19), and of face are highlighted in brown (G27). Time-locked visual activity is highlighted in purple (G9, G14, G17, G18, G20). Anterior grid electrodes revealing a later positive response to the illusory deviant stimulus are indicated where there is a shaded area of the waveform and this area is enlarged in the lower panel (G9, G17, G18). (Positive upwards).

4.5 Discussion

Recordings from the intracranial case study support the separation of detection and discrimination processes likely to be within the visual cortex. The N1 component at 153 ms located at the more posterior electrodes, located over extrastriate occipital areas (BA18/BA19) corresponds to the scalp recorded N1 recorded in Experiment 3.1 (see Section 3.3.4) at 167 ms. The waveforms were similar for the standard, deviant and illusory deviant stimuli. The N1 probably represents visual stimulus detection processes. However, at adjacent posterior electrodes **(S3 and S4)** the deviant stimuli evoked early and later positivities that probably contribute to the scalp recorded MMN. These electrodes were within the extrastriate cortex anterior to the lunate sulcus and ventral to the lateral occipital sulcus, suggesting that this area may be a local generator of visual MMN. With respect to scalp recordings these potentials to stimulus discrimination are inverted in polarity and the first positive component is seen relatively early at around 90 ms. These findings are consistent with a MEG study showing strong activation of the lateral occipital cortex at around 155 ms post stimulus (Halgren, Dale, Mendola, & Chong, 2003). In MEG studies comparison of illusory Kanizsa stimuli with control stimuli reveals activation between 100 – 350ms post stimulus (J. Kaiser et al., 2004) and at around 280 ms (Halgren et al., 2003). It is believed that illusory contour sensitivity may first occur in middle to higher order visual processing areas and that feedback modulation from lateral occipital areas will activate V1 and V2 areas (J. Kaiser et al., 2004).

Polarity inversions between the cortex and the scalp can indicate local generator sources in that region of cortex. As these scalp recorded N1 and MMN fields result from the super imposition of several bilateral generators, it is difficult to understand how focal intracranial potentials contribute to the scalp recorded N1 and MMN. The inverted bifid positive discrimination component may well represent the existence of one or more local generator sources to change detection. Complex and widespread activation has also been recorded to alternating and on/off stimuli at the striate cortex and visual association areas (Farrell, Leeman, & Ojemann, 2007)

further supporting the view that it is difficult to disentangle the generator sources that contribute to responses measured at the scalp.

Intracerebral potentials to rare distractor visual and auditory stimuli have been recorded from frontal regions as a widespread negative-positive-negative waveform at approximate latencies of 210-280-390 ms respectively (Baudena et al., 1995). It is believed that this waveform corresponds with the scalp recorded N2a/P3a/slow wave that is associated with orienting of attention. In the present study, the later positivity to the illusory deviant stimulus seen at around 386ms over pre-motor regions may correspond to this novelty orienting process.

A number of scalp recorded electrophysiological studies have attempted to infer the generators of deviant related negativity. The findings of Urakawa, Inui, Yamashiro, and Kakigi (2010) converge with the results of Experiment 4.1 and suggest that neural generators for the visual MMN are located in the extrastriate cortex (BA 19). They used a passive visual oddball paradigm during which participants watched a silent movie whilst counterbalanced task irrelevant infrequent and frequent red and blue stimuli were presented to their peripheral visual field. Neural responses to infrequent and frequent stimuli were recorded using MEG and then a multi-dipole BESA comparison method was used to elucidate the source and timing of the cortical activity. Urakawa et al.'s findings revealed at 100ms activation of the cuneus (BA17) which was similar for infrequent and frequent stimuli, whilst at 150ms the infrequent compared to the frequent stimuli produced an enhanced peak amplitude for the middle occipital gyrus (MOG, BA19) magnetic activity. In addition, for some participants there was enhanced activation of the right inferior frontal gyrus. There was a divergence of the magnetic responses to the infrequent and frequent stimuli at around 150ms, this divergence concurred with the findings of previous EEG studies such as (Czigler et al., 2002). The timings of this divergence also correspond to the findings of the present experiment.

Using a combination of an oddball and an equiprobable paradigm which has been shown to separate the visual N1 and visual MMN components (Kimura et al., 2009), Kimura et al. (2010) explored the contribution of neural generators to N1

and MMN using current sources as estimated by an sLORETA solution. They found a separation of neural generators for the two components, with N1 neural generators including the occipital visual striate and extrastriate areas (both hemispheres) and the MMN neural generators including the right hemisphere occipital visual extrastriate areas and prefrontal areas. This separation of the components corresponds to the separation of the N1 and MMN found in the current experiment.

In contrast to the results in the current experiment, which suggests visual MMN generators in extrastriate areas, Czigler et al. (2004) found that the deviance related negativity generators include prestriate areas. They presented stimuli to upper and lower visual fields, in common with prior work (Jeffreys & Axford, 1972b). Upper and lower visual field presentations were found to lead to an inversion of polarity and indicated striate origin of such components. They reported that the most likely source of activity underlying automatic visual change detection is the prestriate cortex and therefore that the neural generators include at least, the retinotopically organised visual areas. A number of ERP studies have shown that the N1 component of the visual event related potential occurring (140-200ms) is affected by task-related manipulations such that there is an increase in N1 amplitude in conditions where attention is required (Vogel & Luck, 2000). It is unclear from the paradigm used in this study whether a 'true' MMN was recorded as the ERP recorded and identified as MMN remained within the N1 latency range.

In conclusion, the current results indicate that the generators of the visual N1 and MMN can be temporally and spatially separated, with the generators for the MMN (electrodes S3 and S4) being located more anteriorly over extrastriate areas ventral to the lateral occipital sulcus. However, it is unclear how these are related to the scalp recorded N1 and MMN. In addition, this recording was from only one participant and the brain areas recorded from were limited as they were selected on the basis of clinical need and were confined to the cortical surface.

5 Exploration of hemispheric lateralisation of visual MMN and perception of illusory contours

5.1 Aim

Due to a characteristic abnormality of retinal projections in albinism, the primary visual cortex receives an abnormal visual field representation, such that, in addition to the normal input from the contralateral hemifield, there is abnormal input from the ipsilateral hemifield. This preponderance of temporal retinal fibres from each eye crossing to the contralateral hemisphere affords the opportunity to investigate each hemisphere in relative isolation and explore whether there is a hemispheric lateralisation in the source of the visual MMN and the perception of illusory contours. To date no other study has examined the visual MMN or illusory contour processing in a paediatric albino population.

5.2 Introduction

Albinism is a group of inherited disorders characterised by an abnormality in melanin synthesis in which either eyes (ocular albinism), or the eyes, skin and hair (oculocutaneous albinism) may be affected. In humans, it is estimated to affect approximately one in 17,000 people and is found in all ethnic backgrounds (Witkop, 1979). Clinically, manifestations include congenital nystagmus, iris hypo-pigmentation and translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypoplasia, reduced visual acuity and refractive errors, impaired colour vision and photophobia. Misrouted optic nerve fibres result in strabismus and reduced stereoscopic vision (Gronskov, Ek, & Brondum-Nielsen, 2007).

Despite a variety of phenotypic presentations ranging from hypo-pigmentation to dark skin pigmentation (Apkarian & Bour, 2007), obligatory features of albinism are foveal hypoplasia (Guillery, 1996), which is manifested by the absence of a foveal reflex, and, of particular interest to this study, misrouted optic nerve fibres (Guillery, Okoro, & Witkop, 1975). This distinguishing misrouting of optic nerve fibres has been found not only in humans with albinism but also in albino rats (Lund, 1965), albino cats (Guillery & Kaas, 1971), albino rabbits (Sanderson, 1975), albino mice (Lavail, Nixon, & Sidman, 1978) and a number of other vertebrate species with albinism.

As noted in Section 1.1, mammals with binocular vision normally have a partial decussation at the optic chiasm – the axons from the nasal retina project contralaterally and the axons from the temporal retina project ipsilaterally. Mammals with albinism have different visual pathways to those without albinism such that there is a shift in the line of decussation with the majority of temporal retinal fibres from each eye crossing to the contralateral hemisphere (Dorey, Neveu, Burton, Sloper, & Holder, 2003). This abnormality in temporal retinal projections, means that in addition to normal input from the contralateral hemifield, the visual cortex receives abnormal input from the ipsilateral hemifield (see Figure 5.1). This is a characteristic anomaly that when examined using Visual Evoked Potentials (VEP) results in asymmetrical responses (Apkarian & Bour, 2007; Apkarian & Shallohoffmann, 1991), the response in the contralateral hemisphere is earlier and larger than in the ipsilateral hemisphere.

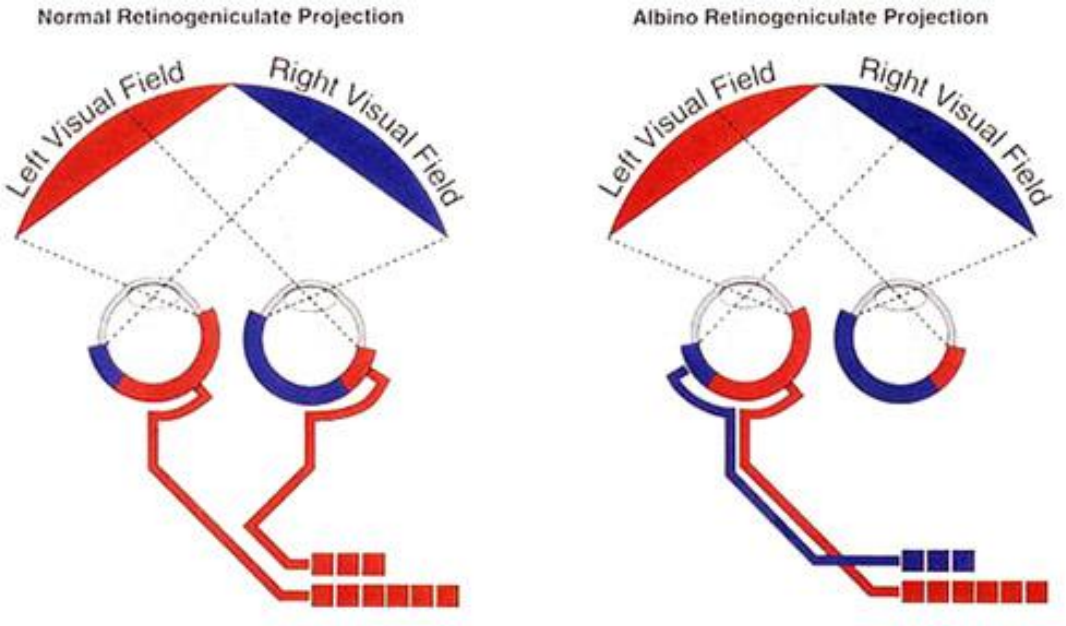


Figure 5.1 Normal and albino visual pathways

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Electrodiagnostic methods for detecting misrouting asymmetry have been developed. Optic pathway misrouting can be recorded with lateralised occipital scalp electrodes using appropriate full-field VEP testing, and can detect optic chiasm misrouting (Apkarian, Reits, Spekreijse, & Vandorp, 1983; Hoffmann, Lorenz, Morland, & Schmidtborn, 2005; Soong, Levin, & Westall, 2000). These methods employ stimuli, such as pattern onset stimuli, that are presented monocularly. When occipital derivations from one eye are subtracted from the other, polarities of inter-hemispheric difference VEPs for left and right eye stimulation should be inverted if the majority of temporal retinal fibres cross to the contralateral hemisphere. Whereas, in a normal population, because the temporal and nasal retinal projections for each eye project equally to both hemispheres, occipital difference polarities are not inverted (Hoffmann et al., 2005).

5.2.1 Hemispheric specialisation

Widely held views of cerebral asymmetries in brain function suggest that the left hemisphere is specialised for linguistic and cognitive processing and fine motor control. For example, auditory MMNs to language specific stimuli show left hemispheric dominance (Naatanen, 2001), whilst it is suggested that the right hemisphere is specialised for visuo-spatial processing. However, studies with split-brain patients have shown this to be an oversimplification as the left hemisphere retains complex visuo-spatial abilities and the right hemisphere can enable some limited language comprehension. It is suggested that both hemispheres can process visuo-spatial information but do so in different ways. For a review of split brain studies, see Gazzaniga (2000).

5.2.2 Importance of the right hemisphere for visual MMN

The importance of the right hemisphere in the generation of the visual MMN has been highlighted in a number of studies. Using the source localisation method sLORETA, Kimura et al. (2010) explored the neural generators of visual N1 and visual MMN in relation to changes in the orientation of a bar. They reported a right hemispheric dominance for visual MMN generators. Their results also suggested that the visual N1 is associated with large areas including the primary and non-

primary visual areas, while visual MMN is associated with more discrete non-primary visual areas. Kimura, Kondo, Ohira, and Schroger (2012) reported that the visual MMN elicited in response to alternations of facial stimuli was mainly generated from occipito-temporal visual extrastriate areas in the right hemisphere and medial and lateral prefrontal areas lateralised to the right. In addition, Kimura et al. (2009) reported a right hemisphere dominance for visual MMN to changes in the orientation of a bar. Grimm et al. (2009), using a multi-level distraction paradigm explored stimulus regularity violations and found the differences between deviant and control stimuli were present in both hemispheres indicating sources in bilateral parieto-occipital areas of cortex but with a right hemisphere dominance. In the experiment reported in Chapter 4 of the current thesis, ERP recordings taken directly from the cortex, provided evidence for the spatial and temporal separation of visual N1 and MMN in the right hemisphere. This may be suggestive of generators of visual MMN in the right hemisphere, although it is acknowledged that this was a case study and that electrode coverage was not extensive and did not cover the left hemisphere. The results of these studies suggest that there may be evidence for the predominance of the right hemisphere in the generation of the visual MMN.

5.2.3 The right hemisphere and illusory contour processing

Illusory figures, as noted in Section 3.2, are ambiguous figures in which the illusion of a square or triangle is perceived in the middle of inducers, such as pacmen, in the absence of real contours (Kanizsa, 1976).The existence of hemispheric lateralisation in the perception of illusory contours and whether their perception involves high level cognitive processes or only low level parallel processes has been debated. For a review of functional neuroimaging findings on the perception of illusory contours, see Seghier and Vuilleumier (2006). Larsson et al. (1999) using positron emission tomography (PET) to measure brain activation to the perception of real and illusory contours suggest a hemispheric asymmetry with evidence of right–sided lateralisation for both real and illusory contour processing. In particular, the perception of illusory contours was associated with stronger activation in the right fusiform gyrus, suggesting differential levels of top-down

processing between illusory and real contours. Korshunova (1999) recorded ERPs in a passive paradigm in which participants were presented, in the central visual field, with Kanizsa stimuli and stimuli that did not form an illusory percept. They found an increase in mean VEP amplitudes in both hemispheres at N180-P230. Comparison of left and right hemisphere activation across all electrodes revealed increased amplitude in the right hemisphere, consistent with its superiority in visuo-spatial processing. Rooted in Feature Integration theory (Treisman & Gelade, 1980) a recent study by Poynter and Roberts (2012) suggests differences in the efficiency of spatial processing between the hemispheres. They suggest the right hemisphere performs global low-level spatial processing more efficiently and that this type of spatial processing is associated with parallel search mechanisms requiring spatially distributed attention. They suggest the left hemisphere is associated with high spatial frequency/serial search mechanisms that require shifts in localised attention.

Proverbio and Zani (2002) did not provide evidence of a right-sided lateralisation. Using ERPs to establish the time course and scalp topography in the perception of illusory figures, they used a behavioural task in which participants had to press a button in order to distinguish whether an illusory figure was present or absent from a visual display. They found that the perception of illusory figures was associated with activation of bilateral cortices at about 145ms post stimulus onset as reflected by an enhanced N1 component. In addition, stronger left than right hemisphere activation to the perception of illusory contours was observed in an event related fMRI study (Ritzl et al., 2003). In a study of split brain patients, (Corballis & Fendrich, 1999) compared the processes involved in the perception of an illusory Kanisza square and a modified Kanisza square in which the contours of the square were not readily visible but had to be inferred. They found that both hemispheres were equally capable of illusory contour perception, but that for the completion of the modified Kanisza square, perception of the stimuli presented to the right hemisphere was significantly better. They suggested that illusory processing was low-level processing available to both hemispheres, whilst the right hemisphere was superior at completion of the modified Kanisza square. Corballis (2003) suggests that hemispheric asymmetries with a right hemisphere dominance

may occur for higher level visual mechanisms and that low level processing can be carried out in both hemispheres.

5.2.4 Rationale

The studies discussed above demonstrate the lack of consensus and debate regarding hemispheric lateralisation in the generation of the visual MMN and illusory contour perception and highlight the need for further investigation. The experiments presented in this chapter were therefore carried out in order to gain further insight into this area using a sample of participants with albinism, whose abnormality in temporal retinal projections, means that in addition to normal input from the contralateral hemifield, the visual cortex receives abnormal input from the ipsilateral hemifield.

Two experiments were carried out. Experiment 5.1 was designed to confirm primary optic pathway misrouting by establishing that the central visual field showed cerebral asymmetries. Experiment 5.2, was designed to assess cerebral asymmetries in the time course of visual MMN and illusory contour processing. Taking into account the established finding that ERPs to monocular recordings for albinism are characterised by faster latencies in the contralateral hemisphere than in the ipsilateral hemisphere, it was predicted that the ERP responses to the stimuli would be earlier in the contralateral than in the ipsilateral hemisphere. It was predicted that the mean P1-N1 peak-to-peak amplitude to the deviant and illusory deviant stimuli would be enhanced compared to the response to the standard stimulus, indicating discrimination processes and this would be larger over the right hemisphere. In addition, it was predicted that the ERP response to illusory deviant would be fastest in the right hemisphere.

5.3 Methods for Experiment 5.1 and Experiment 5.2

5.3.1 Participants

Nine participants were recruited from a group of children, with clinically diagnosed albinism, at Great Ormond Street Hospital for Children. Diagnosis was based on an ophthalmological assessment including fundoscopy, orthoptic assessment and visual electrophysiological testing. The mean age of participants was 13 (range 9 to 17) - see Table 5.1 for clinical characteristics. Parental consent was obtained for their child's participation in the experiments.

Table 5.1 Clinical characteristics of test sample (F=female, M=male), *n*=9

Participant No.	Age (years)	Sex	Type of Albinism Diagnosis	Visual acuity Log Mar	Patient details
1	16	F	Exact subtype not known at time of submission of PhD	Not known	Detailed Ophthalmic symptoms not available at time of submission of PhD
2	15	F	Oculocutaneous	0.6	Reduced vision
3	9	F	Exact subtype not known at time of submission of Phd	0.5	Squint, nystagmus, macula hyperplasia, astigmatism, mild albinism, peripheral translucency of irides.
4	12	M	Oculocutaneous	1.04	Registered blind, horizontal manifest nystagmus
5	10	F	Ocular	0.56	Mild form of albinism with reduced vision
6	17	M	Oculocutaneous	0.16	Left convergent squint
7	11	M	Oculocutaneous	0.42	Foveal hypoplasia, Hermansky pudlak syndrome
8	16	M	Exact subtype not known at time of submission of PhD	Not known	Detailed Ophthalmic symptoms not available at time of submission of PhD
9	13	M	Ocular	0.72	Nystagmus

5.3.2 Procedure

Within the same recording session, two VEP experiments were conducted in participants with albinism. Apart from differences in stimuli, both experiments were carried out under identical conditions. For both experiments, participants were seated comfortably in a darkened room 1 m away from a 50 inch plasma screen (Pioneer PD50) and asked to fixate on a small red dot in the centre of the screen that was present throughout the recordings. Left and right eyes were stimulated monocularly; an eye patch was placed over the eye that was not being tested at the time. The stimuli were presented in separate blocks. Stimuli for Experiment 5.1 were presented to each eye in turn and then the process was repeated for the stimuli in Experiment 5.2.

5.3.3 EEG recording

Nineteen Ag/AgCl electrodes were used to record the EEG activity and were positioned at sites in accordance with the International 10-20 system (Fz, F3, F4, Cz, C3, C4, T3, T4, Pz, P3, P4, Oz, O1, O2, T5, T6, VEOG). The reference electrode and the ground electrode were placed at the right and left mastoid respectively. An electrode was placed above the uncovered eye to enable online artifact rejection of eye blinks. Continuous EEG was collected using Neuroscan SCAN version 4.3, at a sampling rate of 1000Hz, with a low pass of 100Hz and a high pass of 0.05Hz and stored on a computer for offline analysis. Continuous EEG data were epoched offline -50 ms pre-stimulus to +500 ms post-stimulus. The epochs were digitally filtered with a band pass 1-30Hz and baseline corrected. Epochs containing transients greater than ± 100μV were excluded from further analysis. Fz was employed as a reference.

5.4 Experiment 5.1: Procedure to confirm primary optic pathway misrouting

5.4.1 Stimuli

Pattern onset stimuli consisted of black and white checkerboard strips that enabled the visual field to be segmented into four equally spaced segments such that two segments were equally distributed over the left half field (stimuli 5, 4) and two over the right half field (stimuli 2, 3). The order of presentation was 5, 4, 2, 3 (see Figure 5.2). The black and white checkerboard strips were presented at 97% contrast and appeared against a uniform grey background with equal luminance to the strip (mean luminance 93 cd/m^2). The strip (checkerboard) patterns appeared for 240ms and were presented at a rate of 3Hz, each strip subtended 10 degrees of arc. Within a block there were 808 stimuli, comprised of 202 presentations of each stimulus type. Two blocks of the stimuli were presented to each eye.

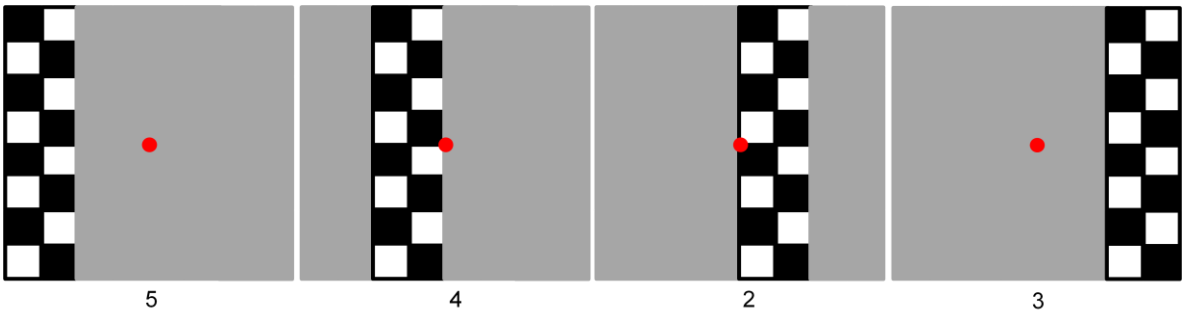

Figure 5.2 Pattern onset stimuli - left half field (stimuli 5, 4), right half field (stimuli 2,3)

5.4.2 VEP data analysis

For each participant, the waveforms for left half-field and right half-field were combined to construct grand average waveforms of all onset strips. A linear derivation whereby the right hemisphere occipital response was subtracted from the left hemisphere occipital response was then applied to the grand average waveforms for the left eye and the right eye. This method reveals misrouting

asymmetry in the form of polarity reversals of the difference potential from left eye to right eye stimulation (Apkarian & Bour, 2007). In addition, grand average ERPs were constructed for each stimulus for each eye.

5.4.3 Results

The distribution of the VEP response lateralisation across the occipital lobes is evident in Figure 5.3 below, where polarity reversals of the difference potentials from left eye to right eye stimulation can be seen (highlighted with arrows) for the participants. This asymmetry confirms the optic pathway misrouting for the majority of the participants, although no optic pathway misrouting is apparent for participants 4 and 5.

Comparison of grand average waveforms for the left and right eye for each of the stimuli at electrodes O1 and O2 reveal that for stimuli 4 and 2 right eye viewing had an earlier response latency in the left hemisphere, whilst left eye viewing had an earlier response latency in the right hemisphere (see Figure 5.3 A,B). In addition, the subtraction waveforms (electrode O2 subtracted from electrode O1 for the left and the right eye) reveal a reversal of polarity of the inter-hemispheric activation difference in the central visual field (stimuli 4 and 2) revealing optic nerve misrouting from the central temporal retina. The absence of the polarity reversal in the periphery (stimuli 5 and 3) reveals the reversion to the normal pattern of optic nerves. This corresponds with the findings of Hoffmann et al. (2005).

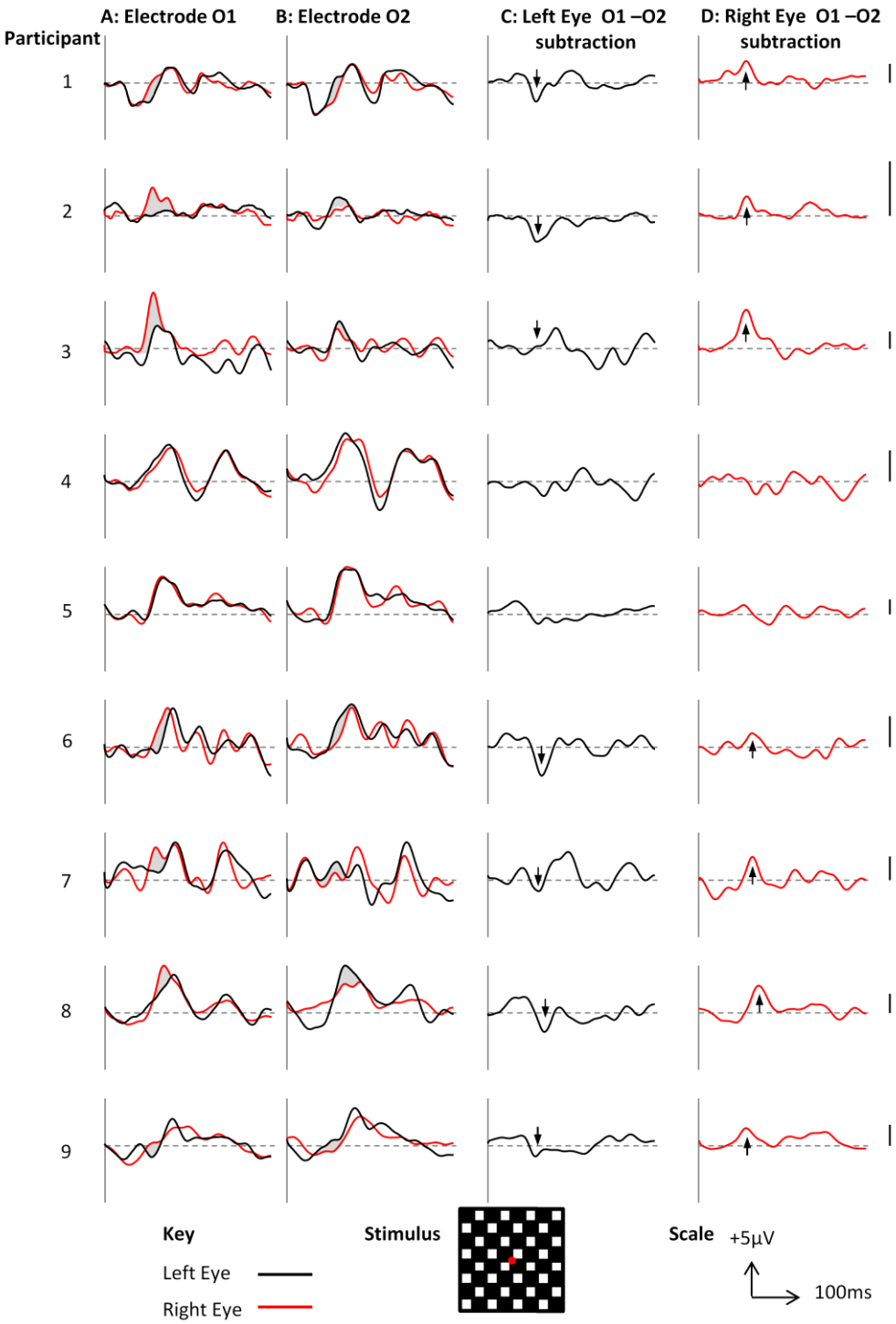

Figure 5.3 Individual participant grand average and subtraction waveforms

Individual participant grand average waveforms for the left and right eye at electrodes O1 and O2 (A, B), polarity reversals are shaded in grey. Individual grand average subtraction waveforms for the left and right eye (C, D) - right hemisphere occipital response subtracted from the left hemisphere occipital response - revealing a misrouting asymmetry highlighted with arrows. Note: participants 4 and 5 do not show a misrouting asymmetry. (Referenced to Fz, positive upwards).

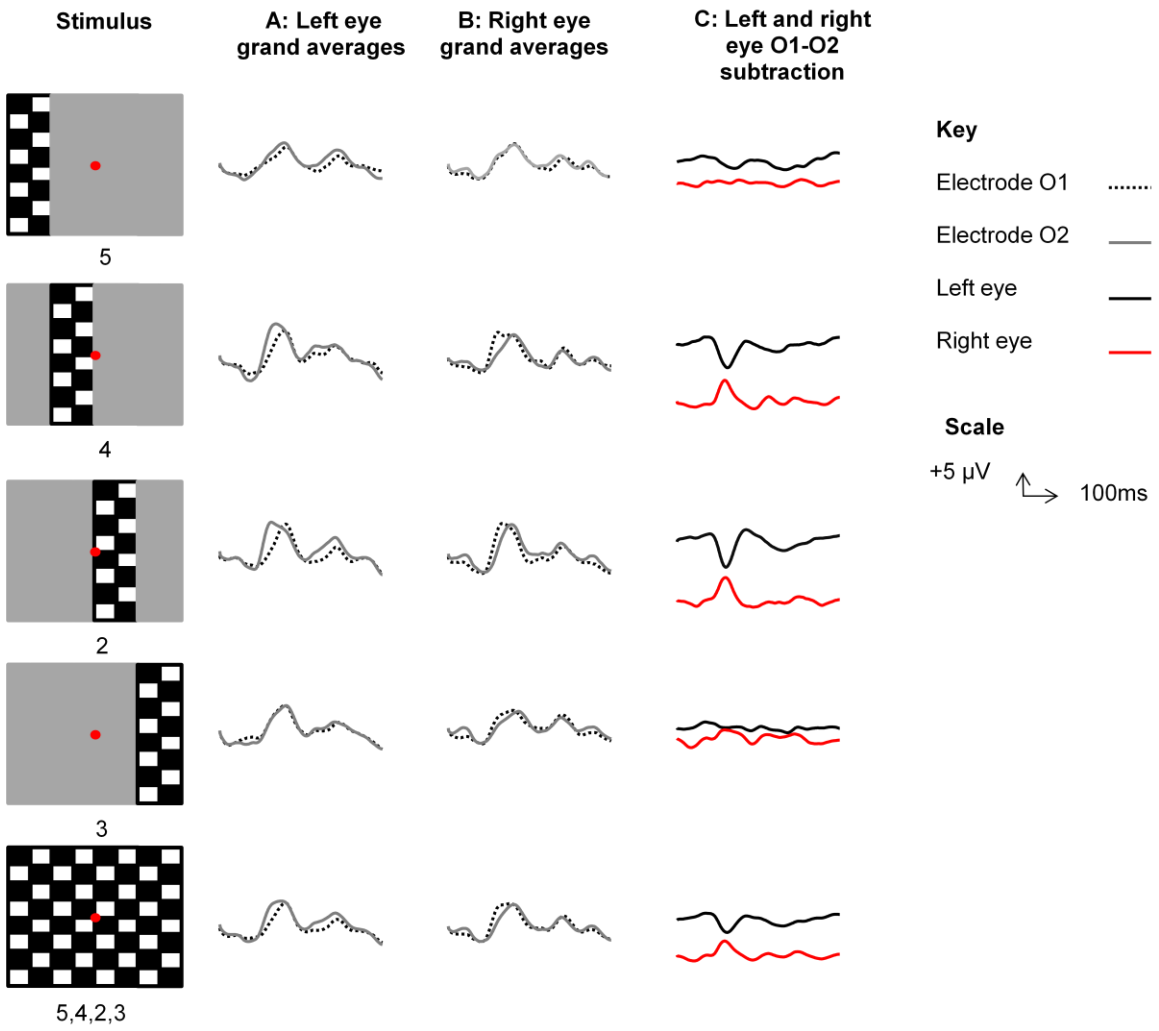

Figure 5.4 Group grand average waveforms for each of the stimuli for the left eye (A) and the right eye (B) at electrode O1 and electrode O2.

Subtraction waveforms O1 minus O2 for the left and right eye (C) for each of the stimuli. Note: Pronounced inter-hemispheric asymmetries are revealed for stimuli 4 and 2. (Referenced to Fz, positive upwards).

5.4.4 Discussion

Pattern onset stimuli segmented into four equally spaced segments were presented monocularly to participants, such that, two segments were equally distributed over the left half-field and two equally distributed over the right half-field. It was established that, for those stimuli presented in the central visual field, patterns of occipital activation exhibited a contralateral dominance characterised by a reversal of polarity of the inter-hemispheric activation difference, whilst, for those stimuli presented in the peripheral visual field no such reversal of polarity was observed. These results are in accordance with other studies and provide evidence of optic nerve misrouting at the central temporal retina for the majority of this group (Hoffmann et al., 2005; Soong et al., 2000).

In a study quantifying the extent of inter-hemispheric asymmetry, Hoffman 2005 found in a sample of 16 albino participants that the projection was confined to the central retina and varied in extent between subjects (2-15º; median 8). This range is consistent with a previous fMRI based retinotopic mapping study that reported abnormalities between 6 and 14º (Hoffmann, Tolhurst, Moore, & Morland, 2003). Inter-hemispheric asymmetries for individuals were not measured in this study; the stimuli in Experiment 5.2 were confined to presentation within the central retina subtending 4º of arc.

The preponderance of temporal retinal fibres from each eye crossing to the contralateral hemisphere therefore provided the rationale for investigating hemispheric lateralisation in the visual MMN and the perception of illusory contours in Experiment 5.2 as each hemisphere can be studied in relative isolation.

5.5 Experiment 5.2 visual oddball paradigm

5.5.1 Participants

Data from three participants were excluded from the visual oddball paradigm results and statistical analysis. In Experiment 5.1, participants 4 and 5 did not exhibit the characteristic hemispheric asymmetry so were excluded from the analysis of Experiment 5.2. In addition, participant 7 was excluded from the analysis as he was unable to tolerate the visual oddball recording, leaving 6 participants for data analysis (see Table 5.1 for clinical characteristics of participants).

5.5.2 Stimuli

The stimuli outlined in Section 3.3.2.1 based on pacmen figures were employed in a behaviourally silent oddball paradigm where the ratio of standards to deviants and illusory deviants was 8:1:1 (see Section 2.4.3.1). The stimuli appeared on the screen for 400 ms with an inter-stimulus interval of 600 ms. As noted in Section 5.3.2, recordings were monocular, two blocks of 225 stimuli were presented to each eye whilst a patch was worn on the other eye. Breaks between blocks were as long as the participant required.

5.5.3 VEP data analysis

To examine the visual MMN, for each participant, ERPs were averaged separately for standard, deviant and illusory deviant stimuli to construct grand average waveforms for each of the stimuli for the left eye and for the right eye. See Figure 5.4 (A) where standard, deviant and illusory deviant waveforms are presented at occipital electrodes for the ipsilateral hemisphere (left eye - electrode O1, right eye – electrode O2) and (B) over the contralateral hemisphere (left eye – electrode O2, right eye – electrode O1).

To examine the processing of the illusory deviant, the peak latency of the illusory deviant VEP component onset, P1, N1 and P2 was measured as the interval in milliseconds from baseline to stimulus onset to the peak of the individual VEP component being measured while the amplitude was measured in microvolts (μV)

from the peak of one VEP component to the peak of another – onset –P1, P1-N1 and N1-P2. These measures were computed for electrodes P3, P4, O1, O2, T5, T6 Peak-to-peak amplitudes were calculated relative to the mean voltage of a 50 ms pre stimulus baseline The peak latencies and peak-to-peak amplitudes were analysed using Analysis of Variance (ANOVA) (see Sections 5.5.3.2 and 5.5.3.2 for statistical analysis of latency and amplitude data).

5.5.4 Results

5.5.4.1 VEP results

Visual mismatch results

A visual response was recorded in all participants consisting of a P1-N1-P2 waveform. For each participant grand average waveforms for the standard, deviant and illusory deviant stimuli were constructed combining bilateral occipital, temporal and parietal electrodes as these areas have been implicated in the generation of visual MMN. Figure 5.5 shows the grand average standard, deviant and illusory deviant ERPs at occipital electrodes by eye (left, right) and hemisphere (ipsilateral, contralateral). The amplitude of the ERP to the deviant stimulus was smaller than the standard irrespective of eye or lateralisation and therefore it is important to note that in this experiment no visual MMN was recorded in relation to the deviant stimulus. Examination of the individual ERP files revealed that *only one* of the six participants showed enhanced N1 amplitude for the deviant compared to the standard stimulus, whilst five participants showed a reduced amplitude. This suggests that the deviant was less well processed than the other stimuli. In view of this finding no further analyses were carried out to explore the generation of the visual MMN.

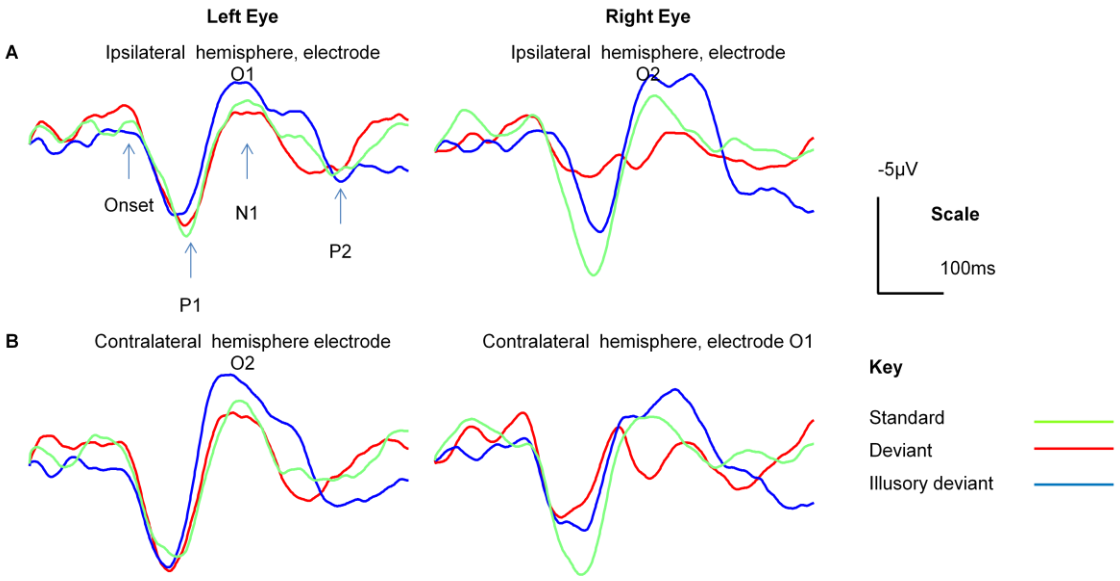

Figure 5.5 Grand average waveforms for standard, deviant and illusory deviant stimuli at occipital electrodes referenced to Fz for the ipsilateral hemisphere (A) and the contralateral hemisphere (B) (Negative upwards).

Illusory contour processing

To explore the lateralisation of the perception of the Kanizsa square, grand average waveforms for illusory deviant were constructed. Figure 5.6 shows the grand average waveforms for the illusory deviant (Kanizsa square) for left and right eye viewing at electrodes O2 and O1. The hemispheric asymmetry can be observed; left eye viewing is faster in the right hemisphere and right eye viewing is faster in the left hemisphere.

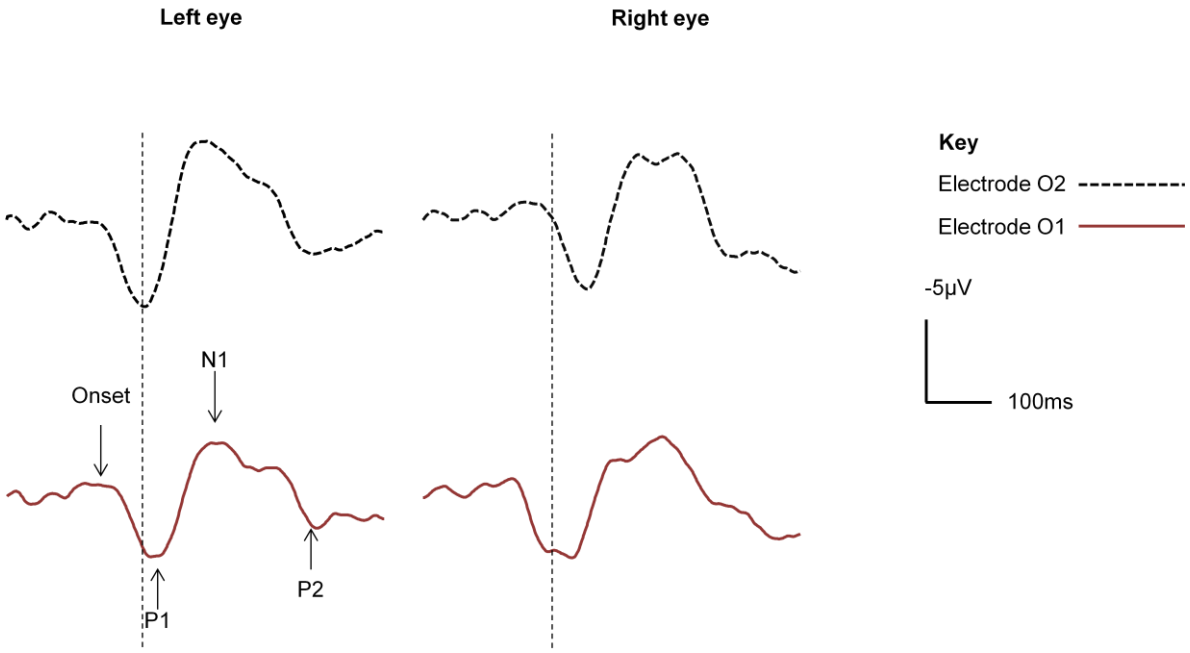

Figure 5.6 Grand average waveforms for the illusory deviant (Kanizsa figure) for left and right eye viewing at electrodes O2 and O1 referenced to Fz, showing the inter-hemispheric asymmetry.

Note that the P1 latency is slowest of all for right eye viewing at electrode O2 (negative upwards).

5.5.4.2 Statistical analysis of illusory deviant latency data

Mean latencies and standard deviations (SD) for the components are shown in table 5.2

Table 5.2 Mean latency (ms) and standard deviation for illusory deviant stimulus type by eye of presentation and electrode site for component onset *(n=6)*

Electrode Site	Component mean latency (ms) and Standard Deviation (±SD) for illusory deviant stimulus							
	Onset		P1		N1		P2	
	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
O1	77.17±18.76	83.83±21.87	138.33±12.71	137.50±31.65	205.00±29.18	211.00±31.50	272.17±61.34	262.50±43.67
O2	67.67±22.13	95.17±36.42	121.67±8.19	151.83±18.43	201.50±25.56	240.17±44.04	261.67±49.11	298.50±78.33
P3	83.00±13.10	84.67±26.35	136.83±12.92	129.67±24.05	201.33±26.42	199.33±37.42	259.17±35.82	267.50±59.00
P4	70.67±20.37	92.17±31.66	120.17±13.41	149.00±18.90	197.83±20.51	222.50±34.88	250.50±35.33	281.00±59.93
T5	75.50±23.67	85.50±18.85	140.17±14.61	147.17±18.50	213.67±33.16	215.50±31.61	287.67±72.44	267.83±46.46
T6	69.33±18.50	93.83±29.36	125.33±5.99	152.67±14.40	205.33±25.84	227.00±25.39	259.00±49.71	267.50±45.92

Given the findings presented in Chapter 3, that the amplitude of the illusory deviant was most prominently seen at occipital, parietal and temporal electrodes, these electrodes were combined. ANOVAs were used to investigate evidence of hemispheric lateralisation, which would translate as a significant interaction.

Onset latency

A two-way (2 x 2) within subjects ANOVA was carried out on onset latency. The first factor was eye (left, right), the second factor was lateralisation (ipsilateral hemisphere, contralateral hemisphere), The main effect of lateralisation was significant ($F(1,5)=7.743$, $p = 0.039$, $\eta p2= 0.608$), indicating that the onset latency, as expected, was faster in the contralateral hemisphere than in the ipsilateral hemisphere and as was shown in Experiment 5.1. The main effect of eye was not significant ($F(1,5)=2.400$, $p = 0.182$, $\eta p2=0.324$). There was no significant interaction between eye and lateralisation ($F(1,5)=0.001$, $p = 0.972$, $\eta p2<0.001$).

P1 Latency

A two-way (eye x lateralisation) ANOVA was carried out on P1 latency. The main effect of lateralisation was significant ($F(1,5)=14.516$, $p = 0.013$, $\eta p2=0.744$) indicating that the P1 latency was faster in the contralateral hemisphere than in the ipsilateral hemisphere. The main effect of eye was not significant ($F(1,5)=4.957$, $p = 0.077$, $\eta p2=0.498$). There was no significant interaction between eye and lateralisation ($F(1,5)=0.117$, $p = 0.747$, $\eta p2=0.023$).

N1 Latency

A two-way (eye x lateralisation) ANOVA was carried out on N1 latency. The main effect of lateralisation was significant ($F(1,5)=8.566$, $p = 0.033$, $\eta p2=0.631$) indicating that the N1 latency was faster in the contralateral hemisphere than in the ipsilateral hemisphere.. The main effect of eye was not significant ($F(1,5)=1.541$, $p = 0.269$, $\eta p2=0.236$). There was no significant interaction between eye and lateralisation ($F(1,5)=2.901$, $p = 0.149$, $\eta p2=0.367$).

P2 Latency

The two way (eye x lateralisation) ANOVA was applied to P2 latency data. The main effect of lateralisation was not significant ($F(1,5)=0.023$, $p = 0.885$, $\eta p2=0.005$). The main effect of eye was not significant ($F(1,5)=0.208$, $p = 0.668$, $\eta p2=0.040$). There was no significant interaction between eye and lateralisation ($F(1,5)=1.500$, $p = 0.275$, $\eta p2=0.231$).

5.5.4.3 Statistical analysis of illusory deviant amplitude data

Mean peak-to-peak amplitudes and standard deviations (SD) for the components are shown in Table 5.3.

Table 5.3 Mean peak-to-peak amplitude (μV) and standard deviation for the illusory deviant stimulus by eye of presentation and electrode site (*n=6*)

	Mean peak-to-peak amplitudes (μV) and Standard Deviations (±SD)					
Electrode Site	**Peak-to-peak**					
	Onset to P1		**P1 to N1**		**N1 to P2**	
	Eye					
	Left	**Right**	**Left**	**Right**	**Left**	**Right**
O1	7.12 ± 2.56	9.34 ± 7.23	11.37± 5.15	14.59 ± 8.21	9.74 ± 4.67	9.05 ± 2.52
O2	8.61 ± 4.28	9.73 ± 2.94	15.29± 9.18	14.37± 4.03	11.61± 8.67	10.83 ± 3.80
P3	4.46 ± 1.43	5.26 ± 2.41	7.73 ± 3.35	8.00 ± 3.56	5.01 ± 1.99	5.01 ± 1.75
P4	4.35 ± 2.07	5.22 ± 1.68	7.27± 3.80	7.06 ± 2.48	5.45 ± 3.36	4.67 ± 0.90
T5	5.92 ± 1.57	7.45 ± 4.42	10.21± 4.55	12.25 ± 5.31	8.08 ± 4.53	8.44 ± 2.51
T6	7.66 ± 2.39	7.68 ± 2.10	12.88 ± 5.74	10.43 ± 2.92	8.53 ± 5.35	7.47 ± 2.08

Onset –P1 mean peak-to-peak amplitude

A two-way 2 x 2 within subjects ANOVA was carried out on onset to P1 mean peak-to-peak amplitude. The first factor was eye (left, light) and the second factor was lateralisation (ipsilateral, contralateral). There was no main effect of eye ($F(1,5)=1.018$, $p = 0.359$, $\eta p2=0.169$) or lateralisation ($F(1,5)=0.194$, $p = 0.678$, $\eta p2=0.037$). The interaction effect was also non-significant ($F(1,5)=0.831$, $p = 0.404$, $\eta p2=0.143$).

P1-N1 mean peak-to-peak amplitude

Two-way within subjects ANOVA was carried out on the P1-N1 mean peak-to-peak amplitude. The main effect of eye was not significant ($F(1,5)=0.042$, $p = 0.845$, $\eta p2=0.008$).The main effect of lateralisation was not significant ($F(1,5)=2.462$, $p = 0.177$, $\eta p2=0.330$). There was no significant interaction between eye and lateralisation ($F(1,5)=0.187$, $p = 0.683$, $\eta p2=0.036$).

N1 – P2 mean peak-to-peak amplitude

The two-way within subjects ANOVA revealed no significant main effect of eye ($F(1,5)=0.117$, $p = 0.746$, $\eta p2=0.023$), no main effect of lateralisation ($F(1,5)=0.473$, $p = 0.522$, $\eta p2=0.086$) and no significant interaction between the factors ($F(1,5)=0.544$, $p = 0.494$, $\eta p2=0.098$).

5.6 Discussion

The preponderance of temporal retinal fibres from each eye crossing to the contralateral hemisphere in albinism can potentially afford the opportunity to investigate each hemisphere in relative isolation and explore whether there is a hemispheric lateralisation in the source of the visual MMN and the perception of illusory contours. However, the critical finding of Experiment 5.2 was that a visual MMN response could not be recorded in this sample group. The deviant stimulus did not elicit an enhanced negative amplitude in comparison to the standard stimulus for five of the six participants. Therefore, no conclusions regarding the lateralisation of the source of the visual MMN could be drawn. In animal models, albino rats have been shown to elicit a somatosensory MMN response analogous to that shown in human somatosensory MMN studies (Astikainen, Ruusuvirta, & Korhonen, 2001). However, to date, there have been no other studies exploring visual, auditory or somatosensory MMN so little is known about the MMN in either humans or animals with albinism.

It is unclear whether the absence of a visual MMN response is due to a characteristic deficit related to albinism or due to the intra-individual and inter-individual differences in participants. The results indicate that processing of the deviant stimulus was less efficient in this sample. Typically, in conjunction with optic pathway misrouting, people with albinism have conditions such as congenital nystagmus (involuntary eye movements), reduced visual acuity and refractive errors, impaired colour vision, photophobia, reduced stereoscopic vision and strabismus (squint). In a study exploring neurodevelopment in children with albinism, Kutzbach, Summers, Holleschau, and MacDonald (2008) reported normal neurodevelopment despite visual impairments. However, compared to age appropriate norms they reported an increased incidence of Attention Deficit Hyperactivity Disorder (ADHD) in the group of 65 children with albinism that they assessed. In the current experiment, beyond the experimenter observing the participants, there was no independent verification that fixation to the screen was maintained. The presence of nystagmus or other unaccounted for visual difficulties or perhaps ADHD in this group may have affected the results.

The second hypothesis tested in Experiment 5.2 was that the illusory deviant stimulus, the Kanizsa square, after taking into account the misrouting asymmetry, would show a hemispheric lateralisation characterised by an earlier latency and/or an enhanced amplitude in the right hemisphere. The current results suggest that both hemispheres were equally capable of processing the illusory deviant stimulus. This evidence is in agreement with (Corballis, 2003; Corballis & Fendrich, 1999) who found no hemispheric advantage in the processing of illusory contours and Proverbio and Zani (2002) who found that the perception of illusory figures was associated with activation of bilateral cortices. The current findings may be suggestive of low level global visual processing and, it may be that, as suggested by Corballis, it is only when higher level visual mechanisms related to visual perception of a stimulus is required that visuo-spatial functions are lateralised.

The current results however are in contrast with a number of other studies exploring illusory contour processing. Korshunova (1999) used centrally presented stimuli similar to those employed in Experiment 5.2. The timing of the N1 component in Experiment 5.2 was comparable to that observed by Korshunova occurring at approximately 200-240ms and they observed enhanced amplitudes to the perception of illusory figures in both hemispheres at N180-P230. However, in contrast to Experiment 5.2, their results indicate increased activation of the right hemisphere. In addition, Hirsch et al. (1995) measured cerebral activation using fMRI whilst participants were presented with visual stimuli (pacmen) that were either oriented to form an illusory figure or were misaligned. They found that the perception of illusory figures was associated with activation of right extra-striate areas that were not activated by control stimuli or real contours. However, they found no evidence of increased activity in the prefrontal cortex which they interpreted as a lack of involvement of higher cognitive processes. Support for the role of the right extrastriate cortex in the perception of illusory figures was also reported by Murray et al. (2002). The results of a PET study by Larsson et al. (1999) reported the perception of illusory contours was associated with stronger activation in the right fusiform gyrus, suggesting differential levels of top-down processing between illusory and real contours.

Experiments 5.1 and 5.2 however, confirm the results of other studies such as Pott, Jansonius, and Kooijman (2003), that, in albinism, comparison of ipsilateral and contralateral hemispheric responses to stimuli, when stimulating one eye, show that because of misrouting the ipsilateral response is delayed compared to the contralateral response.

A review of the literature on the electrophysiology of vision for participants with albinism revealed that research has mainly focused on establishing methods for improving diagnosis of albinism rather than investigating perceptual mechanisms. Experiment 5.2 was novel in that it attempted to use albinism as a model to explore hemispheric lateralisation of visual MMN and illusory contour processing. However, the current finding that a visual MMN response could not be recorded in this group would suggest that albinism may not be an appropriate model to investigate lateralised sources of early ERPs. This may be due to a characteristic response in albinism or to the inter-individual differences in participants. Further research would require greater control for the other visual difficulties that accompany optic misrouting in the sample group chosen. In addition, the statistical analysis of the current data showed no hemispheric lateralisation in the perception of the illusory deviant, which suggests that both hemispheres were equally activated. This may be the case, however, in view of the small sample size and the lack of understanding of visual perception in albinism, the current results must be interpreted with caution.

6 Investigation of early visual processing responses in the pattern onset evoked potential and conscious visual perception

6.1 Aim

Development of a simple paradigm to explore visual stimulus perception that does not require patient participation would be useful for patients with significant language or motor deficits or in patients who present with functional visual loss, a condition in which no underlying visual system pathology can be found despite the patient reporting subnormal vision. This study investigated whether perception to an unseen stimulus (a checkerboard) could be recorded using a paradigm involving brief stimulus presentation and masking. The checkerboard stimulus is a standard clinical probe when used emerging from a grey background (see ISCEV standards, Odom et al., 2010) and produces a typical VEP response pattern that is used in the diagnosis of a range of visual pathologies. The current study investigates the use of a brief stimulus presentation and masking paradigm to explore correlates of visual consciousness. In addition, if components analogous to a typical pattern onset VEP could be elicited subliminally, brief stimulus presentation and masking could be used to investigate stimulus discrimination by introducing an oddball paradigm. As such, this experiment is also a precursor to the experiment outlined in Chapter 7 in which a subliminal oddball paradigm was introduced.

6.2 Introduction

The subjective experience of vision is an important focus of scientific investigation, but where and when in the brain incoming visual information becomes conscious is still a matter of debate. Investigation of electrophysiological correlates of visual consciousness would potentially help address these questions. The identification of electrophysiological correlates to visual stimulus perception may have clinical diagnostic applications, especially in patients who are unable or unwilling to comply with behavioural visual tests. The use of ERPs in the study of visual consciousness has yielded a significant contribution to the literature by exploiting the relatively good temporal resolution afforded by this methodology. The ERP allows the non-invasive evaluation of brain function and organisation during cognitive processing. Furthermore, the

presence or absence of ERP components provides an insight into the extent and location of visual pathway dysfunction. Further quantification of ERPs in terms of amplitude and latency provides information regarding the strength of the signals and the speed at which they are processed.

There has been considerable debate in the literature on the anatomical location and the timing of neural correlates of visual consciousness. Some authors have suggested that early and posterior, occipital cortical processing correlates with visual consciousness (Koivisto, Revonsuo, & Lehtonen, 2006; Koivisto, Revonsuo, & Salminen, 2005; Martinez, DiRusso, et al., 2001; Pins & Ffytche, 2003; Tse, Martinez-Conde, Schlegel, & Macknik, 2005; Zeki, 2003, 2008) while others have suggested that later fronto-parietal circuitry correlates with conscious vision (Del Cul, Baillet, & Dehaene, 2007; Lau & Passingham, 2006). It is more than likely that both earlier sensory and later frontal pathways constitute a neural assembly or network related to consciousness. The methodologies to study the integration of these pathways are still under development but include high density EEG, MEG and co-registration with functional imaging techniques. For a review of ERP correlates of visual consciousness and a discussion of theoretical models that underlie their generation, see Railo et al. (2011).

In the investigation of ERP correlates of visual consciousness a number of different experimental paradigms have been used to manipulate and explore conscious versus unconscious visual perception. These include the manipulation of attention (Pins & Ffytche, 2003), and the application of change blindness (Schankin & Wascher, 2007), attentional blink (Shapiro, Arnell, & Raymond, 1997), and masking paradigms (Wilenius-Emet, Revonsuo, & Ojanen, 2004). The general aim of these studies was to compare the ERPs elicited during an unconscious versus a conscious condition (Koivisto et al., 2006). It should be noted that the plethora of diverse stimuli and paradigms probably contributes to the proliferation of neurobiological models of visual consciousness, whether localised and early (Zeki, 2003) or distributed and late (Lau & Passingham, 2006).

In order to render visual stimuli conscious and unconscious, a variety of masking techniques have been used with the majority of studies investigating

ERP correlates of visual awareness using backward masking. For a review of masking techniques, see Ansorge, Francis, Herzog, and Ogmen (2007). Typically, the mask stimulus causes a reduction in the visibility of an object (the test or target), caused by the presentation of a second object (the mask) nearby in space or time. The temporal sequencing of the mask is critical to its effectiveness in interfering with the processing of the test stimulus, with longer test to mask intervals yielding less interference (Enns & Di Lollo, 2000). Koivisto and Revonsuo (2010) used different stimulus onset asynchronies with metacontrast masking, a form of backward masking where the stimulus does not spatially overlap with the target stimulus, to explore visual consciousness and proposed that a negativity (visual awareness negativity, VAN), in posterior temporal and occipital sites at about 200 ms correlates with visual awareness. Wilenius-Emet et al. (2004) used a backward and forward masking paradigm to vary the subjective perception of line drawings of familiar objects and meaningless non-objects and found that visual consciousness correlated with VAN. In contrast, a metacontrast masking study that manipulates the masking of a grey disk (Mathewson, Gratton, Fabiani, Beck, & Ro, 2009) found that consciousness correlated with the enhancement of a P1, equivalent to the onset/offset VEP CII component, (Di Russo et al., 2002), This is a positivity observed across occipital sites at about 100ms, with visual awareness.

6.2.1 The significance of the checkerboard stimulus in probing the visual system

The pattern onset/offset VEP is used clinically for detection or confirmation of malingering and for evaluation of patients with nystagmus. By presenting participants with a checkerboard stimulus that is exchanged abruptly with a diffuse grey background of the same mean luminance as the checkerboard a standard VEP response can be recorded in a normal population. The standard VEPs to pattern onset consist of three main peaks in adults: CI (positive, approximately 75ms), C2 (negative approximately 125ms) and C3 (positive approximately 125ms) (Odom et al., 2010) (see Figure 6.1).

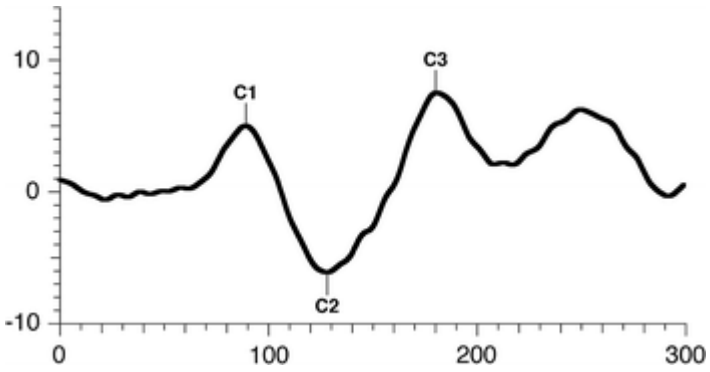

Figure 6.1 Typical pattern onset response (positive upwards)

Reproduced with permission from Odom et al. (2010).

In Experiment 6.1 a simple forward and backward pattern-masking paradigm will be used, where the targets and mask overlap in space to vary conscious perception of a checkerboard stimulus and measure the effect on the pattern onset VEPs. The stability of these pattern onset responses will be further tested in a control study, Experiment 6.2, without masking. By using the same checkerboard stimuli in all conditions, any differences in the visual evoked potentials between the conscious and unconscious conditions will be attributed to visual consciousness.

Rationale and predictions

Clinically, a black and white checkerboard stimulus when emerging from a grey background is known to produce a particular visual ERP response the pattern onset/offset response. By using a briefly presented checkerboard stimulus in a masking paradigm and varying the participant's perception of that stimulus, the resulting ERPs can be compared to those elicited in a typical pattern onset paradigm to explore the effects of the mask on the ERPs to the probe stimulus - the checkerboard. If, the pattern of responses is similar in both instances, this would suggest that briefly presenting stimuli in combination with masking can be used to assess later visual system components. In addition, components elicited in the masked condition can be compared to those elicited in a standard pattern onset/offset paradigm to examine whether any components can be elicited subliminally.

6.3 Methods for Experiments 6.1 and 6.2

6.3.1 Participants

With ethical approval and informed consent, 16 healthy adults (mean age 33.4 years ± 6.1 (13 females) were recruited for experiment 6.1 and 7 healthy adults (mean age 31.5 years ± 6.3 (5 females) for Experiment 6.2. Participants reported no history of neurological disease and had normal or corrected-to-normal visual acuity.

6.3.2 Stimuli and procedure

6.3.2.1 Experiment 6.1

Participants were seated in a comfortable chair one metre away from a stimulus presentation screen. Stimuli were presented in a 14 degree field and the masking stimuli were presented for 500 ms. High contrast checkerboard stimuli of 7, 14 and 21 ms durations were embedded between masking stimuli consisting of complex images whose colours inverted (Figure 6.1). The target checkerboard stimulus had individual check elements that subtended 50 minutes of arc. The checkerboard stimuli were presented in separate blocks for each stimulus duration starting with the shortest. There was a 1-minute break between blocks with each block consisting of three sub-blocks (80 stimuli with 30 second break between sub-blocks). At the end of each block the participants were asked to describe the stimuli they perceived. All stimuli were computer generated (NVIDIA 8800GTS graphics card), presented on a CRT monitor (Samsung Sync Master) running with a screen refresh rate of 160Hz. The stimulus presentation software (E-Prime V2.0, Psychology Software Tools, Inc.) provided markers to be used during averaging of the EEG to produce evoked potential waveforms. Two triggers were allocated, the first at the offset of the checkerboard stimulus (onset of following masking stimulus) and the other at the onset of an identical masking reversal stimulus not preceded by a checkerboard stimulus. The triggers were allocated at these points as the comparison of interest was delineated by subtracting the ERPs elicited to the mask not preceded by a checkerboard from the ERPs to the mask preceded by the checkerboard. The waveforms derived from the masked stimuli will be called the pattern appearance/disappearance VEP. Any differences recorded between the two masks will be attributed to the presence of the checkerboard.

The checkerboard pattern stimuli were separated by four reversing masking stimuli (Figure 6.2).

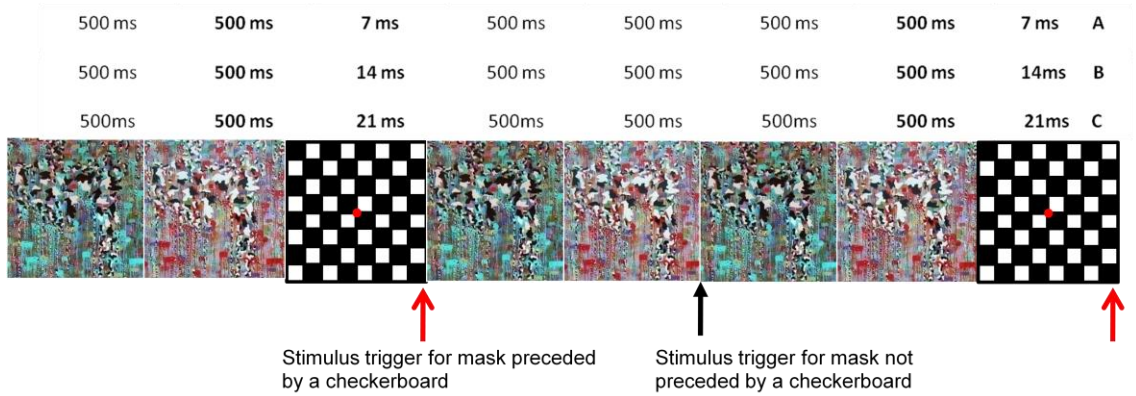

Figure 6.2 Schematic representation of single simulation cycle in the experimental protocol

A, B and C show checkerboard duration of 7, 14 and 21 ms respectively and duration of the mask duration. Red arrows denote onset of mask preceded by a checkerboard stimulus at either 7, 14 or 21 ms. Black arrow denotes onset of mask when there is no preceding checkerboard stimulus

6.3.2.2 Experiment 6.2

The same checkerboard stimuli and procedure as in Experiment 6.1 were utilised with the exception that the complex masking images were replaced by a grey background of equal overall luminance to the checkerboard stimuli (Figure 6.3).

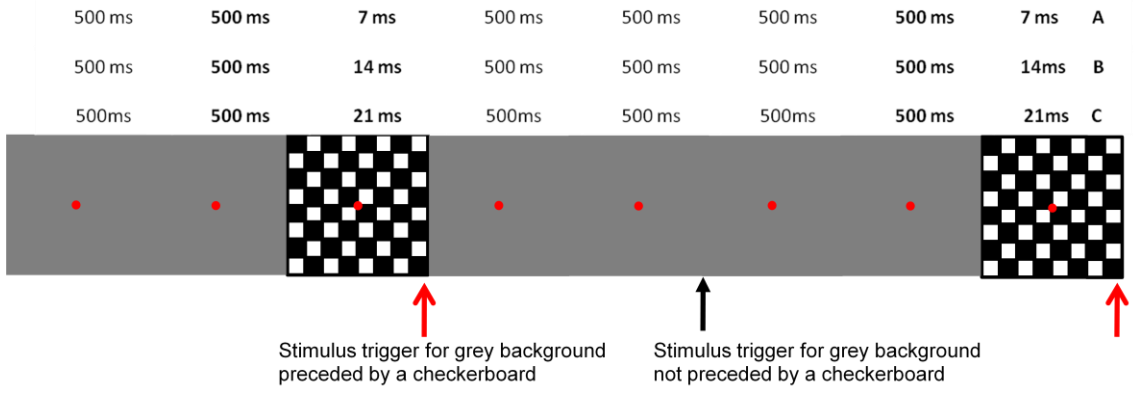

Figure 6.3 Schematic representation of single stimulation cycle in the control protocol

A, B and C show checkerboard duration of 7, 14 and 21 ms respectively and duration of the grey stimulus. Red arrows denote offset of checkerboard stimuli at either 7, 14 or 21 ms preceding grey stimuli. Black arrow denotes onset of grey background in the absence of preceding checkerboard stimulus

6.3.3 EEG recording and data analysis

The EEG activity was recorded from Oz referenced to Fz with the ground electrode at Cz. A limited electrode montage was used in this instance as the checkerboard stimulus is used as a clinical tool and is known to have a response over occipital electrodes. Clinical standards suggest that the active electrode is placed on the scalp over the visual cortex at Oz with the reference electrode at Fz (Odom et al., 2010). Continuous EEG was collected using Neuroscan-SCAN version 4.3 at a sampling rate of 1000 Hz, with a low pass of 100Hz and a high pass of 0.05Hz and stored on a computer for offline analysis. Continuous EEG data was epoched offline -100 ms pre-stimulus to +500 ms post-stimulus. The epochs were digitally filtered with a band pass 1-30Hz and baseline corrected employing the average of -100 to zero ms as zero. Epochs containing transients greater than ± 100μV were excluded from further analysis. For each participant, pattern reversal VEPs were averaged separately for masking stimuli that were and were not preceded by a checkerboard stimulus during the 7, 14 and 21 ms conditions.

Two types of ERP responses were evoked in Experiment 6.1, a pattern reversal response to the masking stimuli and a pattern onset response was elicited to the checkerboard stimulus – the pattern onset VEP in Experiment 6.1 was derived by subtracting the pattern reversal VEPs preceded by a checkerboard from the pattern reversal VEPs not preceded by a checkerboard stimulus and is referred to in the remainder of this chapter as the pattern appearance/disappearance VEP. The pattern reversal VEP is not of direct relevance to the current thesis and analysis of this waveform will not be included here but will be the subject of a separate paper. In Experiment 6.2 a typical pattern onset paradigm was used. The pattern appearance/ disappearance VEPs evoked by the checkerboard pattern onset stimuli were extracted by means of subtracting the grey stimulus VEP preceded by a checkerboard pattern from the grey VEP not preceded by a checkerboard stimulus. The latency and peak-to-peak amplitude pattern appearance/disappearance VEP components were then measured and tabulated (Tables 6.1 and 6.2).

6.3.4 Statistical analyses

A detailed analysis of stimulus duration on the separate VEP components was carried out in each of the experiments and these results are presented in Appendix IV as they are not primary to the thesis. These analyses are presented in an appendix, rather than within the main body of the thesis, as the primary focus of the experiments was to investigate the use of brief stimulus presentation and masking rather than stimulus duration per se. As such, whilst it was important to document changes to the pattern reversal VEPs, the analysis of interest was of the extracted (by subtraction waveforms) checkerboard appearance-disappearance VEPs in each of the stimulus duration conditions.

For the purposes of this thesis, to explore the effects of masking on checkerboard onset waveforms the components evoked from checkerboard onset in Experiments 6.1 and 6.2 were compared in a series of 2x3 repeated measures ANOVAs. Factors were mask or no mask (checkerboard emerging from a grey background of the same overall mean luminance) and duration (7ms, 14ms, 21ms) were analysed for each component latency and peak-to-peak amplitude (CI, CII, CIII, CIV; baseline to CI, CI-CII, CII-CIII, CIII-CIV).

6.4 Results

6.4.1 Experiment 6.1

All participants were unable to report the appearance of the checkerboard stimulus at 7 ms presentation but were able to identify it at 21 ms duration. At 14 ms duration all participants reported a visual event interspersed between the reversing masking stimuli but only 4 of the 16 participants reported being able to identify this event as the appearance of a checkerboard pattern.

6.4.1.1 Subtraction waveforms – pattern appearance/disappearance VEPs subtracted from a mask stimulus

Subtraction waveforms were constructed to reveal the pattern appearance/disappearance VEP components to the checkerboard stimuli for the 7 ms, 14 ms and 21 ms conditions (Figure 6.4a and see Tables 6.1 and 6.2 for component latencies and peak-to-peak amplitudes). The pattern reversal VEPs preceded by a checkerboard were subtracted from the pattern reversal

VEPs not preceded by a checkerboard stimulus. The subtraction waveforms employing the pattern appearance nomenclature revealed a distinct CI component in each stimulus duration condition. However, the CII, CIII and CIV components were more visible in the 14 and 21 stimulus onset conditions.

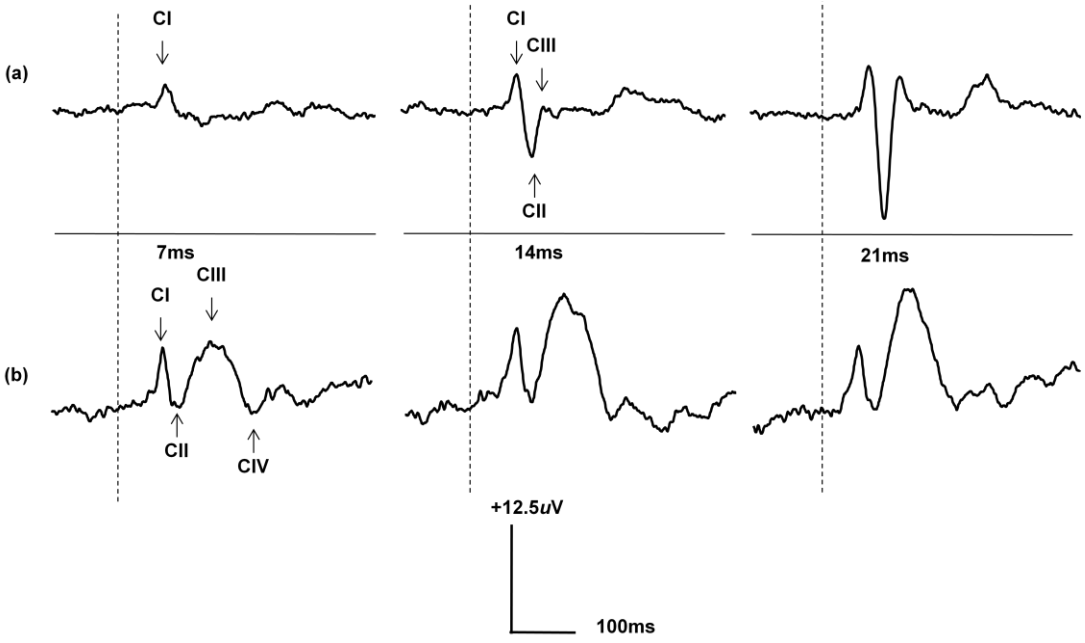

Figure 6.4 Subtraction and ERP waveforms when the pattern appearance/ disappearance VEP was subtracted from a masked background or emerged from a grey background

a) Subtraction of waveforms shown in (a) revealing components to onset of preceding checkerboard stimuli. Note the single positive component following 7ms checkerboard stimulation corresponding to a subthreshold CI component b) Control recording. Average ERP waveforms (n=7) to onset of checkerboard stimulus delivered at either 7, 14 or 21 ms preceding a uniform grey background of 1 second duration. Note consistency of early positive peak at approximately 85 ms corresponding to CI component shown in (b).

Table 6.1 Mean latency (ms) and standard deviation (SD) of pattern appearance/disappearance VEP responses subtracted from the masking reversal stimuli

	CI	CII	CIII	CIV
Pattern onset from mask -7ms	89.9±6.6	115.0±28.7	151.0±40.6	191.3±59.
Pattern onset from mask-14ms	82.7±5.5	119.9±7.4	170.4±12.7	230.0±19.3
Pattern onset from mask-21ms	70.3±7.8	114.2±7.9	165.8±16.1	235.2±26.0

Table 6.2 Mean peak-to-peak amplitude (μV) of pattern onset responses subtracted from the masking reversal stimuli

	baseline-CI	CI-CII	CII-CIII	CIV
Pattern onset from mask -7ms	5.9±2.4	10.5±4.5	7.7±3.2	3.7±2.2
Pattern onset from mask-14ms	6.8±2.8	15.8±4.5	13.6±4.8	5.9±2.9
Pattern onset from mask-21ms	7.2±2.7	17.1±5.5	17.2±5.4	8.6±4.1

6.4.2 Experiment 6.2

All participants were able to identify the checkerboard stimulus presented at 7, 14, and 21 ms appearing from a uniform grey background. In all participants, pattern onset VEPs for the 7, 14 and 21 ms checkerboard durations revealed well-defined CI, CII and CIII components (Figure 6.4b and see Tables 6.3 and 6.4 for component latencies and peak-to-peak amplitudes).

Table 6.3 Mean latency (ms) and standard deviation (SD) of pattern onset VEPs to checkerboard appearing from a grey background

	CI	CII	CIII	CIV
Pattern onset from grey -7ms	70.2±11.5	105.6±10.0	162.6±30.1	254.7±32.3
Pattern onset from grey-14ms	68.6±4.8	100.0±7.7	156.1±21.8	251.1±27.0
Pattern onset from grey-21ms	56.7±7.7	89.7±6.0	163.6±39.4	241.4±15.6

Table 6.4 Mean peak-to-peak amplitude (μV) and standard deviation (SD) of pattern onset VEPs to checkerboard appearing from a grey background

	baseline-CI	CI-CII	CII-CIII	CIII-CIV
Pattern onset from grey -7ms	5.9±4.0	9.0±2.1	12.5±8.7	15.0±5.4
Pattern onset from grey-14ms	6.1±4.3	9.1±2.3	14.7±9.6	15.7±7.2
Pattern onset from grey-21ms	5.2±4.8	8.8±3.7	14.4±10.0	17.0±7.7

6.4.2.1 Comparison of pattern appearance / disappearance responses between Experiment 6.1 and 6.2 (masked versus unmasked conditions)

Masking the checkerboard stimulus increased the latency of CI and CII and decreased the latency of the CIV. CIII latency was not significantly different whether emerging from the mask or the grey background. Longer checkerboard duration led to decreases in component latency for CI and CII but latency for CIII and CIV was not significantly different in the 7, 14 or 21 ms condition.

Baseline to CI amplitude was not significantly different whether the checkerboard was masked or unmasked or between different between checkerboard durations. Emerging from the grey background CI-CII amplitude was similar for all checkerboard durations. The amplitude of CI-CII was reduced when emerging from the grey background in comparison to emerging from the mask. Emerging from the mask CI-CII amplitude increased with increased checkerboard duration. At 21 ms presentation the amplitude of the CII-CIII component increased when the stimulus was masked, but decreased with masking in comparison to emerging from a grey background at 7 and 14 ms. CIII-CIV amplitude was reduced when the checkerboard was masked, and was smaller for shorter checkerboard durations. The results of the ANOVAs are reported below.

CI latency

The main effect of mask was significant ($F(1,6) = 20.834$, $p = 0.004$, $\eta p2 = 0.776$), masking the stimulus increased the latency of the CI. The main effect of duration was significant ($F(2,12) = 29{,}490$, $p < 0.001$, $\eta p2 = 0.831$), increasing the duration of the checkerboard reduced the latency of CI. There was no significant interaction between masking and duration ($F(2,12) = 1.161$, $p = 0.346$, $\eta p2 = 0.162$).

CII latency

The main effect of mask was significant ($F(1,6) = 43.014$, $p = 0.001$, $\eta p2 = 0.878$), masking the stimulus increased the latency of the CII. The main effect of duration was significant ($F(2,12) = 26.047$, $p < 0.001$, $\eta p2 = 0.813$), increasing the duration of the checkerboard reduced the latency of CII. There was no significant interaction between masking and duration ($F(2,12) = 2.572$, $p = 0.118$, $\eta p2 = 0.300$).

CIII latency

The main effect of mask was not significant ($F(1,6) = 1.259$, $p = 0.305$, $\eta p2 = 0.173$). The main effect of duration was not significant ($F(2,12) = 0.612$, $p = 0.558$, $\eta p2 = 0.093$). There was no significant interaction between masking and duration ($F(2,12) = 0.865$, $p = 0.446$, $\eta p2 = 0.126$).

CIV latency

The main effect of mask was significant ($F(1,6) = 8.229$, $p = 0.028$, $\eta p2 = 0.578$), masking the stimulus reduced the latency of the CIV. The main effect of duration was not significant ($F(2,12) = 0.342$, $p = 0.717$, $\eta p2 = 0.0.54$) (see figure 6.6). There was no significant interaction between masking and duration ($F(2,12) = 1.899$, $p = 0.192$, $\eta p2 = 0.240$).

Baseline to CI amplitude

The main effect of mask was not significant ($F(1,6) = 0.368$, $p = 0.556$, $\eta p2 = 0.058$). The main effect of duration was not significant ($F(2,12) = 0.130$, $p = 0.879$, $\eta p2 = 0.021$) There was no significant interaction between masking and duration ($F(2,12) = 0.445$, $p = 0.651$, $\eta p2 = 0.069$).

CI to CII amplitude

The main effect of mask was significant (F(1,6) = 10.444, p = 0.018, ηp2 = 0.635 as was the main effect of duration (F(2,12) =3.743, p = 0.055, ηp2 = 0.384), There was a significant interaction between masking and duration (F(1.150,6.901) = 5.895, p = 0.043, ηp2 = 0.496). Emerging from the grey background the amplitude was similar for all checkerboard durations. However, when emerging from the mask CI-CII amplitude increased with increased checkerboard duration (see Figure 6.5).

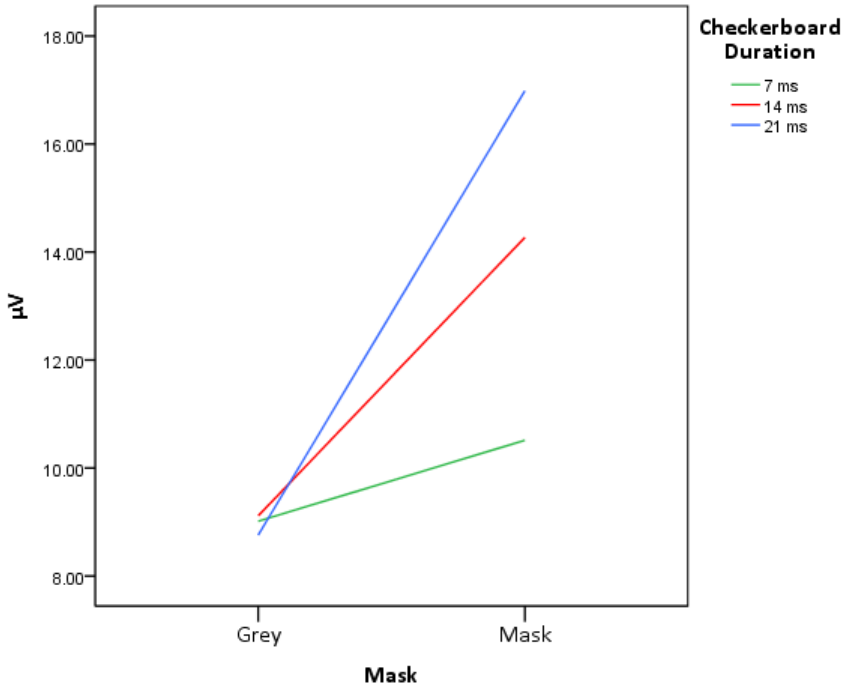

Figure 6.5 Mean peak-to-peak amplitudes (µV) of CI to CII at stimulus durations of 7, 14 and 21 ms when the pattern appearance/disappearance VEP emerged either from a grey background or was subtracted from a masked background

Simple effects revealed that at 7 ms checkerboard duration, CI-CII amplitude was not significantly different whether emerging from the mask or the grey background (*t* =-.820; df=6; p=0.444). At 14ms and 21 ms checkerboard duration, CI-CII amplitude was significantly larger emerging from the mask (t =-2.481; df=6; p=0.048) and (*t* =-4.561; df=6; p=0.004) respectively. In addition, CI-CII amplitude for the masked stimulus had a significantly larger amplitude when the checkerboard was presented for 14ms than for 7 ms (*t* =-3.377; df=6; p=0.015). However, there was no significant difference in CI-CII amplitude for

the ERP emerging from the mask whether it was presented for 14ms or 21ms (*t* =-1.034; df=6; p=0.341).

CII to CIII amplitude

The main effect of mask was not significant (F(1,6) = 0.195, p = 0. 674, ηp2 = 0.031). The main effect of duration was significant (F(1.183,7.099) = 13.678, p = 0.006, ηp2 = 0.696). There was a significant interaction between masking and duration (F(2,12) = 18.647, p < 0.001, ηp2 = 0.757). At 21 ms presentation the amplitude of the CII-CIII component increased when the stimulus was masked, but decreased with masking in comparison to emerging from a grey background at at 7 and 14 ms (see Figure 6.6)

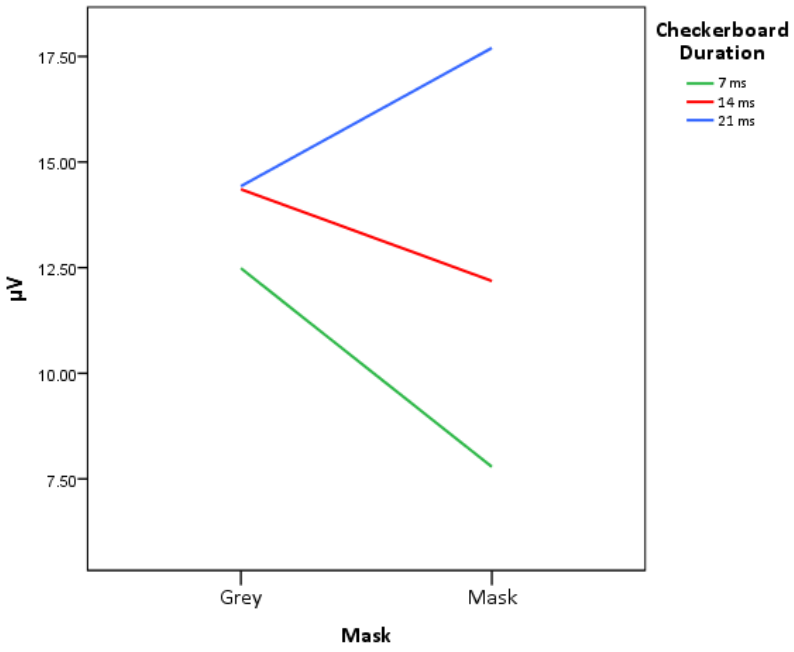

Figure 6.6 Mean peak-to-peak amplitudes (µV) of CII to CIII at stimulus durations of 7, 14 and 21 ms when the pattern appearance/disappearance VEP emerged either from a grey background or was subtracted from a masked background.

Simple effects revealed that at 7ms, 14 and 21 ms checkerboard duration, CII-CIII amplitude was not significantly different whether emerging from the mask or the grey background (*t* =1.889; df=6; p=0.108), (*t* =0.842; df=6; p=0.432) and (*t* =-0.981; df=6; p=0.364) respectively. The amplitude of the CI-CII emerging from the grey mask was not significantly different between the 7 and 14 ms checkerboard duration (*t* =-2.275; df=6; p=0.063) or between the 14 and 21ms checkerboard duration (*t* =-0.073; df=6; p=0.945). When emerging from the mask, the amplitude of the CI-CII was significantly larger as checkerboard

duration increased. When the checkerboard was presented for 21ms the amplitude was significantly larger than when presented for 14ms(*t* =-3.719; df=6; p=0.010) and when presented for 14ms was significantly larger than when presented for 7 ms (*t* =-5,393; df=6; p=0.002).

CIII to CIV amplitude

The main effect of mask was significant (F(1,6) = 29.649, p = 0. 002, ηp2 = 0.832). The main effect of duration was significant (F(2,12) = 11.023, p = 0.002, ηp2 = 0.648). There was no significant interaction between masking and duration (F(2,12) = 1.318, p = 0.304, ηp2 = 0.180). CIII-CIV amplitude was reduced when masked, and was smaller for shorter checkerboard durations.

6.5 Discussion

The results of the current experiments suggest that briefly presented stimulus presentation combined with masking is a useful method for exploring stimulus detection. The current experiments revealed that a correlate of very early visual processing can be observed for very briefly masked stimuli. This seems to be independent of awareness in that participants do not report seeing this at 7 ms stimulus duration. The experiments reported in this chapter indicate that component CI (60-80 ms) a correlate of very early cortical visual processing can be recorded to a checkerboard stimulus and can be observed for very briefly presented masked stimuli consciously seen or unseen. Differences in visual processing are only evident at as early as 90 ms (CII), implying that this component may represent a correlate of visual consciousness/awareness.

Earlier studies exploring the generator sources of pattern VEP components (Jeffreys & Axford, 1972a, 1972b) found that for the left and right half-field responses, the transverse distribution of CI but not CII showed lateral polarity reversal across the occipital midline. They concluded that CI and CII have separate spatial generator sources. The longitudinal distribution of CII appeared to conform with a simple dipole model related to the retinotopic representation at the extrastriate cortex (areas 20 and 21). Since then a number of studies have identified the neural generators of CI to Brodmann's area 17 of the primary visual cortex and CII and CIII to extrastriate cortex of the middle occipital gyrus and ventral extrastriate cortex of the fusiform gyrus respectively (Di Russo et al., 2002). Taken together with the current results this would place an anatomical site for visual consciousness/awareness at area 18/19.

Further support for CI as a marker of unconscious visual processing is that it appears not to be modified by manipulations of selective attention and that the earliest event related potential (ERP) components enhanced by attention occurred in the time range 70-130 ms post-stimulus onset (Martinez, DiRusso, et al., 2001). The neural generators of these components were estimated to lie in the dorsal and ventral extrastriate visual cortex. Psychophysical evidence for lack of conscious awareness of V1 activity has also been reported by Crick and Koch (1995). However, the current results are in contrast to those reported by Proverbio et al. (2010) who reported modifications of CI for manipulations of

selective attention for spatial frequency stimuli, suggesting generators in the striate cortex.

Pins and Ffytche (2003) found a difference between early VEP responses (P100) for stimuli which were consciously seen versus those which were not. Using fMRI they also showed differential responses in V1 and the lateral and the middle occipital cortex areas between seen and unseen stimuli. Koivisto et al. (2006) reported that an 'early' posterior negative wave at 130-350 ms following stimulus was the earliest correlate of conscious awareness, in an experiment which distinguished visual awareness from the scope of attention.

Zeki (2003, 2008) presented fMRI data from patients and normal participants to show that conscious perception of movement corresponded to increased activation of V5 and no other areas and proposed that visual perception as well as visual processing occurred in the extrastriate cortex. Tse et al. (2005) also used a mixture of monoptic and dichoptic masking and found fMRI changes corresponding to consciousness of simple visual stimuli starting at V2 but not extending outside occipital cortex.

Other authors have reported seemingly contradictory results indicating a later and more anterior correlate with visual consciousness. Del Cul et al. (2007) used high density ERP recordings with masking of varying stimulus onset asynchrony and found that the changes that correlated with conscious perception occurred after 270 ms and postulated a widely distributed fronto-temporal-parietal circuit as a correlate of conscious reporting. Lau and Passingham (2006) used variable metacontrast masking to influence perception separately from performance in conjunction with fMRI and found correlation between the left dorso-lateral prefontal cortex (Brodmann's area 46) and conscious vision.

Stimulus factors found to affect CII and CIII differentially from CI include resting contrast level where CII and CIII attenuate more rapidly than CI as resting contrast increased from zero (Jeffreys, 1977); defocusing of the stimulus pattern, to which CI is more resistant than CII and CIII (Jeffreys, 1977); pattern pre-exposure again attenuating CII and CIII but not CI (James & Jeffreys, 1975; Jeffreys, 1977); increased spatial frequency attenuating CI amplitude but

increasing CII amplitude (Hudnell, Boyes, & Otto, 1990); and stationary pattern adaptation which selectively attenuated CII but not CI (Hudnell et al., 1990).

Finally, it is worth considering that there is some confusion in the literature as to the nomenclature of these early onset components. Early work demonstrated differing polarities of the early CI component and a positive CII component (Jeffreys & Axford, 1972a, 1972b). In the Di Russo et al. (2005) study, pattern onset components are described as C1, P1, N1 (corresponding to our CI, CII and CIII respectively) and in an earlier paper they refer to Jeffreys and Axford's CII as a P1 (Di Russo et al., 2002) whilst the International Standard for Clinical Evoked Potentials refer to the CII as a negative component around 125ms (Odom et al., 2010). One explanation for the discrepancy in the labelling of components may arise from uncontrolled changes in visual field stimulation. In the current experiments visual fixation was not monitored beyond participant observation following the instructions given at the start of the recordings. However, the labelling of the CI-CIII components in terms of amplitude and latency is consistent with the more recent ISCEV standard. The CIV component is not mentioned in the ISCEV standard and may reflect its variability across studies and paradigms. In fact, the latency and amplitude distribution of the CIV may suggest it is related to the P200 component typically recorded in ERP studies to stimulus identification and discrimination.

In conclusion, these findings suggest a correlation between the early components of the pattern appearance/disappearance visual evoked potential and conscious perception. The CI component may determine if the visual system has detected the short duration stimulus while the CII and CIII responses may give an indication of whether this stimulus had been processed any further and possibly perceived. Alternatively, these early C components may activate later more anterior systems known to be involved with perception and awareness. Having validated the use of forward/backward masking paradigm with the checkerboard onset stimulus the following experiment will explore whether this masking paradigm can be used to investigate unconscious stimulus discrimination processing.

There are potentially some important practical applications for these findings such as investigation of challenging cases of non-organic (functional) visual loss or malingering. Such patients have been shown to be able to suppress voluntarily pattern reversal VEP responses (Manresa, Bonaventura, Martinez, Gomez, & Aguilar, 1996) and to a lesser extent pattern appearance VEPs (typically presented in the region of 200ms). Short duration checkerboard stimuli not perceived by the participant could potentially be embedded in a cartoon video. It has previously been demonstrated that well defined responses can be recorded checkerboard stimuli of 66 ms durations within a video stream (Flynn, Thompson, & Liasis, 2006).

7 Visual mismatch negativity to masked stimuli presented at very brief presentation rates

7.1 Aim

The aim of the current experiment was to establish whether visual evoked potentials reflecting discrimination processes – the visual MMN – could be recorded to very briefly presented masked visual stimuli. The stimuli were presented both below and above levels of subjective perception using an oddball paradigm in which the standard and deviant stimuli differed from each other in terms of orientation.

7.2 Introduction

Whether the visual MMN elicitation is dependent on attention is a controversial issue in MMN research. Although it has been proposed that generation of the visual MMN is an automatic process independent of attention, this has proved difficult to establish empirically. In the auditory domain the MMN can be recorded even during sleep, suggesting it is an automatic detection of stimulus change and that it does not require conscious attention (Nielsenbohlman, Knight, Woods, & Woodward, 1991). As outlined in Section 1.9, the MMN is best recorded in the absence of focused attention. However, within the visual system it is difficult to design a methodologically adequate 'ignore' condition due to vision's primacy in directing continuous behaviour (Czigler, 2007; Kimura, 2012). This is an issue that has made it difficult to establish whether the visual MMN's that have been reported in many studies are in fact 'true' visual MMNs as it has been difficult to assess whether attention has been paid to the stimuli irrelevant to the behavioural task.

The experiments outlined in Chapter 3 of this thesis employed an illusory square as a distractor in order to take attention away from the standard-deviant transition (Experiment 3.1). However, it was shown in a control experiment (Experiment 3.2) that the illusory figure could not attract fully the attentional resources away from the standard-deviant transition. There are a number of ways in which attention can be taken from a visual stimulus, and these include:

focusing the participant's attention on a second task, presenting stimuli that are irrelevant to the task in the peripheral visual field while participants focus their attention on the centre of the visual field and presenting stimuli at very brief presentation rates. An extension of the latter approach is to present stimuli at very brief exposure times in combination with a mask so that the stimuli can no longer be reported as seen. For the purposes of this thesis such stimuli are said to be subliminal or subliminally presented.

General agreement suggests that stimuli that are not accessible to conscious awareness can still be analysed. The question of whether a visual MMN can be elicited by deviant stimuli even when they cannot consciously be reported may provide insight into the dependence of the MMN on attention. Studies such as Hsieh and Colas (2012) have shown that stimuli that are not consciously detected can still be analysed and influence perceptual and cognitive function, for a review of similar evidence, see Lin and He (2009). Much of the current debate has moved from whether subliminal stimuli can be perceived to identifying the nature of the processing that can be achieved without awareness. Whether stimuli that are not accessible to conscious awareness are processed in a similar way remains an open research question.

7.2.1 Subliminal ERPs to neutral stimuli

A number of studies have used subliminal methods to explore ERP components to neutral stimuli. Much of the work relating to the recording of ERPs to emotionally neutral subliminal stimuli has focused on the P3 component. In a group of thirteen patients with intractable epilepsy, Brázdil et al. (2001) recorded ERPs directly from the cortex to stimuli that were presented below subjective levels of awareness and stimuli that were presented supraliminally (above the threshold of sensation). Two stimuli, a yellow X (target) and a yellow O (standard), were presented on a white background within a visual oddball paradigm. Before the actual experiments the subjective threshold was determined for each participant by altering the level of contrast of the stimuli until the participant was no longer able to distinguish the stimuli from one another. The experiment was carried out in two phases, in the first phase the stimuli were presented for 200ms duration (supraliminal condition) in a standard oddball paradigm and participants had to press a button as quickly as

possible on detection of the target. A P3 response was recorded to the target stimuli. In a second phase of the experiment the supraliminal stimuli were interspersed with stimuli presented for 10 ms duration (subliminal condition). Analysis of the ERPs evoked to the subliminal target stimuli revealed a waveform that corresponded to the P3 evoked to the supraliminal stimuli although it was smaller in amplitude and earlier in latency (peaking at 258 ms in the subliminal condition and 391 ms in the supraliminal condition). Brázdil et al. (2001) interpreted these results as implying that perception of the stimuli and higher level processing could occur even if the participant was unaware of the information, but concluded that the P3 evoked in the subliminal condition reflects conscious discrimination even if the participant was unaware of it.

In another study Bernat, Shevrin, and Snodgrass (2001) used a passive experiment to investigate P3 activity in order to assess whether components of subliminal ERPs have similar functional properties to components of conventional supraliminal ERPs. Prior to the experimental presentation of the stimuli, the participant's objective detection threshold was established. The words LEFT and RIGHT were presented in a counterbalanced oddball design subliminally for 1 ms using a tachistoscope. The findings confirmed that a P3 component was significantly greater for the less frequent (either LEFT or RIGHT) than for the frequent stimulus across Fz, Cz and Pz, suggesting that the oddball P3 could be recorded to subliminal stimuli. These studies demonstrate that ERPs to stimuli presented below levels of subjective and objective detection (Cheesman & Merikle, 1984) can be elicited in the absence of focused attention.

A number of studies have explored the visual MMN to briefly presented masked neutral stimuli. Czigler, Weisz, and Winkler (2007) conducted a series of experiments using a visual oddball paradigm to present green/black and red/black checkerboard stimuli that were counterbalanced between participants to act either as standard or deviant stimuli. The stimuli were followed by a mask consisting of red/green hexagons of a similar size to the checkerboard squares, test and mask stimuli were presented for 14 ms. Stimulus onset asynchronies (SOAs) were varied in the experiments between 14-174 ms and a behavioural task varied in the experiments between detecting changes in the size of

elements of a central fixation cross and detecting the deviant stimulus. The experiments were designed to assess the effects of the length of test to mask SOAs on ERPs and to measure the effects of masking on detection performance. With increases in test to mask SOAs there were increases in behavioural detection of the deviant. At 14 ms behavioural results suggested that the participants had difficulty detecting the difference between standard and deviant stimuli and no visual MMN response was recorded. The ERPs showed an enhanced negative component in response to the deviant stimuli in the visual MMN latency range 124-132 ms to stimuli with a minimum SOA of 40 ms but they reported behavioural stimulus detection performance increased from SOA of 13 ms. The results of the study suggest that stimulus discrimination responses were not elicited in the absence of conscious report.

Kogai, Aoyama, Amano, and Takeda (2011) in a MEG study presented vertical grating stimuli that varied between standard, deviant and mask in terms of spatial frequency, with differences in spatial frequency such that it was difficult to distinguish the standard from the deviant. An oddball sequence, in which masked stimuli were presented for 433 ms interspersed with standard and deviant stimuli presented for 17 ms was carried out. During stimulus presentation, the participant's task was to respond by pressing a button on detection of the deviant. Behavioural results suggested that the participants could not consciously detect the difference between standard and deviant stimuli. Results of the MEG revealed equivalent current dipole sources in the calcarine sulcus and the parieto-occipital sulcus. A response to deviant stimuli that was significantly larger than to standard stimuli was recorded in the latency period 143-153 ms, suggesting an automatic response analogous to an MMN could be recorded to masked visual stimuli for changes to spatial frequency.

7.3 Rationale and aim

The current experiment used a backward and forward masking paradigm to investigate discrimination processes in stimuli that changed in orientation. A number of studies have shown that visual MMN can be elicited to a change in orientation (Astikainen et al., 2008; Flynn et al., 2009). The results of the experiments presented in Chapter 6 showed that using a continuous visual

stream masking paradigm with briefly presented checkerboard stimuli it was possible to record pattern onset responses, CI at 7 ms duration and CII and CIII at 14 ms duration even though the majority of participants were unable to identify the appearance of the checkerboard at 14 ms. The current study introduced an oddball paradigm to establish whether a deviant stimulus could elicit registration of stimulus discrimination that was independent of the ability to report that stimulus. A novel aspect to this experiment is that no behavioural task was required of the participant. Evidence of stimulus discrimination in the absence of awareness would imply that the response to a change in orientation satisfied the criteria of recording a visual MMN in the absence of focused attention. Whereas, evidence that stimulus discrimination was associated with the ability to report the stimulus would imply that the criterion of absence of attention had not been met.

7.4 Methods Experiment 7.1

7.4.1 Participants

With ethical approval and informed consent 17 healthy adults (mean age 21.8 years range 18 to 38 (12 females) were recruited for the experiment. Participants reported no history of neurological disease and had normal or corrected-to-normal visual acuity. Participants were recruited from a student population and received two and a half hours research participation credit. Two participants were excluded from the analysis, one due to technical issues during the recording and one due to excessive artifacts in the data.

7.4.2 Stimuli and procedure

Two stimuli, comprising of black and white checkerboard elements differing from each other only in terms of their orientation to form either a + or an x were presented in a behaviourally silent oddball paradigm where the ratio of standards to deviants was 8:2. The stimuli were embedded between masking stimuli consisting of complex images whose colours inverted (see Section 6.3.2.1). The background of the stimuli consisted of the same complex image. The two stimuli were presented at very brief presentation times, below levels of subjective awareness for 7ms in the first instance and then above levels of subjective awareness at 14ms. The masking stimuli were presented for

between 486 and 500 ms and details of stimuli, stimulus sequence and durations during experiment are illustrated in Figure 7.1 conditions A and B. The test to mask SOA was determined by the computer refresh rate and was 7 ms.

Participants were seated comfortably in a darkened room 1 m away from the computer screen and requested to fixate on a small red dot in the centre of the screen that was present throughout recording. Within the oddball paradigm, stimuli were presented in a pseudo-random sequence ensuring deviant stimuli were interspersed with standard stimuli. Five blocks of the 7 ms duration stimuli were presented. Each block contained 500 stimuli (400 standards, 100 deviants). This was followed by one block of 100 stimuli during which the masked + was presented alone and one block where the masked x was presented alone. The same procedure was then carried out for the 14ms duration stimuli. There was a break of one minute break between blocks.

Following the first block of the 14 ms presentation, participants were asked if they observed anything different from the earlier presentations. If their answer was yes, they were asked to describe what that was. If the answer was no, at the end of all the presentations they were asked to describe what they saw. If they had not reported seeing anything other than the masking stimulus they were shown the + and x stimulus and were asked if they had seen them during the recording and their responses noted.

All stimuli were presented on a CRT monitor (Samsung Sync Master) running with a screen refresh rate of 160Hz. The stimulus presentation software (E-Prime V2) provided markers to be used during averaging of the EEG to produce evoked potential waveforms.

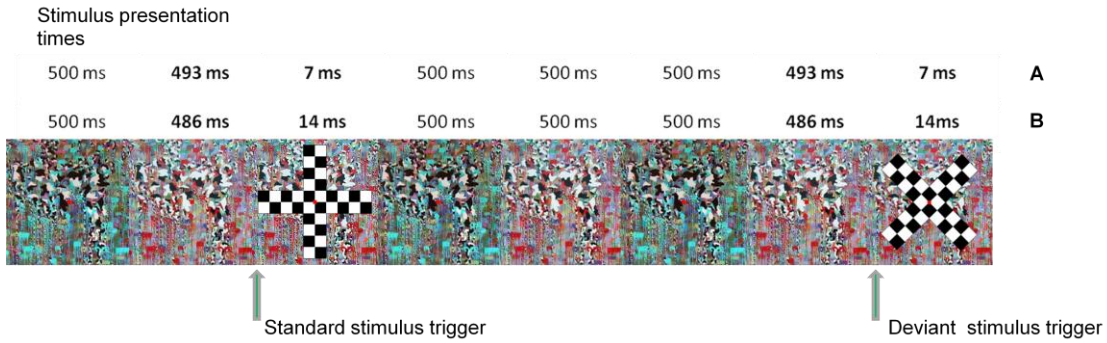

Figure 7.1 Schematic representation of single stimulation cycle presented in the oddball paradigm

A and B show stimulus presentation times for 7 ms and 14 ms respectively

7.4.3 EEG data recording

Eleven silver-silver chloride electrodes were used to record the EEG activity and were positioned at sites in accordance with the International 10-20 system (Fz, Cz, Pz, Oz, O1, O2, VEOG, M1, M2) (see Sections 2.2 and 2.3).

7.4.4 VEP data analysis

Continuous EEG data were epoched offline -100 ms pre-stimulus to +500 ms post-stimulus. The epochs were digitally filtered with a band pass 1-30Hz and baseline corrected. Epochs containing transients greater than ± 100μV were excluded from further analysis. For each participant, ERPs were averaged separately for standard and deviant stimuli, the data re-referenced to Fz and grand average waveforms were constructed.

From the grand average waveforms MMN-like differences were identified on the basis of known negative polarity, known emergence over posterior electrode positions and typical latency range 150 – 400 ms (Kimura, 2012). In both experiments, the maximal difference between ERPs to standards and deviants was identified at 170 ms and 320 ms post stimulus presentation at occipital sites and a 30 ms time window was centred at these latencies for electrodes O1, and O2 (Astikainen et al., 2008). In addition, subtraction waveforms were constructed of deviant minus standard and deviant minus deviant alone (see Section 2.3.7.3). Mean amplitudes for the time windows were calculated relative to the mean voltage of a 100 ms pre stimulus baseline for each participant for

the standard and deviant stimuli. The mean amplitudes were analysed using ANOVA (see Section 7.5.2).

7.5 Results

7.5.1 VEP data analysis

A visual response was recorded in all participants consisting of a P1-N1-P2-N2 waveform for the stimuli presented at 7 ms and 14 ms duration. All participants were unable to report the appearance of the + and x stimulus at 7 ms stimulus duration. At 14 ms 12 of the 15 participants were able to identify this event as the appearance of the + and the x. Grand average waveforms were constructed for the standard and deviant stimuli (see Figure 7.2 A and D) for waveforms at electrodes O1 and O2. Visual inspection of the grand average waveforms reveal an enhanced negativity in the ERP response for the deviant when stimuli were presented for 14 ms, with a maximal difference at approximately 170 ms compared to the standard stimuli. This amplitude difference was not apparent in the 7ms condition. An enhanced amplitude for deviants compared to standards was noted at around 320 ms for both durations - this was larger in the 14 ms condition. A 30 ms time window was centred at each of these latencies for electrodes O1 and O2. For all participants mean amplitudes for these time windows were calculated relative to the mean voltage of a 100 ms pre-stimulus baseline for standards and deviants. Mean amplitudes and standard deviations for the standard and deviant are shown in Table 7. 1.

Difference waveforms of deviant minus standard at 7 ms revealed possible visual discrimination components at approximately 320 ms, this was larger for electrode O1 than electrode O2 (Figure 7.2 B). At 14 ms visual discrimination components were revealed (Figure 7.2 E) peaking at approximately 170ms and at approximately 320 ms. Comparison of the deviant to the standard ERP using the point-by-point *t*- test algorithm ($p<0.05$; one-tailed) against baseline, did not reach significance suggesting that MMN was not elicited when the stimulus duration was either 7 ms or 14 ms.

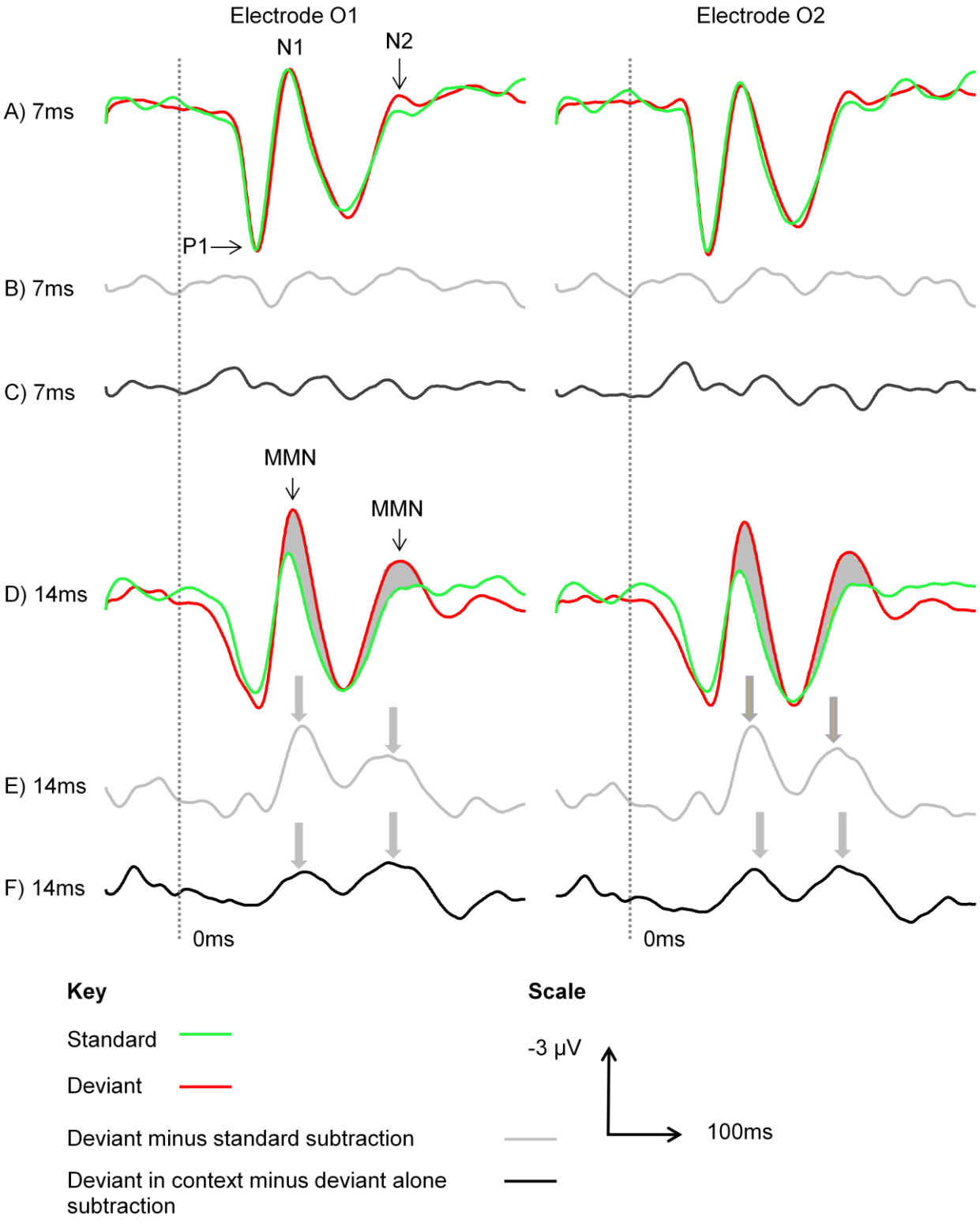

Figure 7.2 Grand average waveforms referenced to Fz (negative upwards) at electrodes O1 and O2

A) and D), standard and deviant waveforms at 7 ms and 14 ms duration respectively, B) and E) deviant minus standard subtraction waveforms at 7 ms and 14 ms duration respectively, C) and F) deviant in context minus deviant alone subtraction waveform at 7 ms and 14 ms duration respectively. Note the discrimination responses highlighted in grey

7.5.2 Statistical analysis of amplitude data

Table 7.1 Mean amplitude (μV) and standard deviation (SD) for each stimulus type at occipital electrode sites for the 155-185 ms and 305-335 time windows for the stimuli presented at 7 ms and 14 ms (*n* = 15)

		Mean amplitude (μV) and Standard Deviation (±SD)			
		Stimulus Type and Stimulus Duration			
Electrode	**Time window**	**Standard 7ms**	**Deviant 7ms**	**Standard 14ms**	**Deviant 14ms**
O1	155-185ms	0.05 ± 2.79	-0.26 ± 2.28	-0.38 ± 2.83	-2.41 ± 2.69
O2	155-185ms	0.41 ± 3.36	0.20 ± 2.82	0.05± 3.45	-2.14 ± 2.63
O1	305-335ms	0.36 ± 1.20	-0.23 ± 1.10	0.04 ± 1.41	-1.20 ± 2.31
O2	305-335ms	0.16 ± 1.16	-0.28 ± 1.04	-0.10 ± 1.78	-1.62 ± 2.39

The mean amplitude data at bilateral occipital electrodes in the 155-185 ms and the 305-335 ms time window was analysed using a pair of ANOVAs. At each time window, a two-way within subjects ANOVA was used to examine the effects of stimulus type (standard, deviant) and stimulus duration (7 ms, 14 ms) on the ERP responses. As the analyses were exploratory Bonferroni corrections were not applied.

7.5.2.1 Time window 155-185ms

The main effect of stimulus type ($F(1,14) = 9.832$; $p = 0.007$), and stimulus duration ($F(1,14) = 9.918$; $p = 0.007$) were both significant. This should be interpreted in light of the statistically significant interaction between stimulus type and stimulus duration ($F(1,14) = 12.899$; $p = 0.016$). This interaction depicted in Figure 7.2 appears to show that the amplitude of the deviant stimulus is more negative at 14 ms than at 7 ms and than the standard stimulus at 7 ms and 14 ms stimulus durations.

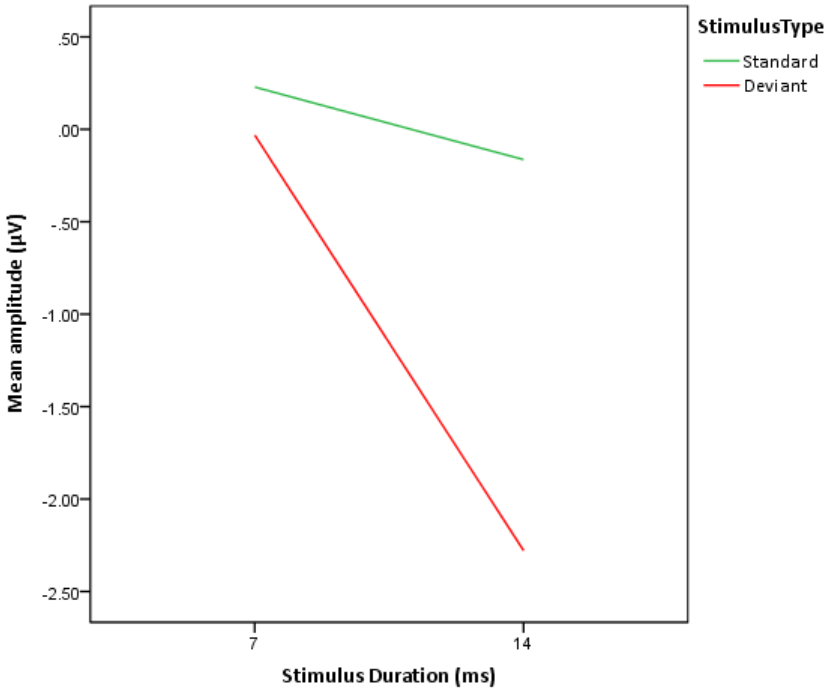

Figure 7.3 Mean amplitude (µV) of component waveforms at bilateral occipital electrodes in the 155-185 ms time window as a function of stimulus type and stimulus duration (ms)

To examine the stimulus type x stimulus duration interaction, simple effects were carried out. At 14 ms duration, there was an increased negative amplitude to the deviant stimulus compared to the standard stimulus (t = -3.262; df = 14; p = 0.006). There was also an increased negative response when the deviant stimulus was presented for 14 ms compared to 7ms duration (t = -4.324; df = 14; p = 0.001). The amplitude of the component did not differ significantly between standard and deviant stimuli at 7 ms duration (t = -0.842; df = 14; p = 0.414) or between standard stimuli at 7 ms and 14 ms duration (t = -0.705; df = 14; p = 0.492).

7.5.2.2 Time window 305-335ms

The main effect of stimulus type was significant (F(1,14) = 14.731; p = 0.002), deviant stimuli had a significantly a greater negative amplitude compared to standard stimuli. The main effect of stimulus duration was significant (F(1,14) = 5.293; p = 0.037), stimuli presented for 14 ms had a significantly greater

negative amplitude than stimuli presented for 7 ms. There was no statistically significant interaction between stimulus type and stimulus duration ($F(1,14) = 2.700$; $p = 0.123$).

To assess any discrimination responses at very brief presentation durations, simple effects were also carried out. These revealed that although the amplitude of the ERP in this time window to the deviant stimulus was significantly greater than the standard at 14 ms duration ($t = -3.397$; $df = 14$; $p = 0.004$), there was no such difference at 7 ms ($t = -1.676$; $df = 14$; $p = 0.116$).

7.6 Discussion

The results of Experiment 7.1 show that for stimuli that were not reportable using the backward and forward masking paradigm employed, i.e. those presented at 7ms, there was little variation in the ERPs evoked to standard and deviant stimuli in the N1 latency period. A small but enhanced negativity to the deviant stimulus was observed at around 320 ms in the grand average waveforms. Although this negativity was smaller, it did correspond in terms of latency with that observed when the stimuli were presented for 14 ms and is in the expected latency period of visual MMN. This negativity did not reach statistical significance however when tested using point-to-point *t*-tests or simple effects. Overall therefore, these results suggest that visual MMN was not elicited when participants could not report seeing the stimuli.

When stimuli were presented at 14 ms duration, twelve of the fifteen participants were able to report the appearance of the standard and the deviant stimuli. The deviant stimulus produced an enhanced negative amplitude in the order of 2.2μV and 1.5μV compared to the standard stimulus at approximately 170 ms and 320 ms respectively. Analysis of the subtraction waveform, deviant minus standard, by point-to-point *t*-tests did not reach significance. However, analysis of grand average waveforms by ANOVA and simple effects revealed that, at bilateral occipital electrodes, the response to the deviant was significantly more negative than the response to the standard in both the early and the late time window. The ERP waveforms and the statistical analysis suggest that discrimination responses, possibly reflecting a visual MMN response, were recorded in the 14 ms stimulus condition.

In contrast to the results reported by Czigler et al. (2007) whose masking study varied test to mask SOAs and found that a visual MMN response did not emerge below SOA of 40 ms, in the current experiments, visual MMN emerged with a test to mask SOA of 7 ms. However, it should be noted that in the current experiment behavioural detection of the deviant stimulus was high when the stimulus was presented for 14 ms, whereas, behavioural detection in the study by Czigler et al. (2007) was low at 14 ms deviant duration. These results suggest that conscious perception of the stimuli was required before visual MMN could emerge.

The results of the current study are also in contrast to those of Kogai et al. (2011) who used an oddball sequence, in which masked grating stimuli were presented for 433 ms interspersed with standard and deviant grating stimuli presented for 17 ms. They reported that despite behavioural results suggesting that the participants could not consciously detect the difference between standard and deviant stimuli, a MEG response to deviant stimuli that was significantly larger than to standard stimuli emerged. They interpreted this as suggesting an automatic response analogous to an MMN could be recorded to masked visual stimuli for changes to spatial frequency. Kogai et al. (2011) result raise the possibility that MEG offers a more sensitive methodology with which to investigate visual MMN is the absence of awareness.

A number of studies have reported recording ERPs to subliminal stimuli. Bernat, Shevrin, et al. (2001) reported a significant parietal P3 to stimuli presented below objective detection threshold levels. Brázdil et al. (2001) reported an ERP to subliminal stimuli that corresponded to the P3 evoked to the supraliminal stimuli. It was however, smaller in amplitude and earlier in latency in the subliminal condition. A study by Bernat, Bunce, and Shevrin (2001) showed that a subliminal P3 ERP could be elicited to emotionally valent words that had a component structure similar to a supraliminal P3, although smaller in amplitude by at least a factor of four. The visual MMN response is smaller in amplitude, often in the region of 1-3μVs, than that of a P3. One explanation for a lack of visual MMN in the 7 ms condition could be that if the amplitude of the response was reduced in the subliminal condition and it may be difficult to demonstrate its

emergence with scalp recorded EEG methods but iEEG or MEG may detect differences.

Recent interpretations of the component structure of the visual MMN suggest an initial negative component occurring between 150-200 ms and a later negative component between 200-400 ms. These components, corresponding to visual N1 and N2 respectively, are apparent in the present experiment. The early visual MMN component, in the N1 latency period, is thought to be due to differential activation of afferent neuronal populations between stimuli thus reflecting their state of habituation. Differences in habituation are thought to be due to differences in stimulus probability and, as such, the amplitude of VEPs evoked to deviant stimuli are larger than those evoked to standard stimuli (Kimura, 2012). Several studies have suggested that the enhanced negativity observed in the deviant minus standard subtraction waveforms, in the N1 latency period, is therefore due to the refractory state of the neurons due to the rareness of the deviant stimuli in comparison to the standard stimulus (Kenemans et al., 2003; Mazza et al., 2005). Although other studies have interpreted this difference in the N1 latency period as a genuine visual MMN response (Czigler & Sulykos, 2010).

The late visual MMN component, in the N2 latency period, is thought to be representative of sensory memory formation or prediction error responses that are generated when a current event is incongruent with events predicted on the basis of sequential regularities (Kimura, 2012; Kimura et al., 2011). Studies incorporating an 'equiprobable paradigm' specifically designed to separate the effects of refractoriness and sensory memory/prediction error responses, elicit enhanced negativities in the latency periods observed in the current 14 ms condition (Czigler, Weisz, et al., 2006; Kimura et al., 2009).

In the current experiment the use of the same stimulus only changing its orientation was used to control for habituation. However, some of the changes observed may be due to the activation of fresh neuronal populations within the oddball condition. When the ERP response to the deviant stimulus presented alone and out of context was subtracted from the deviant ERP response to the deviant presented in the oddball paradigm, no significant differences were

revealed when analysed by point-to-point *t*-tests. This, in combination with the observed reduction in the subtraction waveform (Figure 7.2 F) suggests that some of the differences observed in the 14 ms condition may be due to stimulus characteristics. Although the stimuli used as standard and deviant were the same, only changing in orientation, stimulus differences cannot be ruled, these however, may be reflected in the enhanced negativity in the N1 latency period.

The current experiment used a backward and forward masking paradigm to investigate discrimination processes in stimuli that changed in orientation by introducing an oddball paradigm to establish whether a deviant stimulus could elicit registration of stimulus discrimination that was independent of the ability to report that stimulus. No visual MMN was recorded to masked stimuli presented for 7 ms. Visual MMN components only emerged when the stimuli were presented for 14 ms and the majority of participants were able to report their appearance. This would suggest that using the current paradigm it was not possible to capture the automaticity of the visual MMN in the absence of attention and that for visual MMN elicitation some degree of attention is required.

8 General Discussion

8.1 Introduction

The motivation for this thesis has been to develop visual diagnostic techniques that can be used with children and others who cannot actively participate in a behavioural task. Currently available electrophysiological methods such as the VEP can, in combination with other diagnostic tests, assess the functional integrity of the visual pathways to the level of the cortex. However, clinical VEP assessment does not always give an indication of higher cortical function and does not have a direct relationship with visual acuity. For example, in cases of cerebral palsy, relatively good VEPs can be recorded but visual acuity can be poor. In cases of optic atrophy, poor degraded VEPs can be recorded whilst visual acuity can be relatively good. Cortical visual impairment is another condition where pattern reversal VEPs sometimes do not seem to give an accurate reflection of the conscious perception of the child. Therefore, currently available VEP assessment tools do not fully explain how vision is integrated at the level of the cortex.

In the auditory system the MMN and its magnetic counterpart the MMNm provide an objective assessment of the accuracy of central auditory processing (Näätänen, 2000; Näätänen & Escera, 2000). In addition, it can be recorded in the absence of attention which makes it attractive for use with clinical populations as a behavioural response is not required. By assessing visual functioning at the level of the cortex, the visual MMN may thus potentially be developed into a diagnostic tool reflecting the integration of visual processes required for visual stimulus discrimination. However, the validity of any diagnostic test and its clinical usefulness is reliant on accurate measurement and an understanding of the underlying mechanisms which it taps. Therefore, characterising the visual MMN could have important clinical applications and, in particular, experimental evidence of sensory memory and pre-attentive processing has been sought (Czigler, 2007). This chapter discusses the findings of the studies in this thesis as a whole, and in relation to the above aims. It begins with a summary of the findings of each experiment and then integrates these findings with reference to a wider literature. Future directions are then discussed.

8.2 Summary of experiments

When the experiments reported in this thesis were designed, the existence of the visual MMN was debated and its characterisation was in early stages of testing. Research over the past decade or so, has focused on establishing whether the same characteristics observed in the auditory MMN are present in the visual MMN, and the studies in this thesis make a contribution to this research effort. Where it has been specifically investigated in this programme of research, visual MMN components have been observed (apart from Experiment 5.2, for the sample of participants with albinism). These findings and the findings of others indicate that there is now substantial evidence for the existence of visual MMN (Kimura, 2012; Kimura et al., 2011).

Uniquely, in the experiments presented here, these visual MMN components have been elicited in paradigms in which there was no behavioural task. It had generally been understood that a concurrent active task is mandatory in eliciting visual MMN to control for the effects of attention, so that resources are allocated away from the standard-deviant discrimination towards the active task (Czigler, 2007; Heslenfeld, 2003). A typical MMN paradigm is a selective attention task, whereby the stimulus sequence is usually task-irrelevant or unattended. Thus, participants are typically presented with a visual display that can contain a target stimulus amongst a variable number of distractor stimuli to which the participant is asked to respond (an active paradigm), or a number of task irrelevant stimuli are presented peripherally whilst the participant is asked to focus their attention on a task in the middle of the visual field (a passive paradigm). The paradigms in the experiments presented here used an illusory figure to attract attention from the standard deviant transition instead of a behavioural task to control for the effects of attention. Or, stimuli were presented close to thresholds of awareness to modulate attention. Importantly, these paradigms have the potential to be used in populations who cannot meet the demands of an active task.

In Experiment 3.1, in a non-clinical population, the illusory deviant stimulus elicited the expected P3a novelty orienting response demonstrating that the illusory figure captured attention. A visual MMN was recorded over posterior electrode sites indicating visual discrimination responses. The introduction of a

behavioural task in Experiment 3.2 elicited a P3b attentional response to the target and visual MMN components were attenuated. To the author's knowledge, this was the first experiment to demonstrate explicitly that visual MMN was subject to attentional modulation.

Experiments 4.1, 5.1 and 5.2 utilised novel approaches to explore the source and laterality of visual MMN as some studies have shown that there is a right hemisphere dominance in the generation of the visual MMN (e.g. Kimura et al., 2010). For the first time, in Experiment 4.1, intracranial electrodes recorded directly from the cortex of an adolescent male, components which may correspond to the scalp recorded visual N1 and MMN. Visual N1 and MMN components could be separated temporally and spatially with MMN recorded more anteriorly than N1. Experiments 5.1 and 5.2 were innovative in approach in that the characteristic contralateral dominance in albinism was used as a model to explore hemispheric lateralisation of visual MMN, although no visual MMN response could be recorded in this sample. Little is known about the MMN response in albinism as, to date, no other studies have investigated either auditory or visual MMN in this population.

Experiments 6.1, 6.2 and 7.1 were designed to explore the automaticity of the visual MMN using stimuli presented below and above participants' subjective levels of perception. Experiments 6.1 and 6.2 were precursors to Experiment 7.1 in that they investigated whether a combined masking and brief stimulus presentation continuous visual stream paradigm could elicit similar components emerging from a masked background (Experiment 6.1) in comparison to those emerging from a grey background (Experiment 6.2). Similar components could be elicited in the masked and unmasked condition indicating that this paradigm could be used to investigate later visual discrimination components. In addition, early visual component (CI) was recorded in all stimulus durations whereas components CII and CIII were recorded at 14 and 21 ms stimulus duration only, which may suggest that CII may be a correlate of visual consciousness. Experiment 7.1 investigated whether visual MNN responses could be recorded subliminally, in the absence of the participant's ability to report seeing the stimulus. In this experiment behavioural identification of the stimuli was required for elicitation of visual MMN suggesting that the visual MMN may require some attentional resources.

In summary, visual MMN can be elicited in a non-clinical sample and directly from the the cortex of an adolescent suffering with epilepsy. Visual MMN could be separated temporally and spatially from N1. These experiments indicate that visual MMN is subject to attentional modulation and its pre-attentive nature was not captured. The implications of these findings are discussed in relation to the wider MMN literature below.

8.3 Visual MMN as a pre-attentive mechanism

Although the visual MMN has often been described as a pre-attentive process, it is unclear in the visual MMN whether it is elicited in the absence of attention or whether the N1/N2-like waves observed in the subtraction waveforms demonstrate the same degree of automaticity as the auditory MMN. In fact, there is some debate in recent years as to whether even the auditory MMN is truly elicited in the absence of attention (Haroush, Hochstein, & Deouell, 2010; Rissling et al., 2013), as attentional manipulations have been shown to lead to increases (Domenico Restuccia, Rubino, Marra, Valeriani, & Della Marca, 2005) and decreases (Yucel et al., 2005) in MMN amplitude. The experiments designed in this thesis have attempted to establish whether a 'pre-attentive' or 'attention independent' visual discrimination response can be recorded in the absence of a behavioural task and to explore the generators of the mechanism.

Evidence of the pre-attentive nature of the visual MMN in many studies is sought by the manipulation of attentional resources of the participant away from the task irrelevant stimulus sequence that is of interest to the experimenter. As noted in Section 8.2, in an active visual MMN paradigm, the participant's task is typically to detect a target stimulus amongst distractor stimuli. Studies that have reported visual MMN in an active paradigm include (Fu et al., 2003; Kimura, Katayama, & Murohashi, 2006; Kimura, Murohashi, et al., 2006; Maekawa et al., 2005; Maekawa et al., 2009).

In a passive visual MMN paradigm task, irrelevant stimuli are typically presented peripherally whilst the participant is asked to focus their attention on a task in the middle of the visual field or to focus on an on an auditory task whilst ignoring visual stimuli presented. Such studies include (Astikainen et al., 2004; Astikainen et al., 2008; Clery et al., 2013; Czigler et al., 2002; Czigler &

Pato, 2009; Kenemans et al., 2003; Kremlacek et al., 2006; Stagg et al., 2004; Stefanics, Kimura, & Czigler, 2011; Tales, Newton, Butler, Troscianko, & Wilcock, 2002; Tales et al., 1999). However, it is unclear from these studies whether evidence for the elicitation of the visual MMN is truly independent of attention because there is no way of being certain that the stimuli are truly ignored.

In the current thesis, it was attempted to modulate attention in two ways. Firstly, an illusory deviant stimulus was used in the absence of a behavioural task to attract attention away from the standard deviant transition. Secondly, by manipulation of presentation durations close to the threshold of awareness. The elicitation of the visual MMN in the absence of the ability to consciously report the changes in the deviant would provide strong support for the automaticity of the visual MMN mechanism (Paavilainen, 2013) and would be suggestive of pre-attentive cognitive operations in vision. However, it is noted that there is debate as to whether consciousness, visual awareness and attention are separable processes and there is still a lack of understanding as to the relationship between these concepts and they are often conflated although some authors suggest they can be experimentally separated. For a discussion of these issues, see (Chica, Lasaponara, Lupianez, Doricchi, & Bartolomeo, 2010; Hohwy, 2012; Koch & Tsuchiya, 2007; Koivisto, Kainulainen, & Revonsuo, 2009) . It is not an aim of this thesis to review or try to resolve these issues but just to note an awareness of them.

The first experiments in this thesis (reported in Chapter 3), used an illusory figure, a Kanizsa square, in place of a behavioural task to distract attention away from the standard deviant transition. Experiment 3.1 was novel, in that, no other studies have reported using an illusory figure in a passive oddball paradigm to control for the effects of attention. The deviant stimulus elicited a more negative response than the standard stimulus and the illusory deviant stimulus elicited a more negative response than either the standard or the deviant stimulus. An additional component reflecting a P3a was elicited to the illusory deviant only, suggesting that, as predicted, the illusory figure captured attention. The incorporation of a behavioural task in Experiment 3.2, in which participants had to respond to the presence of a square in the fixation point,

enabled the examination of the effect of an active task on the visual MMN. In Experiment 3.2, a P3b reflecting engagement with the task was elicited. However, when a task was incorporated into the paradigm, an attenuated visual MMN was recorded. In combination the two experiments show that discrimination to a change in the orientation of stimulus elements could be recorded in the absence of a behavioural task. However, the attenuation of the visual MMN when a behavioural task was incorporated, suggests that direction of attention modulated visual MMN amplitude. This suggests that some aspects of the visual MMN process are susceptible to attentional modulation, a finding that has been subsequently corroborated by Czigler and Sulykos (2010).

The experiments reported in Chapter 6 used a standard clinical probe stimulus, the checkerboard, known to elicit particular electrophysiological ERPs. It was possible to show that comparable components could be elicited when this stimulus emerged from a grey background and when it was briefly presented and masked to vary the participant's perception of the stimulus. When the participants could not report seeing the stimulus, early responses were still recorded – the CI at a latency of about 60-80 ms. Masking the stimuli increased the amplitude of CII components. These findings may suggest an association between the early components of the pattern appearance/disappearance VEP and conscious perception. The CI component may determine if the visual system has detected the short duration stimulus while the CII and CIII responses may give an indication of whether this stimulus had been processed any further and possibly perceived. Alternatively, these early C components may activate later more anterior systems known to be involved with perception and awareness. It may be that the cortical processing represented by CII and CIII is necessary but not sufficient for conscious perception and trigger later and more anterior circuitry which actually represents conscious perception. However, such an account would contradict the findings of Zeki (2008) and Tse et al. (2005).

One problem in experiments using subthreshold stimuli is to establish absence of stimulus awareness. This should be based on sound methodological grounds and relates to the problem of determining the sensory threshold, which can vary as a result of different participant criteria in deciding for the presence of a

stimulus. In the experiments reported in Chapters 6 and 7 it was chosen to rely on subjective appraisal of stimulus perception without using signal detection protocols as it was the modulation of attention that was of current interest, rather than establishing individual perceptual thresholds. The signal detection paradigm is more critical in that it instructs the participants to judge whether a stimulus had been presented or not within a designated interval following a warning stimulus. By using a false alarm and hit rate, it is possible to establish the decision criteria of the participant. This is a relatively time consuming procedure and not suitable for routine clinical testing. Another problem with using signal detection protocols is that they incorporate a decision process rather than recording brain activity related purely to the physical stimulus. However, the methods for measuring awareness are controversial. Based on Signal Detection Theory there is a distinction between a subjective threshold, which is the level of discriminative responding at which observers claim not to be able to detect or recognise perceptual information at a better than chance level of performance and an objective threshold which is the level of discriminative responding corresponding to chance level performance. Some authors (Cheesman & Merikle, 1984, 1986; Merikle & Cheesman, 1986) advocate the use of subjective measures; they argue that perceptual awareness or consciousness is a subjective state that accesses the phenomenological experience of consciousness. Other authors (Bernat, Shevrin, et al., 2001; Shevrin, 2001) suggest the use of objective measures as being more rigorous, as subjective measures are prone to differences in an individual's willingness to report awareness. For a review of objective and subjective measures see Snodgrass, Bernat, and Shevrin (2004).

Having validated the use of brief stimulus presentation in combination with a masking paradigm, the experiment reported in Chapter 7 investigated discrimination processes in relation to stimuli that changed in orientation. The introduction of an oddball paradigm was used to establish whether a deviant stimulus, when compared to a standard stimulus, could elicit registration of stimulus discrimination that was independent of the ability to report that stimulus. Evidence of visual MMN in the elicited waveforms when participants were unable to report stimulus change would provide strong support for the automaticity of the visual MMN. However, no visual discrimination components

were recorded when the stimuli were presented for 7 ms, apparently below levels of subjective perception and when participants did not report seeing the stimuli. Visual MMN components only emerged when the stimuli were presented for 14 ms and the majority of participants were able to report their appearance. The current results are in agreement with those of Czigler et al. (2007), who using a backward masking paradigm to elicit visual MMN reported that visual MMN was only elicited as behavioural identification of the deviant increased. These results also suggest that some degree of attention may be required to elicit a visual MMN. However, the current results are in contrast with those reported by Berti (2011), who reported the automaticity of the visual MMN using an attentional blink paradigm. The results of Experiment 7.1 may suggest that in some instances the visual MMN is not fully automatic. Alternatively, it may be that the paradigms developed in this thesis cannot tap the automaticity of the visual MMN. In future studies, reduction of stimulus contrast to render the stimuli unreportable as opposed to using a mask may be a useful way forward.

To some degree automaticity of the visual MMN can be assumed in the current experiments as the participant's focal attention was not directed to the stimuli – the criteria accepted for many visual MMN studies, including all of the experiments referenced in paragraph two of this section. However, the evidence in Experiments 3.1, 3.2, 6.1, 6.2 and 7.1, suggest that the visual MMN is sensitive to attentional modulation. Rather than specifying the nature of visual MMN generation as pre-attentive, it may be more appropriate to describe it as elicited in the absence of focal attention. The issue of how the specificity of the automaticity of the MMN generation can be characterised is still an issue to be resolved (Kimura, 2012; Rissling et al., 2013).

8.4 Neuronal mechanisms underlying visual MMN

Cognitively, mismatch responses are thought to be the consequence of change-sensitive processes that are reflective of the automatic detection of sensory change/regularity violation and pre-attentive processing. However, this does not explain the neural mechanisms underlying the mismatch response. Two competing hypotheses have dominated the literature to explain the results from experiments investigating the neural mechanisms leading to the generation of the visual MMN, the 'adaptation hypothesis' and the 'memory mismatch'

hypothesis. It is now suggested that the results found for visual MMN can be accounted for more parsimoniously within a predictive coding framework. The theories will be outlined below.

Within a neural adaptation account (Näätänen, 1990b), the enhanced negativity observed when the ERP to the standard stimulus is subtracted from the ERP to the deviant stimulus is accounted for by the refractory state of neurons. It is suggested that neurons that respond to a visual feature may become less responsive when that feature is repeated with short intervals. Whereas, with infrequent presentations of the deviant stimulus with longer stimulus intervals, neuronal responsivity is maintained. Therefore the enhanced amplitude in the N1 latency period is thought to be representative of differential activation of afferent neuronal populations between stimuli thus reflecting their state of habituation. Differences in habituation are thought to be due to the differences in stimulus probability and, as such, the amplitude of VEPs evoked to deviant stimuli are larger than those evoked to standard stimuli. A number of visual MMN experimental results can be explained within this framework including those of (Berti & Schroger, 2004; Kenemans et al., 2003; Mazza et al., 2005).

Within a memory mismatch account (Näätänen, 1990b; Näätänen et al., 2005), the underlying mechanism for the emergence of the enhanced negativity observed in the visual MMN is that after a number of presentations of the standard stimulus, a sensory memory trace is represented in the neural architecture. When the deviant stimulus is compared to the neural representation that has been formed by the standard stimulus, there is a mismatch resulting in the differential electrical activity observed. An update of the memory mismatch account suggests that instead of being reliant on the physical characteristics of a stimulus, it is the regularity of a sequential pattern that is encoded in the neural representation and that the mismatch process is better characterised as a violation of regularity (Czigler, 2007; Czigler et al., 2002). This account of the visual MMN therefore suggests that the visual MMN is generated by a mechanism that responds to a difference between consecutive stimuli rather than the stimulus itself.

A number of studies provide support for a mismatch interpretation, for a review see (Kimura, 2012). The visual MMN is not elicited by deviant stimuli when they are presented without the intervening standards or when inter-stimulus intervals are long (Astikainen et al., 2008). Therefore the visual MMN is not elicited by any stimulus, without a number of preceding repetitions of a different stimulus (the standard) or when the transient memory trace of the stimulus has decayed. This is indicative of a relationship between the present stimulus and the representation of the preceding stimulus. For comparable results in the auditory domain see Sams et al. (1985). The visual MMN can also be elicited by stimulus omission in a stimulus sequence (Czigler, Várnagy, et al., 2006). For comparable results in the auditory domain, see (Yabe et al., 1997). Violations of regularity in a sequence rather than physical differences between stimuli have been shown to elicit visual MMN (Czigler, Weisz, et al., 2006).

The prevailing theory explaining the neural mechanisms that underly MMN generation are predictive coding theories. Predictive coding theories unify the competing hypotheses of neuronal adaptation and memory mismatch and can provide an overarching account for the experimental results observed supporting each of these hypotheses (Garrido et al., 2009; Kimura et al., 2011; Winkler & Czigler, 2012). In addition, they provide an extension of the memory mismatch account by explaining a number of experiment results that cannot be explained within a memory mismatch account (e.g. Czigler, Weisz, et al., 2006; Stefanics et al., 2011). Studies such as Stefanics et al. (2011) have provided evidence to suggest that the visual MMN, rather than being reliant on a sensory memory trace based on deviations in the physical stimulus characteristics of the standard and deviant, can be based on violations of regular sequential patterns.

Predictive coding theories are models of perceptual inference based on the assumption that rather than passively registering environmental regularities, the brain actively predicts the causes of sensory inputs (Friston, 2005, 2010; Rao & Ballard, 1999). Within this framework the brain's perceptual system is seen as a system that tries to utilise limited resources efficiently by minimising error by actively predicting the causes of sensory inputs. It is assumed the brain's perceptual system is made up of a series of hierarchically organised generative models, with higher levels becoming ever more general. The brain infers the

causes of sensory inputs by predicting them and adjusts these predictions in order to minimise error which leads to perceptual learning. Minimisation of prediction error is assumed to be reliant of a hierarchical network that operates on an empirical Bayes scheme with extrinsic (forward and backward connections between cortical sources) and intrinsic (local) connectivity (Friston, 2005). Within this framework, sensory input entering the primary cortex is actively compared with top-down predictions and the MMN is elicited when there is a failure to suppress prediction error (Friston, 2005; Garrido et al., 2009). For a review of visual MMN and auditory MMN studies interpreted within this framework see Winkler and Czigler (2012).

In the current experiments, neuronal refractoriness was controlled for by the use of a 'deviant alone' condition (see Section 2.3.7.3). A deviant alone condition removes the standard from the sequence which is one method of testing a memory mismatch account. To examine whether the differences observed in the subtraction waveforms were confounded by pure stimulus differences, the discrimination waveform to the deviant stimulus was compared to the discrimination waveform when that same stimulus was presented alone i.e. out of context and not in an oddball paradigm. Results suggested that differences observed were due to the context in which the stimuli were presented, although refractory effects could not be completely discounted.

In the eight years that this thesis has been in development, methods for characterising the neuronal mechanisms underlying visual MMN generation have developed. The introduction and use of an equiprobable paradigm, in combination with an oddball paradigm (Kimura et al., 2009), has enabled the separation of mechanisms thought to underly the elicitation of the visual MMN. By presenting stimuli including the deviant with equal probabilities in one stimulus sequence (a control condition), and comparing that deviant to the deviant when presented in an oddball paradigm, the probability of the deviant in both conditions is maintained. This ensures that the state of neuronal refractoriness of the deviant is the same in both conditions. If the elicitation of the visual MMN is reliant on a sensory memory trace, no MMN is expected in the equiprobable condition, but an observed enhanced negativity in the deviant in the oddball paradigm minus the deviant in the control subtraction waveforms

provides evidence for a memory mismatch account. Largely based on studies using a combination of an equiprobable and oddball paradigm, current literature suggests that the visual MMN is made up of two components an early component in the N1 latency range which is reported as being related to neural refractoriness whilst a later component in the N2 latency range of 200-400 is related to memory based change or 'unintentional temporal-context-based prediction in vision' (Kimura et al., 2009; Kimura et al., 2011) p 671.

A limitation of the experiments designed to elicit visual MMN in this thesis, is that they were not primarily designed to distinguish between hypotheses relating to the neural mechanisms underlying visual MMN. The best method for experimentally separating hypotheses as to the underlying neural mechanisms generating visual MMN responses is currently thought to be the use of the equiprobable paradigm in combination with an oddball paradigm (Kimura et al., 2009). Therefore it is difficult to establish from the designs employed here whether in fact a 'true' visual MMN was indeed recorded.

8.5 Generators of the visual MMN and hemispheric lateralisation

The identification of neural generators of the visual MMN currently suggests areas in the extrastriate cortex are implicated, particularly in the right hemisphere. The generators of the visual MMN were investigated in Chapter 4 by using recordings directly from the surface of the right hemispheric cortex from a patient undergoing pre-surgical evaluation for epilepsy. By using the illusory figure within an oddball paradigm and recording from strip electrodes it was possible to show that extrastriate areas BA18 and BA19 were implicated in the elicitation of visual MMN. In addition, it was possible to separate what may be recorded from the scalp as N1 and MMN components both temporally and spatially. Recordings to visual MMN were recorded more anteriorly than those to the N1 and this converges with the results of other studies (e.g. Urakawa, Inui, Yamashiro, & Kakigi, 2010; Urakawa, Inui, Yamashiro, Tanaka, & Kakigi, 2010), who found that the Middle Occipital Gyrus (MOG) (BA19) was implicated in the generation of the visual MMN. Other studies have shown that the extrastriate cortex is implicated in the generation of the MMN. Kimura et al. (2010) using sLORETA reported generator sources in the right extrastriate

cortex. Other studies have also identified generator sources in frontal areas. For example, Yucel, McCarthy, and Belger (2007) found that deviant compared to standard stimuli evoked increased hemodynamic activation along the geniculo-striate pathways such that visual deviant stimuli evoked significant activation not only in early visual areas, but also in the posterior parietal cortex (BA19/7 and BA7). In addition, deviant stimuli elicited significant activation in prefrontal regions (BA9/10) in the left and more prominently the right hemisphere. Kimura et al. (2009) reported generators of the visual MMN in the right occipital lobe (BA19) and in the right orbitofrontal areas (BA47 and BA11). Due to the limited electrode coverage in Experiment 4.1, frontal generators were not investigated.

The illusory deviant paradigm was used to investigate hemispheric lateralisation in the source of the visual MMN in a group of participants with albinism (Chapter 5). A characteristic preponderance of temporal retinal fibres from each eye crossing to the contralateral hemisphere afforded the opportunity to investigate each hemisphere in relative isolation and explore whether there was a hemispheric lateralisation in the source of the visual MMN. A number of studies have reported that the right hemisphere is the dominant hemisphere for the visual MMN. For example, Kimura et al. (2012) reported that the visual MMN was mainly generated from occipito-temporal visual extrastriate areas in the right hemisphere and medial and lateral prefrontal areas lateralised to the right. In addition, Kimura et al. (2009) reported a right hemisphere dominance for visual MMN to changes in the orientation of a bar. Grimm et al. (2009), found the differences between deviant and control stimuli were present in both hemispheres indicating sources in bilateral parieto-occipital areas of cortex but with a right hemisphere dominance. However, in Experiment 5.2 a visual MMN response was not recorded in this group and no conclusions regarding the lateralisation of visual MMN could be made.

8.6 Development of visual diagnostic tests and future directions

Cortical visual impairment is the major cause of blindness in children in the Western countries (Good, 2001), followed by retinal dystrophies which account for 14% of children newly diagnosed with blindness in the UK (Hamblion, Moore, Rahi, & British Childhood Onset, 2012). Due to the plastic properties of the cortex, methods of documenting and monitoring visual function/performance are becoming increasingly important especially with the need for evidence based medicine and quantifiable outcome measures. The experiments presented in this thesis have attempted to develop visual paradigms that address how information is initially processed by the brain and subsequently integrated for higher visual functions.

Experiments 3.1, 3.2 and 7.1 showed electrophysiological markers of visual discrimination. Although these responses were modulated by attention the presence of these responses in a clinical group would indicate transfer of information from V1 to higher visual areas that ultimately correlate to visual function/performance. In addition, Experiments 3.1 and 3.2, have also shown that robust responses to an illusory square in comparison to other visual stimuli can be recorded eliciting a P3a reflective of attentional reorienting.

The experiments outlined in Chapter 6 address the speed at which the visual cortex is able to process individual stimuli during a continuous visual stream. This has potential clinical applications, for example in determining the effect of visual rehabilitation strategies involving the temporal processing of information. From a scientific perspective, the results of Experiments 6.1 and 7.1 suggest that stimuli are required to be perceived by the participant for visual MMN to be evoked. This may aid in future work in designing studies to be used in developing visual MMN paradigms.

A general problem in electrophysiological recordings is the identification of potentials just above the level of noise, such as the visual MMN. This signal to noise ratio is generally worse in a clinical paediatric environment and this problem is compounded by the need to determine exact onset and offset latencies in order to measure amplitudes. However, strategies have been developed to extract information that are now widely used to identify, for

example, epileptic spikes from background EEG (Wilson & Emerson, 2002). Such an algorithm developed and validated for use with the visual MMN would facilitate the use of the visual MMN in clinical visual testing. Another approach to identify/classify ERP components is to use Fast Fourier Transform (FFT) techniques. Here, the frequency at which the component occurs is extracted from a bandwidth spectrum. Cong et al. (2012) have used FFT techniques to identify the auditory MMN in children. This may be useful in combination with other methods described above to validate the existence of small visual MMN components. In addition, the incorporation of an equiprobable paradigm to the experiments designed within this thesis may provide further information on the mechanisms underlying visual MMN.

8.7 Conclusion

There are inherent difficulties in designing simple visual paradigms to investigate visual processing. The experiments presented in this thesis have demonstrated that robust responses to visual detection and discrimination can be elicited in the absence of a behavioural task in non-clinical populations. Therefore these paradigms have the potential for further research in non-clinical and clinical populations. Although it is unclear whether a 'true' visual MMN was recorded the results presented in this thesis suggest that the visual MMN in some instances is subject to attentional modulation.

References

Alain, C., Woods, D. L., & Knight, R.T. (1998). A distributed cortical network for auditory sensory memory in humans. *Brain Research*(1), 23-22).

Alho, K., Woods, D. L., & Algazi, A. (1994). Processing of auditory-stimuli during auditory and visual-attention as revealed by event-related potentials. *Psychophysiology, 31*(5), 469-479. doi: 10.1111/j.1469-8986.1994.tb01050.x

Allison, T., Wood, C. C., & McCarthy, G. (1986). The Central Nervous System. In M.G.H. Coles, Donchin. E. & S.W. Porges (Eds.), *Psychophysiology: systems, processes and applications* (pp. 5-25). New York: Guilford.

Ansorge, Ulrich, Francis, Gregory, Herzog, Michael H., & Ogmen, Haluk. (2007). Visual masking and the dynamics of human perception, cognition, and consciousness A century of progress, a contemporary synthesis, and future directions. *Advances in Cognitive Psychology, 3*(1-2), 1-8.

Apkarian, P., & Bour, L.J. (2007). Aberrant albino and achiasmat visual pathways: noninvasive electrophysiological assessment. In JR Heckenlively, Arden, GB. (Ed.), *Principles and Practice of Clinical Electropysiology of vision* (2nd ed., pp. 369-397). Cambridge, Massachusetts: The MIT Press.

Apkarian, P., Reits, D., Spekreijse, H., & Vandorp, D. (1983). A decisive electro-physiological test for human albinism. *Electroencephalography and Clinical Neurophysiology, 55*(5), 513-531. doi: 10.1016/0013-4694(83)90162-1

Apkarian, P., & Shallohoffmann, J. (1991). VEP projections in congenital nystagmus - VEP asymmetry in albinism - a comparison study. *Investigative Ophthalmology and Visual Science, 32*(9), 2653-2661.

Astikainen, P., Korhonen, T., Ruusuvirta, T., & Wikgren, J. (2004). The human brain processes visual changes that are not cued by attended auditory stimulation. *Neuroscience Letters, 368*(2), 231-234.

Astikainen, P., Lillstrang, E., & Ruusuvirta, T. (2008). Visual mismatch negativity for changes in orientation - a sensory memory-dependent response. *European Journal of Neuroscience, 28*(11), 2319-2324.

Astikainen, P., Ruusuvirta, T., & Korhonen, T. (2001). Somatosensory event-related potentials in the rabbit cerebral and cerebellar cortices: a correspondence with mismatch responses in humans. *Neuroscience Letters, 298*(3), 222-224. doi: 10.1016/s0304-3940(00)01747-x

Baldeweg, T. (2007). ERP repetition effects and mismatch negativity generation - A predictive coding perspective. *Journal of Psychophysiology, 21*(3-4), 204-213. doi: 10.1027/0269-8803.21.34.204

Baudena, P., Halgren, E., Heit, G., & Clarke, J. M. (1995). Intracerebral Potentials to Rare Target and Distracter Auditory and Visual-Stimuli .3. Frontal-Cortex. *Electroencephalography and Clinical Neurophysiology, 94*(4), 251-264.

Bear, M.F., Connors, B.W., Paradiso, M.A. (2007). *Neuroscience: exploring the brain* (3rd ed.). Baltimore: Lippincott Williams and Wilkins.

Belliveau, J. W., Kennedy, D. N., McKinstry, R. C., Buchbinder, B. R., Weisskoff, R. M., Cohen, M. S., Vevea, J.M. & Rosen, B. R. (1991). Functional mapping of the human visual-cortex by magnetic resonance imaging. *Science, 254*(5032), 716-719. doi: 10.1126/science.1948051

Bernat, E., Bunce, S., & Shevrin, H. (2001). Event-related brain potentials differentiate positive and negative mood adjectives during both supraliminal and subliminal visual processing. *International Journal of Psychophysiology, 42*(1), 11-34. doi: 10.1016/s0167-8760(01)00133-7

Bernat, E., Shevrin, H., & Snodgrass, M.l. (2001). Subliminal visual oddball stimuli evoke a P300 component. *Clinical Neurophysiology*(1), 159-171.

Berti, S. (2011). The attentional blink demonstrates automatic deviance processing in vision. *Neuroreport, 22*(13), 664-667. doi: 10.1097/WNR.0b013e32834a8990

Berti, S., & Schroger, E. (2004). Distraction effects in vision: behavioral and event-related potential indices. *Neuroreport, 15*(4), 665-669.

Besle, J., Fort, A., & Giard, M. H. (2005). Is the auditory sensory memory sensitive to visual information? *Experimental Brain Research, 166*(3-4), 337-344. doi: 10.1007/s00221-005-2375-x

Brázdil, M., Dufek, M., Jurák, P., Rektor, I., & Daniel, P. (2001). Intracerebral event-related potentials to subthreshold target stimuli. *Clinical Neurophysiology, 112*(4), 650-661.

Brazdil, M., Rektor, I., Dufek, M., Daniel, P., Jurak, P., & Kuba, R. (1999). The role of frontal and temporal lobes in visual discrimination task - depth ERP studies. *Neurophysiologie Clinique-Clinical Neurophysiology, 29*(4), 339-350. doi: 10.1016/s0987-7053(99)90047-3

Cheesman, J., & Merikle, P. M. (1984). Priming without awareness. *Perception and Psychophysics, 36*(4), 387-395. doi: 10.3758/bf03202793

Cheesman, J., & Merikle, P. M. (1986). Distinguishing Conscious from Unconscious Perceptual Processes. *Canadian Journal of Psychology-Revue Canadienne De Psychologie, 40*(4), 343-367.

Cheourluhtanen, M., Alho, K., Kujala, T., Sainio, K., Reinikainen, K., Renlund, M., Aaltonen, O., Eerola, R., Näätänen, R. (1995). Mismatch negativity indicates vowel discrimination in newborns. *Hearing Research, 82*(1), 53-58.

Chica, A. B., Lasaponara, S., Lupianez, J., Doricchi, F., & Bartolomeo, P. (2010). Exogenous attention can capture perceptual consciousness: ERP and behavioural evidence. *Neuroimage, 51*(3), 1205-1212. doi: 10.1016/j.neuroimage.2010.03.002

Clark, Vincent P., Fan, Silu, & Hillyard, Steven A. (1995). Identification of early visual evoked potential generators by retinotopic and topographic analyses. *Human Brain Mapping, 2*(3), 170-187.

Clarke, J.M., Halgren, E., & Chauvel, P. (1999a). Intracranial ERPs in humans during a lateralized visual oddball task: I. Occipital and perio-Rolandic recordings. *Clinical Neurophysiology, 110*(7), 1210-1225.

Clarke, J.M., Halgren, E., & Chauvel, P. (1999b). Intracranial ERPs in humans during a lateralized visual oddball task: II. Temporal, parietal and frontal recordings. *Clinical Neurophysiology, 110*(7), 1226-1244.

Clery, H., Andersson, F., Fonlupt, P., & Gomot, M. (2013). Brain correlates of automatic visual change detection. *Neuroimage, 75*, 117-122. doi: 10.1016/j.neuroimage.2013.02.050

Coles, M.G.H., Rugg, M.D. (1995). Event-related brain potentials an introduction. In M.D. Rugg & M.G.H. Coles (Eds.), *Electrophysiology of Mind: Event-Related Brain Potentials and Cognition* New York: Oxford University Press.

Cong, Fengyu, Huang, Yixiang, Kalyakin, Igor, Li, Hong, Huttunen-Scott, Tiina, Lyytinen, Heikki, & Ristaniemi, Tapani. (2012). Frequency-response-

based Wavelet Decomposition for Extracting Children's Mismatch Negativity Elicited by Uninterrupted Sound. *Journal of Medical and Biological Engineering, 32*(3), 205-213. doi: 10.5405/jmbe.908

Cooper, R., Osselton, J.W., & Shaw, J.C. (1969). *EEG Technology*. London: Butterworths.

Cooper, R., Winter, A. L., Crow, H. J., & Walter, W. G. (1965). Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalography and Clinical Neurophysiology, 18*, 217-228. doi: 10.1016/0013-4694(65)90088-x

Corballis, P. M. (2003). Visuospatial processing and the right-hemisphere interpreter. *Brain and Cognition, 53*(2), 171-176. doi: 10.1016/s0278-2626(03)00103-9

Corballis, P. M., & Fendrich, R. (1999). Illusory contour perception and amodal boundary completion: Evidence of a dissociation following callosotomy. *Journal of Cognitive Neuroscience, 11*(4), 459-466.

Cowan, N., Winkler, I., Teder, W., & Näätänen, R. (1993). Memory prerequisites of mismatch negativity in the auditory event-related potential (ERP). *Journal of Experimental Psychology-Learning Memory and Cognition, 19*(4), 909-921. doi: 10.1037//0278-7393.19.4.909

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual-cortex. *Nature, 375*(6527), 121-123. doi: 10.1038/375121a0

Csepe, V., Karmos, G., & Molnar, M. (1987). Evoked-potential correlates of stimulus deviance during wakefulness and sleep in cat-animal model of mismatch negativity. *Electroencephalography and Clinical Neurophysiology, 66*(6), 571-578. doi: 10.1016/0013-4694(87)90103-9

Czigler, I. (2007). Visual mismatch negativity - Violation of nonattended environmental regularities. *Journal of Psychophysiology, 21*(3-4), 224-230. doi: 10.1027/0269-8803.21.34.224

Czigler, I., Balázs, L., & Pató, L.G. (2004). Visual change detection: event-related potentials are dependent on stimulus location in humans. *Neuroscience Letters, 364*(3), 149-153.

Czigler, I., Balázs, L., & Winkler, I. (2002). Memory-based detection of task-irrelevant visual changes. *Psychophysiology, 39*(6), 869-873.

Czigler, I., & Csibra, G. (1992). Event-related potentials and the identification of deviant visual stimuli. *Psychophysiology, 29*(4), 471-485.

Czigler, I., & Pato, L. (2009). Unnoticed regularity violation elicits change-related brain activity. *Biological Psychology, 80*(3), 339-347.

Czigler, I., & Sulykos, I. (2010). Visual mismatch negativity to irrelevant changes is sensitive to task-relevant changes. *Neuropsychologia, 48*(5), 1277-1282. doi: 10.1016/j.neuropsychologia.2009.12.029

Czigler, I., Várnagy, A., Weisz, J., Winkler, I. , Pató, L. , & Balázs, L. . (2006). Visual temporal window of integration as revealed by the visual mismatch negativity event-related potential to stimulus omissions. *Brain Research, 1104*(1), 129-140.

Czigler, I., Weisz, J., & Winkler, I. (2006). ERPs and deviance detection: visual mismatch negativity to repeated visual stimuli. *Neuroscience Letters, 401*(1-2), 178-182.

Czigler, I., Weisz, J., & Winkler, I. (2007). Backward masking and visual mismatch negativity: Electrophysiological evidence for memory-based detection of deviant stimuli. *Psychophysiology, 44*(4), 610-619.

Davis, G., & Driver, J. (1994). Parallel detection of kanizsa subjective figures in the human visual-system. *Nature, 371*(6500), 791-793. doi: 10.1038/371791a0

Del Cul, Antoine, Baillet, Sylvain, & Dehaene, Stanislas. (2007). Brain dynamics underlying the nonlinear threshold for access to consciousness. *PLoS Biology, 5*(10), e260. doi: 10.1371/journal.pbio.0050260

Deouell, L. Y., Bentin, S., & Giard, M. H. (1998). Mismatch negativity in dichotic listening: Evidence for interhemispheric differences and multiple generators. *Psychophysiology, 35*(4), 355-365. doi: 10.1017/s0048577298970287

Di Russo, F., Martinez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping, 15*(2), 95-111. doi: 10.1002/hbm.10010

Di Russo, F., Pitzalis, S., Spitoni, G., Aprile, T., Patria, F., Spinelli, D., & Hillyard, S. A. (2005). Identification of the neural sources of the pattern-reversal VEP. *Neuroimage, 24*(3), 874-886. doi: 10.1016/j.neuroimage.2004.09.029

Dorey, S. E., Neveu, M. M., Burton, L. C., Sloper, J. J., & Holder, G. E. (2003). The clinical features of albinism and their correlation with visual evoked potentials. *British Journal of Ophthalmology, 87*(6), 767-772.

Dragoi, V. (1997). Visual Processing: Cortical Pathways. In J. H Byrne (Ed.), Neuroscience Online: An Electronic Textbook for the Neurosciences. Houston: Department of Neurobiology and Anatomy, The University of Texas Medical School at Houston (UTHealth). Retrieved from http://nba.uth.tmc.edu/neuroscience/.

Duncan, C. C., Barry, R. J., Connolly, J.F., Fischer, C., Michie, P. T., Näätänen, R., Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120*(11), 1883-1908.

Enns, James T., & Di Lollo, Vincent. (2000). What's new in visual masking? *Trends in Cognitive Sciences, 4*(9), 345-352.

Farrell, D. F., Leeman, S., & Ojemann, G. A. (2007). Study of the human visual cortex: Direct cortical evoked potentials and stimulation. *Journal of Clinical Neurophysiology, 24*(1), 1-10. doi: 10.1097/WNP.0b013e31802fb614

Felleman, D. J., & Van Essen, D. C. (1991). Distributed Hierarchical Processing in the Primate Cerebral Cortex. *Cerebral Cortex, 1*(1), 1-47. doi: 10.1093/cercor/1.1.1

Flynn, M., Liasis, A., Gardner, M., Boyd, S., & Towell, T. (2009). Can illusory deviant stimuli be used as attentional distractors to record vMMN in a passive three stimulus oddball paradigm? *Experimental Brain Research, 197*(2), 153-161. doi: 10.1007/s00221-009-1901-7

Flynn, M., Thompson, D., & Liasis, A. (2006). *Towards subliminal stimulation in paediatric electrodiagnositcs*. Paper presented at the British Society for Clinical Electrophyisiology of Vision (BriSCEV), Fontevraud Abbey, France.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: A review. *Psychophysiology, 45*(1), 152-170. doi: 10.1111/j.1469-8986.2007.00602.x

Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society B-Biological Sciences, 360*(1456), 815-836.

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience, 11*(2), 127-138. doi: 10.1038/nrn2787

Fu, Shimin, Fan, Silu, & Chen, Lin. (2003). Event-related potentials reveal involuntary processing of orientation changes in the visual modality. *Psychophysiology, 40*(5), 770-775.

Garrido, Marta I., Kilner, James M., Stephan, Klaas E., & Friston, Karl J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology, 120*(3), 453-463.

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication - Does the corpus callosum enable the human condition? *Brain, 123*, 1293-1326. doi: 10.1093/brain/123.7.1293

Giard, M. H., Lavikainen, J., Reinikainen, K., Perrin, F., Bertrand, O., Pernier, J., & Näätänen, R. (1995). Separate representation of stimulus frequency, intensity, and duration in auditory sensory memory - an event-related potential and dipole-model analysis. *Journal of Cognitive Neuroscience, 7*(2), 133-143. doi: 10.1162/jocn.1995.7.2.133

Good, W. V. (2001). Development of a quantitative method to measure vision in children with chronic cortical visual impairment. *Transactions of the American Ophthalmological Society, 99*.

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences, 15*(1), 20-25. doi: 10.1016/0166-2236(92)90344-8

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., . . . Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of Neuroengineering and Rehabilitation, 5*. doi: 10.1186/1743-0003-5-25

Gronskov, K., Ek, J., & Brondum-Nielsen, K. (2007). Oculocutaneous albinism. *Orphanet Journal of Rare Diseases, 2*. doi: 10.1186/1750-1172-2-43

Guillery, R. W. (1996). Why do albinos and other hypopigmented mutants lack normal binocular vision, and what else is abnormal in their central visual pathways? *Eye, 10*, 217-221.

Guillery, R. W., & Kaas, J. H. (1971). Study of normal and congenitally abnormal retinogeniculate projections in cats. *Journal of Comparative Neurology, 143*(1), 73-99. doi: 10.1002/cne.901430106

Guillery, R. W., Okoro, A. N., & Witkop, C. J. (1975). Abnormal Visual Pathways in Brain of a Human Albino. *Brain Research, 96*(2), 373-377.

Guthrie, D., & Buchwald, J. S. (1991). Significance Testing of Difference Potentials. *Psychophysiology, 28*(2), 240-244.

Hagen, G. F., Gatherwright, J. R., Lopez, B. A., & Polich, J. (2006). P3a from visual stimuli: Task difficulty effects. *International Journal of Psychophysiology, 59*(1), 8-14.

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Liegeois, C., Chauvel, P., & Musolino, A. (1995). Intracerebral Potentials to Rare Target and Distracter Auditory and Visual-Stimuli .1. Superior Temporal Plane and Parietal Lobe. *Electroencephalography and Clinical Neurophysiology, 94*(3), 191-220.

Halgren, E., Dale, A. M., Mendola, J., & Chong, C.D. R. (2003). Cortical activation to illusory shapes as measured with magnetoencephalography. *Neuroimage, 18*(4), 1001-1009.

Halgren, E., Marinkovic, K., & Chauvel, P. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalography and Clinical Neurophysiology, 106*(2), 156-164.

Hamalainen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography - Theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65*(2), 413-497. doi: 10.1103/RevModPhys.65.413

Hamblion, E. L., Moore, A. T., Rahi, J. S., & British Childhood Onset, Hereditary. (2012). Incidence and patterns of detection and management of childhood-onset hereditary retinal disorders in the UK. *British Journal of Ophthalmology, 96*(3), 360-365. doi: 10.1136/bjo.2010.201178

Hari, R., Hamalainen, M., Ilmoniemi, R., Kaukoranta, E., Reinikainen, K., Salminen, J., Alho, K., Naatanen, R. & Sams, M. (1984). Responses of the primary auditory-cortex to pitch changes in a sequence of tone pips - neuromagnetic recordings in man. *Neuroscience Letters, 50*(1-3), 127-132. doi: 10.1016/0304-3940(84)90474-9

Haroush, K., Hochstein, S., & Deouell, L. Y. (2010). Momentary Fluctuations in Allocation of Attention: Cross-modal Effects of Visual Task Load on Auditory Discrimination. *Journal of Cognitive Neuroscience, 22*(7), 1440-1451. doi: 10.1162/jocn.2009.21284

Hashiguchi, K., Morioka, T., Yoshida, F., Miyagi, Y., Nagata, S., Sakata, A., & Sasaki, T. (2007). Correlation between scalp-recorded

electroencephalographic and electrocorticographic activities during ictal period. *Seizure-European Journal of Epilepsy, 16*(3), 238-247. doi: 10.1016/j.seizure.2006.12.010

Heslenfeld, D.J. (2003). Visual Mismatch Negativity. In J. Polich (Ed.), *Detection of Change: Event-Related Potential and fMRI Findings* (pp. 41-60). Boston / Dordrecht / New York / London: Kluwer Academic Publishers.

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 353*(1373), 1257-1270. doi: 10.1098/rstb.1998.0281

Hirsch, J., Delapaz, R. L., Relkin, N. R., Victor, J., Kim, K., Li, T., Bordent, P., Rubin, N. & Shapley, R. (1995). Illusory contours activate specific regions in human visua- cortex - evidence from Functional Magnetic Resonance Imaging. *Proceedings of the National Academy of Sciences of the United States of America, 92*(14), 6469-6473. doi: 10.1073/pnas.92.14.6469

Hoffmann, M. B., Lorenz, B., Morland, A. B., & Schmidtborn, L. C. (2005). Misrouting of the optic nerves in albinism: Estimation of the extent with visual evoked potentials. *Investigative Ophthalmology and Visual Science, 46*(10), 3892-3898. doi: 10.1167/iovs.05-0491

Hoffmann, M. B., Tolhurst, D. J., Moore, A. T., & Morland, A. B. (2003). Organization of the visual cortex in human albinism. *Journal of Neuroscience, 23*(26), 8921-8930.

Hohwy, Jakob. (2012). Attention and conscious perception in the hypothesis testing brain. *Frontiers in Psychology, 3*, 96. doi: 10.3389/fpsyg.2012.00096

Hopf, J. M., Vogel, E., Woodman, G., Heinze, H. J., & Luck, S. J. (2002). Localizing visual discrimination processes in time and space. *Journal of Neurophysiology, 88*(4), 2088-2095. doi: 10.1152/jn.00860.2001

Hruby, T., & Marsalek, P. (2003). Event-Related Potentials - the P3 Wave. *Acta Neurobiologiae Experimentalis, 63*(1), 55-63.

Hsieh, P. J., & Colas, J. T. (2012). Awareness Is Necessary for Extracting Patterns in Working Memory but Not for Directing Spatial Attention.

Journal of Experimental Psychology-Human Perception and Performance, 38(5), 1085-1090. doi: 10.1037/a0028345

Hudnell, H. K., Boyes, W. K., & Otto, D. A. (1990). Stationary pattern adaptation and the early components in human visual evoked-potentials. *Electroencephalography and Clinical Neurophysiology, 77*(3), 190-198. doi: 10.1016/0168-5597(90)90037-e

James, C. R., & Jeffreys, D. A. (1975). Properties of individual components of pattern-onset evoked-potentials in man. *Journal of Physiology-London, 249*(1), P57-P58.

Jasper, H.H. (1958). The ten twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10*(371-377).

Jeffreys, D. A. (1977). The physiological significance of pattern visual evoked potentials. In J.E. Desmedt (Ed.), *Visual Evoked Potentials (Clinical Neurophysiology Updates)* (pp. 134-167). Oxford: Clarendon Press.

Jeffreys, D. A., & Axford, J. G. (1972a). Source locations of pattern-specific components of human visual evoked-potentials .1. Component of striate cortical origin. *Experimental Brain Research, 16*(1), 1-21.

Jeffreys, D. A., & Axford, J. G. (1972b). Source locations of pattern-specific components of human visual evoked-potentials .2. Component of extrastriate cortical origin. *Experimental Brain Research, 16*(1), 22-40.

Kaiser, D. A. (2005). Basic principles of quantitative EEG. *Journal of Adult Development, 12*(2-3), 99-104. doi: 10.1007/s10804-005-7025-9

Kaiser, Jochen, Bühler, Mira, & Lutzenberger, Werner. (2004). Magnetoencephalographic gamma-band responses to illusory triangles in humans. *Neuroimage, 23*(2), 551-560.

Kane, N. M., Curry, S. H., Rowlands, C. A., Manara, A. R., Lewis, T., Moss, T., Butler, S. R. (1996). Event related potentials - Neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Medicine, 22*(1), 39-46. doi: 10.1007/bf01728329

Kanizsa, Gaetano. (1976). Subjective contours. *Scientific American, 234*(4), 48-52.

Kenemans, J. Leon, Jong, Tineke Grent-'t, & Verbaten, Marinus N. (2003). Detection of visual change: Mismatch or rareness? *Neuroreport: For Rapid Communication of Neuroscience Research*, Neurorepor-1242.

Kimura, M. (2012). Visual mismatch negativity and unintentional temporal-context-based prediction in vision. *International Journal of Psychophysiology, 83*(2), 144-155. doi: 10.1016/j.ijpsycho.2011.11.010

Kimura, M., Katayama, J., & Murohashi, H. (2006). Independent processing of visual stimulus changes in ventral and dorsal stream features indexed by an early positive difference in event-related brain potentials. *International Journal of Psychophysiology, 59*(2), 141-150.

Kimura, M., Katayama, J., Ohira, H., & Schroger, E. (2009). Visual mismatch negativity: New evidence from the equiprobable paradigm. *Psychophysiology, 46*(2), 402-409. doi: 10.1111/j.1469-8986.2008.00767.x

Kimura, M., Kondo, H., Ohira, H., & Schroger, E. (2012). Unintentional Temporal Context-Based Prediction of Emotional Faces: An Electrophysiological Study. *Cerebral Cortex, 22*(8), 1774-1785. doi: 10.1093/cercor/bhr244

Kimura, M., Murohashi, H., & Katayama, J. (2006). An ERP study of visual change detection: Effects of magnitude of spatial frequency changes on the change-related posterior positivity. *International Journal of Psychophysiology, 62*(1), 14-23.

Kimura, M., Ohira, H., & Schroger, E. (2010). Localizing sensory and cognitive systems for pre-attentive visual deviance detection: An sLORETA analysis of the data of Kimura et al. (2009). *Neuroscience Letters, 485*(3), 198-203. doi: 10.1016/j.neulet.2010.09.011

Kimura, M., Schroger, E., & Czigler, I. (2011). Visual mismatch negativity and its importance in visual cognitive sciences. *Neuroreport, 22*(14), 669-673. doi: 10.1097/WNR.0b013e32834973ba

Knight, R. T., Hillyard, S. A., Woods, D. L., & Neville, H. J. (1980). The effects of frontal and temporal-parietal lesions on the auditory evoked-potential in man. *Electroencephalography and Clinical Neurophysiology, 50*(1-2), 112-124. doi: 10.1016/0013-4694(80)90328-4

Koch, C., & Tsuchiya, N. (2007). Attention and consciousness: two distinct brain processes. *Trends in Cognitive Sciences, 11*(1), 16-22. doi: 10.1016/j.tics.2006.10.012

Kogai, T., Aoyama, A., Amano, K., & Takeda, T. (2011). Visual mismatch response evoked by a perceptually indistinguishable oddball. *Neuroreport, 22*(11), 535-538. doi: 10.1097/WNR.0b013e328348ab76

Koivisto, M., Kainulainen, P., & Revonsuo, A. (2009). The relationship between awareness and attention: Evidence from ERP responses. *Neuropsychologia, 47*(13), 2891-2899. doi: 10.1016/j.neuropsychologia.2009.06.016

Koivisto, M., & Revonsuo, A. (2010). Event-related brain potential correlates of visual awareness. *Neuroscience and Biobehavioral Reviews, 34*(6), 922-934.

Koivisto, M., Revonsuo, A., & Lehtonen, M. (2006). Independence of visual awareness from the scope of attention: An electrophysiological study. *Cerebral Cortex, 16*(3), 415-424. doi: 10.1093/cercor/bhi121

Koivisto, M., Revonsuo, A., & Salminen, N. (2005). Independence of visual awareness from attention at early processing stages. *Neuroreport, 16*(8), 817-821. doi: 10.1097/00001756-200505310-00008

Komatsu, H., & Goda, N. (2009). Color Information Processing in Higher Brain Areas. In A. Tremeau, R. Schettini & S. Tominaga (Eds.), *Computational Color Imaging* (Vol. 5646, pp. 1-11). Berlin: Springer-Verlag Berlin.

Korshunova, S. G. (1999). Visual evoked potentials induced by illusory outlines (Kanizsa's square). *Neuroscience and Behavioral Physiology*, Neuroscien-Dec.

Kraus, N., Sharma, A., McGee, T., & Carrell, T. D. (1995). Neurophysiologic bases of speech discrimination. *Ear and Hearing, 16*(1), 19-37.

Kremlacek, J., Kuba, M., Kubova, Z., & Langrova, J. (2006). Visual mismatch negativity elicited by magnocellular system activation. *Vision Research, 46*(4), 485-490.

Kujala, T., Tervaniemi, M., & Schroger, E. (2007). The mismatch negativity in cognitive and clinical neuroscience: Theoretical and methodological considerations. *Biological Psychology, 74*(1), 1-19. doi: 10.1016/j.biopsycho.2006.06.001

Kukleta, M., Brazdil, M., Roman, R., & Jurak, P. (2003). Identical event-related potentials to target and frequent stimuli of visual oddball task recorded by intracerebral electrodes. *Clinical Neurophysiology, 114*(7), 1292-1297.

Kutzbach, B. R., Summers, C. G., Holleschau, A. M., & MacDonald, J. T. (2008). Neurodevelopment in children with albinism. *Ophthalmology, 115*(10), 1805-1808. doi: 10.1016/j.ophtha.2008.03.006

Larsson, J., Amunts, K., Gulyas, B., Malikovic, A., Zilles, K., & Roland, P. E. (1999). Neuronal correlates of real and illusory contour perception: functional anatomy with PET. *European Journal of Neuroscience, 11*(11), 4024-4036. doi: 10.1046/j.1460-9568.1999.00805.x

Lau, H. C., & Passingham, R. E. (2006). Relative blindsight in normal observers and the neural correlate of visual consciousness. *Proceedings of the National Academy of Sciences of the United States of America, 103*(49), 18763-18768. doi: 10.1073/pnas.0607716103

Lavail, J. H., Nixon, R. A., & Sidman, R. L. (1978). Genetic-control of retinal ganglion-cell projections. *Journal of Comparative Neurology, 182*(3), 399-421. doi: 10.1002/cne.901820304

Levanen, S., Ahonen, A., Hari, R., McEvoy, L., & Sams, M. (1996). Deviant auditory stimuli activate human left and right auditory cortex differently. *Cerebral Cortex, 6*(2), 288-296. doi: 10.1093/cercor/6.2.288

Levin, C. S., & Hoffman, E. J. (1999). Calculation of positron range and its effect on the fundamental limit of positron emission tomography system spatial resolution. *Physics in Medicine and Biology, 44*(3), 781-799. doi: 10.1088/0031-9155/44/3/019

Liasis, A., Towell, A., Alho, K., & Boyd, S. (2001). Intracranial identification of an electric frontal-cortex response to auditory stimulus change: A case study. *Cognitive Brain Research*(2), 227-233

Liasis, A., Towell, A., & Boyd, S. (1999). Intracranial auditory detection and discrimination potentials as substrates of echoic memory in children. *Cognitive Brain Research, 7*(4), 503-506. doi: 10.1016/s0926-6410(98)00049-4

Liasis, A., Towell, A., & Boyd, S. (2000). Intracranial evidence for differential encoding of frequency and duration discrimination responses. *Ear and Hearing, 21*(3), 252-256. doi: 10.1097/00003446-200006000-00009

Lin, Z. C., & He, S. (2009). Seeing the invisible: The scope and limits of unconscious processing in binocular rivalry. *Progress in Neurobiology, 87*(4), 195-211. doi: 10.1016/j.pneurobio.2008.09.002

Luck, S. J. (2005). *An introduction to the Event Related Potential Technique*. Cambridge, MA: MIT Press.

Lund, R. D. (1965). Uncrossed Visual Pathways of Hooded and Albino Rats. *Science (New York, N.Y.), 149*(3691), 1506-1507. doi: 10.1126/science.149.3691.1506

Maekawa, T., Taniwaki, T., Kinukawa, N., Kanba, S., Goto, Y., & Tobimatsu, S. (2005). Functional characterization of mismatch negativity to a visual stimulus. *Clinical Neurophysiology, 116*(10), 2392-2402.

Maekawa, T., Tobimatsu, S., Ogata, K., Onitsuka, T., & Kanba, S. (2009). Preattentive visual change detection as reflected by the mismatch negativity (MMN)-Evidence for a memory-based process. *Neuroscience Research, 65*(1), 107-112. doi: 10.1016/j.neures.2009.06.005

Mangun, G.R. (1995). Neural Mechanisms of visual selective attention. *Psychophysiology, 32*(1), 4-18. doi: 10.1111/j.1469-8986.1995.tb03400.x

Mangun, G.R., Hillyard, S. A., & Luck, S. J. (1993). Electrocortical substrates of visual selective attention. *Attention and Performance, 14*, 219-243.

Manresa, M. J., Bonaventura, I., Martinez, I., Gomez, L., & Aguilar, M. (1996). Voluntary changes of visual evoked potentials in cases with hysteria and/or simulation. [Alteracion voluntaria de los potenciales evocados visuales (VEP) en casos de histeria y/o simulacion.]. *Revista de Neurología, 24*(127), 285-286.

Martinez, A., Anllo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., Wong, E.C., Hinrichs, H., Heinze, H.J. & Hillyard, S. A. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience, 2*(4), 364-369.

Martinez, A., Di Russo, F., Anllo-Vento, L., & Hillyard, S. A. (2001). Electrophysiological analysis of cortical mechanisms of selective attention to high and low spatial frequencies. *Clinical Neurophysiology, 112*(11), 1980-1998. doi: 10.1016/s1388-2457(01)00660-5

Martinez, A., DiRusso, F., Anllo-Vento, L., Sereno, M. I., Buxton, R. B., & Hillyard, S. A. (2001). Putting spatial attention on the map: timing and localization of stimulus selection processes in striate and extrastriate visual areas. *Vision Research, 41*(10-11), 1437-1457. doi: 10.1016/s0042-6989(00)00267-4

Mathewson, K. E., Gratton, G., Fabiani, M., Beck, D. M., & Ro, T. (2009). To See or Not to See: Prestimulus alpha Phase Predicts Visual Awareness. *Journal of Neuroscience, 29*(9), 2725-2732. doi: 10.1523/jneurosci.3963-08.2009

Mazza, V., Turatto, M., & Sarlo, M. (2005). Rare stimuli or rare changes: What really matters for the brain? *Neuroreport: For Rapid Communication of Neuroscience Research*, Neurorepor-1064.

Merikle, P. M., & Cheesman, J. (1986). Consciousness is a subjective state. *Behavioral and Brain Sciences, 9*(1), 42-42.

Meyer-Lindenberg, A. (2010). From maps to mechanisms through neuroimaging of schizophrenia. *Nature, 468*(7321), 194-202. doi: 10.1038/nature09569

Murray, M. M., Wylie, G. R., Higgins, B. A., Javitt, D. C., Schroeder, C. E., & Foxe, J. J. (2002). The spatiotemporal dynamics of illusory contour processing: Combined high-density electrical mapping, source analysis, and functional magnetic resonance imaging. *Journal of Neuroscience, 22*(12), 5055-5073.

Naatanen, R. (2001). The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). *Psychophysiology, 38*(1), 1-21. doi: 10.1017/s0048577201000208

Näätänen, R. (1988). Implications of ERP data for psychological theories of attention. *Biological Psychology, 26*(1-3), 117-163. doi: 10.1016/0301-0511(88)90017-8

Näätänen, R. (1990a). The role of attention in auditory information-processing as revealed by event-related potentials and other brain measures of cognitive function. *Behavioral and Brain Sciences, 13*(2), 201-232.

Näätänen, R. (1990b). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behavioral and Brain Sciences, 13*, 201-288.

Näätänen, R. (1992). The Mismatch Negativity *Attention and Brain Function* (pp. 136-200). Hillsdale, NJ: Lawrence Erlbaum.

Näätänen, R. (2000). Mismatch negativity (MMN): perspectives for application. *International Journal of Psychophysiology, 37*(1), 3-10. doi: 10.1016/s0167-8760(00)00091-x

Näätänen, R. (2003). Mismatch negativity: Clinical research and possible applications. *International Journal of Psychophysiology, 48*(2), 179-188.

Näätänen, R. (2009). Somatosensory mismatch negativity: a new clinical tool for developmental neurological research? *Developmental Medicine and Child Neurology, 51*(12), 930-931.

Näätänen, R., & Escera, C. (2000). Mismatch negativity: clinical and other applications. *Audiology and Neuro-Otology, 5*(3-4), 105-110.

Näätänen, R., Gaillard, A. W. K., & Mantysalo, S. (1978). Early selective-attention effect on evoked-potential reinterpreted. *Acta Psychologica, 42*(4), 313-329. doi: 10.1016/0001-6918(78)90006-9

Näätänen, R., Jacobsen, T., & Winkler, I. (2005). Memory-based or afferent processes in mismatch negativity (MMN): A review of the evidence. *Psychophysiology, 42*(1), 25-32. doi: 10.1111/j.1469-8986.2005.00256.x

Näätänen, R., Kujala, T., Escera, C., Baldeweg, T., Kreegipuu, K., Carlson, S., & Ponton, C. (2012). The mismatch negativity (MMN) - A unique window to disturbed central auditory processing in ageing and different clinical conditions. *Clinical Neurophysiology, 123*(3), 424-458. doi: 10.1016/j.clinph.2011.09.020

Näätänen, R., Kujala, T., & Winkler, I. (2011). Auditory processing that leads to conscious perception: A unique window to central auditory processing opened by the mismatch negativity and related responses. *Psychophysiology, 48*(1), 4-22. doi: 10.1111/j.1469-8986.2010.01114.x

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clinical Neurophysiology, 118*(12), 2544-2590.

Neumann, O., Vanderheijden, A. H. C., & Allport, D. A. (1986). Visual selective attention - introductory remarks. *Psychological Research-Psychologische Forschung, 48*(4), 185-188. doi: 10.1007/bf00309082

Nielsenbohlman, L., Knight, R. T., Woods, D. L., & Woodward, K. (1991). Differential auditory processing continues during sleep. *Electroencephalography and Clinical Neurophysiology, 79*(4), 281-290. doi: 10.1016/0013-4694(91)90124-m

Odom, J. V., Bach, M., Brigell, M., Holder, G. E., McCulloch, D. L., Tormene, A. P., & Vaegan. (2010). ISCEV standard for clinical visual evoked

potentials (2009 update). *Documenta Ophthalmologica, 120*(1), 111-119. doi: 10.1007/s10633-009-9195-4

Paavilainen, Petri. (2013). The mismatch-negativity (MMN) component of the auditory event-related potential to violations of abstract regularities: A review. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 88*(2), 109-123. doi: 10.1016/j.ijpsycho.2013.03.015

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science, 292*(5516), 510-512. doi: 10.1126/science.1057099

Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details. *Methods and Findings in Experimental and Clinical Pharmacology, 24*, 5-12.

Pazo-Alvarez, P., Cadaveira, F., & Amenedo, E. (2003). MMN in the visual modality: a review. *Biological Psychology, 63*(3), 199-236.

Picton, T.W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., . . . Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology, 37*(2), 127-152.

Picton, T.W., Lins, O., & & Scherg, M. . (1995). The recording and analysis of event-related potentials *In F. Boller & J. Grafman (Series Eds.), & R. Johnson, Jr (Section Ed), Handbook of neuropsychology. Event-related brain potentials and cognition* (Vol. 10, pp. 3-73).

Picton, T.W., Ritter, W., Achim, A., Alain, C., & Otten, L. (2000). Mismatch negativity: different water in the same river. *Audiology and Neuro-Otology, 5*(3-4), 111-139.

Pins, D., & Ffytche, D. (2003). The neural correlates of conscious vision. *Cerebral Cortex, 13*(5), 461-474. doi: 10.1093/cercor/13.5.461

Polich, J. (2003). Theoretical overview of P3a and P3b. In J. Polich (Ed.), *Detection of Change: Event-Related Potential and fMRI Findings* (pp. 83-98). Dordrecht, Netherlands: Kluwer Academic Publishers.

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128-2148.

Polich, J., & Comerchero, M. D. (2003). P3a from visual stimuli: Typicality, task, and topography. *Brain Topography, 15*(3), 141-152.

Pott, J. W. R., Jansonius, N. M., & Kooijman, A. C. (2003). Chiasmal coefficient of flash and pattern visual evoked potentials for detection of chiasmal misrouting in albinism. *Documenta Ophthalmologica, 106*(2), 137-143.

Poynter, W., & Roberts, C. (2012). Hemispheric asymmetries in visual search. *Laterality, 17*(6), 711-726. doi: 10.1080/1357650x.2011.626558

Proverbio, A., Del Zotto, Marzia, & Zani, Alberto. (2010). Electrical neuroimaging evidence that spatial frequency-based selective attention affects V1 activity as early as 40-60 ms in humans. *BMC Neuroscience, 11*. doi: 10.1186/1471-2202-11-59

Proverbio, A., & Zani, Alberto. (2002). Electrophysiological indexes of illusory contours perception in humans. *Neuropsychologia*(5), 479-491.

Railo, H., Koivisto, M., & Revonsuo, A. (2011). Tracking the processes behind conscious perception: A review of event-related potential correlates of visual consciousness. *Consciousness and Cognition, 20*(3), 972-983.

Rao, R. P. N., & Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature Neuroscience, 2*(1), 79-87. doi: 10.1038/4580

Rauss, K., Schwartz, S., & Pourtois, G. (2011). Top-down effects on early visual processing in humans: A predictive coding framework. *Neuroscience and Biobehavioral Reviews, 35*(5), 1237-1253. doi: 10.1016/j.neubiorev.2010.12.011

Restuccia, D., Zanini, S., Cazzagon, M., Del Piero, I., Martucci, L., & Della Marca, G. (2009). Somatosensory mismatch negativity in healthy children. *Developmental Medicine and Child Neurology, 51*(12), 991-998. doi: 10.1111/j.1469-8749.2009.03367.x

Restuccia, Domenico, Rubino, Marco, Marra, Camillo, Valeriani, Massimiliano, & Della Marca, Giacomo. (2005). Attentional load of the primary task influences the frontal but not the temporal generators of mismatch negativity. *Brain Research: Cognitive Brain Research, 25*(3), 891-899.

Rinne, T., Alho, K., Ilmoniemi, R. J., Virtanen, J., & Näätänen, R. (2000). Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage, 12*(1), 14-19. doi: 10.1006/nimg.2000.0591

Rinne, T., Gratton, G., Fabiani, M., Cowan, N., Maclin, E., Stinard, A.,Sinkkonen, J. & Näätänen, R. (1999). Scalp-recorded optical signals

make sound processing in the auditory cortex visible. *Neuroimage, 10*(5), 620-624. doi: 10.1006/nimg.1999.0495

Rissling, A. J., Park, S. H., Young, J. W., Rissling, M. B., Sugar, C. A., Sprock, J., Mathias, D.J., Pela, M., Sharp, R.F., Braff, D.L. & Light, G. A. (2013). Demand and modality of directed attention modulate "pre-attentive" sensory processes in schizophrenia patients and nonpsychiatric controls. *Schizophrenia Research, 146*(1-3), 326-335. doi: 10.1016/j.schres.2013.01.035

Ritzl, A., Marshall, J. C., Weiss, P. H., Zafiris, O., Shah, N. J., Zilles, K., & Fink, G. R. (2003). Functional anatomy and differential time courses of neural processing for explicit, inferred, and illusory contours - An event-related fMRI study. *Neuroimage, 19*(4), 1567-1577. doi: 10.1016/s1053-8119(03)00180-0

Roman, Robert, Brazdil, Milan, Jurak, Pavel, Rektor, Ivan, & Kukleta, Miloslav. (2005). Intracerebral P3-like waveforms and the length of the stimulus-response interval in a visual oddball paradigm. *Clinical Neurophysiology, 116*(1), 160-171.

Rompelman, O., & Ros, H. H. (1986). Coherent Averaging Techniqe - A Tutorial Review .1. Noise-reduction and the equivalent filter. *Journal of Biomedical Engineering, 8*(1), 24-29. doi: 10.1016/0141-5425(86)90026-9

Rosburg, T., Korzyukov, O. A., Elger, C. E., Boutros, N. N., Trautner, P, Dietl, T., Korzyukov, O.A., Boutros, N.N., Schaller, C., Elger, C.E. & Kurthen, M. (2005). Subdural recordings of the mismatch negativity (MMN) in patients with focal epilepsy. *Brain, 128*(Pt4), 819-828.

Sams, M., Paavilainen, P., Alho, K., & Näätänen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalography and Clinical Neurophysiology, 62*(6), 437-448. doi: 10.1016/0168-5597(85)90054-1

Sanderson, K. J. (1975). Retinogeniculate projections in rabbits of albino allelomorphic series. *Journal of Comparative Neurology, 159*(1), 15-27. doi: 10.1002/cne.901590103

Schankin, A., & Wascher, E. (2007). Electrophysiological correlates of stimulus processing in change blindness. *Experimental Brain Research, 183*(1), 95-105. doi: 10.1007/s00221-007-1023-z

Scherg, M., Vajsar, J., & Picton, T. W. (1989). A source analysis of the late human auditory evoked potentials. *Journal of Cognitive Neuroscience, 1*(4). doi: 10.1162/jocn.1989.1.4.336

Schröger, E., Giard, M. H., & Wolff, C. (2000). Auditory distraction: event-related potential and behavioral indices. *Clinical Neurophysiology, 111*(8), 1450-1460.

Schröger, E., & Wolff, C. (1998). Attentional orienting and reorienting is indicated by human event-related brain potentials. *Neuroreport, 9*(15), 3355-3358.

Schroger, Erich. (1998). Measurement and interpretation of the mismatch negativity. *Behavior Research Methods, 30*(1), 131-145. doi: 10.3758/bf03209423

Seghier, M. L., & Vuilleumier, P. (2006). Functional neuroimaging findings on the human perception of illusory contours. *Neuroscience and Biobehavioral Reviews, 30*(5), 595-612. doi: 10.1016/j.neubiorev.2005.11.002

Senkowski, Daniel, Rottger, Stefan, Grimm, Sabine, Foxe, John J., & Herrmann, Christoph S. (2005). Kanizsa subjective figures capture visual spatial attention: Evidence from electrophysiological and behavioral data. *Neuropsychologia, 43*(6), 872-886.

Shapiro, K. L., Arnell, K. M., & Raymond, J. E. (1997). The attentional blink. *Trends in Cognitive Sciences, 1*(8), 291-296. doi: 10.1016/s1364-6613(97)01094-2

Shevrin, H. (2001). Event-related markers of unconscious processes. *International Journal of Psychophysiology, 42*(2), 209-218.

Simson, R., Vaughan, H. G., & Ritter, W. (1977). Scalp topography of potentials in auditory and visual discrimination tasks. *Electroencephalography and Clinical Neurophysiology, 42*(4), 528-535. doi: 10.1016/0013-4694(77)90216-4

Snodgrass, M., Bernat, E., & Shevrin, H. (2004). Unconscious perception: A model-based approach to method and evidence. *Perception and Psychophysics, 66*(5), 846-867. doi: 10.3758/bf03194978

Soong, F., Levin, A. V., & Westall, C. A. (2000). Comparison of techniques for detecting visually evoked potential asymmetry in albinism. *Journal of AAPOS, 4*(5), 302-310. doi: 10.1067/mpa.2000.107901

Spackman, L. A., Boyd, S. G., & Towell, A. (2007). Effects of stimulus frequency and duration on somatosensory discrimination responses. *Experimental Brain Research, 177*(1), 21-30. doi: 10.1007/s00221-006-0650-0

Spackman, L. A., Towell, A., & Boyd, S. G. (2010). Somatosensory discrimination: An intracranial event-related potential study of children with refractory epilepsy. *Brain Research, 1310*, 68-76. doi: 10.1016/j.brainres.2009.10.072

Stagg, C., Hindley, P., Tales, A., & Butler, S. (2004). Visual mismatch negativity: The detection of stimulus change. *Neuroreport, 15*(4), 659-663.

Stefanics, G., Kimura, M., & Czigler, I. (2011). Visual mismatch negativity reveals automatic detection of sequential regularity violation. *Frontiers in Human Neuroscience, 5*, 9. doi: 4610.3389/fnhum.2011.00046

Tales, A., Newton, P., Butler, S. R., Troscianko, T., & Wilcock, G. K. (2002). Age-related changes in the preattentional detection of visual change. *Neuroreport, 13*(7), 969-972.

Tales, A., Newton, P., Troscianko, T., & Butler, S. (1999). Mismatch negativity in the visual modality. *Neuroreport, 10*(16), 3363-3367.

Treisman, A. (1991). Search, similarity, and integration of features between and within dimensions. *Journal of Experimental Psychology-Human Perception and Performance, 17*(3), 652-676. doi: 10.1037/0096-1523.17.3.652

Treisman, A., & Gelade, G. (1980). Feature-integration theory of attention. *Cognitive Psychology, 12*(1), 97-136. doi: 10.1016/0010-0285(80)90005-5

Tse, P. U., Martinez-Conde, S., Schlegel, A. A., & Macknik, S. L. (2005). Visibility, visual awareness, and visual masking of simple unattended targets are confined to areas in the occipital cortex beyond human V1/V2. *Proceedings of the National Academy of Sciences of the United States of America, 102*(47), 17178-17183. doi: 10.1073/pnas.0508010102

Urakawa, T., Inui, K., Yamashiro, K., & Kakigi, R. (2010). Cortical dynamics of the visual change detection process. *Psychophysiology, 47*(5), 905-912.

Urakawa, T., Inui, Koji, Yamashiro, Koya, Tanaka, Emi, & Kakigi, Ryusuke. (2010). Cortical dynamics of visual change detection based on sensory memory. *Neuroimage, 52*(1), 302-308.

Vogel, E. K., & Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology, 37*(2), 190-203. doi: 10.1111/1469-8986.3720190

Wallach, Hans, & Slaughter, Virginia. (1988). The role of memory in perceiving subjective contours. *Perception and Psychophysics, 43*(2), 101-106.

Wilenius-Emet, Maria, Revonsuo, Antti, & Ojanen, Ville. (2004). An electrophysiological correlate of human visual awareness. *Neuroscience Letters, 354*(1), 38-41.

Wilson, S. B., & Emerson, R. (2002). Spike detection: a review and comparison of algorithms. *Clinical Neurophysiology, 113*(12), 1873-1881. doi: 10.1016/s1388-2457(02)00297-3

Winkler, I., & Czigler, I. (2012). Evidence from auditory and visual event-related potential (ERP) studies of deviance detection (MMN and vMMN) linking predictive coding theories and perceptual object representations. *International Journal of Psychophysiology, 83*(2), 132-143. doi: 10.1016/j.ijpsycho.2011.10.001

Witkop, C. J. (1979). Albinism - hematalogic-storage disease, susceptibility to skin-cancer, and opticl neuronal defects share in all types of oculocutaneous and ocular albinism. *Alabama Journal of Medical Sciences, 16*(4), 327-330.

Woodman, G. F. (2010). A brief introduction to the use of event-related potentials in studies of perception and attention. *Attention Perception & Psychophysics, 72*(8), 2031-2046. doi: 10.3758/app.72.8.2031

Woodman, G. F., & Luck, S. J. (1999). Electrophysiological measurement of rapid shifts of attention during visual search. *Nature, 400*(6747), 867-869.

Yabe, H., Tervaniemi, M., Reinikainen, K., & Näätänen, R. (1997). Temporal window of integration revealed by MMN to sound omission. *Neuroreport, 8*(8), 1971-1974. doi: 10.1097/00001756-199705260-00035

Yucel, G., McCarthy, G., & Belger, A. (2007). fMRI reveals that involuntary visual deviance processing is resource limited. *Neuroimage, 34*(3), 1245-1252.

Yucel, G., Petty, C., McCarthy, G., & Belger, A. (2005). Visual task complexity modulates the brain's response to unattended auditory novelty. *Neuroreport, 16*(10), 1031-1036. doi: 10.1097/00001756-200507130-00001

Zeki, S. (1993). *A vision of the brain*. Oxford: Blackwell Scientific Publications.

Zeki, S. (2003). The disunity of consciousness. *Trends in Cognitive Sciences, 7*(5), 214-218. doi: 10.1016/s1364-6613(03)00081-0

Zeki, S. (2008). The disunity of consciousness *Models of Brain and Mind: Physical, Computational and Psychological Approaches* (Vol. 168, pp. 11-18). Amsterdam: Elsevier Science Bv.

APPENDICES

APPENDIX I

Participant Information Sheet: Experiment 3.1

A study of visual electrophysiological responses

The aim of the study: The aim of our study is to gather more information about how the eye and brain process visual input.

Why is this study being done?: This study is being done to provide information on very early cognitive processing within the visual system. Once we understand how early visual cognitive processing occurs within a healthy population we can develop tests that can be used for clinical populations.

How are the vision studies to be done?

- Small areas of the scalp will be cleaned with a slightly gritty soap on a cotton wool bud.
- Electrodes will be positioned on the head with a washable gel. This will take approximately 40 minutes. The electrodes detect brain waves linked with visual processing.
- You will be asked to sit on a chair in front of a computer screen.
- The lights in the room will be turned off. Black and white patterns will be shown on the computer screen and you will be asked to focus on a red dot in the centre of the screen. Data recording will take about an hour and a half and will be interspersed with short breaks – therefore the total participation time will be approximately two and a half hours.

The researcher will remain in the room whilst the tests are taking place to ensure that you are looking at the screen during the presentation.

Should you have any issues with any part of this research, or if there is anything about this research you wish to discuss, please contact Maria Flynn flynnm@westminster.ac.uk (Ext. 2181). You have the right not to participate. Should you choose to participate, you have the right to halt the trial and/or withdraw at any time. You do not have to give a reason.

APPENDIX II

Participant Information Sheet: Experiment 3.2

A study of visual electrophysiological responses

The aim of the study: The aim of our study is to gather more information about how the eye and brain process visual input.

Why is this study being done?: This study is being done to provide information on very early cognitive processing within the visual system. Once we understand how early visual cognitive processing occurs within a healthy population we can develop tests that can be used for clinical populations.

How are the vision studies to be done?

- Small areas of the scalp will be cleaned with a slightly gritty soap on a cotton wool bud.
- Electrodes will be positioned on the head with a washable cream. This will take approximately 40 to 50 minutes. The electrodes detect brain waves linked with visual processing.
- You will be asked to sit on a chair in front of a computer screen.
- The lights in the room will be turned off. Black and white patterns will be shown on the computer screen and you will be asked to focus on a red circle in the centre of the screen, when the dot changes to a square you will be asked to press a response pad button as quickly as possible. Data recording will take about one hour and will be interspersed with short breaks – therefore the total participation time will be approximately two hours.

The researcher will remain in the room whilst the tests are taking place to ensure that you are looking at the screen during the presentation.

Should you have any issues with any part of this research, or if there is anything about this research you wish to discuss, please contact Maria Flynn flynnm@westminster.ac.uk (Ext. 2181). You have the right not to participate. Should you choose to participate, you have the right to halt the trial and/or withdraw at any time. You do not have to give a reason.

APPENDIX III

Consent Form

CONSENT FORM AND AGREEMENT TO PARTICIPATE IN A STUDY OF ELECTROPHYSIOLOGICAL RESPONSES

All information provided for this study is being used for research purposes under the leadership of Professor Tony Towell, University of Westminster, 309 Regent Street, London, W1B 2UW

I understand that all the information provided by me will be kept confidential and will be stored in such a manner that no specific details will be linked to individuals.

Data will be stored on computers and on discs.

I understand that I will not get any individual feedback but that a summary of the findings will be available to me at a later stage.

I confirm that I have normal or corrected-to-normal vision Yes/No

I confirm that I have no history of neurological disease Yes/No

I confirm that I have received an information sheet and have been given an opportunity to ask questions about the study.

I understand that I am able to withdraw from this project at any time without having to provide an explanation.

Signed (participant)_____ date _____

Please print your name_____

Signed (researcher)_____ date _____

APPENDIX IV

Experiment 6.1 and 6.2 Statistical analysis of stimulus duration

To explore the effect of stimulus duration on the latency and peak-to-peak amplitude of the pattern appearance/disappearance VEP components revealed through the subtraction of the pattern reversal VEPs preceded by a checkerboard from the pattern reversal VEPs not preceded by a checkerboard stimulus, a one-way ANOVA with the factor stimulus duration (7 ms, 14 ms and 21 ms) was carried out for each component latency and peak-to-peak amplitude (CI, CII, CIII, CIV; baseline – CI, CI-CII, CII-CIII, CIII-CV).

For experiment 6.2, to establish whether a stable ERP response was present to the checkerboard stimulus emerging from the grey background stimulus across the different times, a one-way ANOVA with the factor duration (7 ms, 14 ms and 21 ms) was carried out for each pattern onset component latency and peak-to-peak amplitude (CI, CII, CIII, CIV; baseline to CI, CI-CII, CII-CIII, CIII-CIV).

Effect of duration checkerboard duration on the pattern appearance/ disappearance VEPs

For the pattern appearance/disappearance VEP components one-way ANOVAs were used to examine the latency (CI, CII, CIII and CIV) and peak-to-peak amplitudes (baseline –CI, CI-CII, CII-CIII, CIII-CIV) when the duration of the checkerboard was 7 ms, 14 ms and 21 ms.

One-way ANOVAs revealed that increasing the duration of the checkerboard stimulus reduced CI latency ($F(2, 30) = 43.544$, $p < 0.001$) and increased CIV latency $F(2, 30) = 5.346$, $p = 0.001$). T-tests showed that in the 21ms condition CI latency was significantly shorter than in the 14ms condition ($t=5.745$, $df=15$, $p<0.001$) and that in the 14ms condition ($t=4.362$, $df=15$, $p=0.001$) CI latency was significantly shorter than in the 7ms condition. T-tests showed that in the 7ms condition ($t=-2.654$, $df=15$, $p=0.018$) CIV latency was significantly longer than in the 14ms condition but CIV latency was not significantly different between the 14 and 21ms conditions ($t=--0.516$, $df=15$, $p=0.614$). There were no significant differences in CII latency ($F(1.058, 15.870) = 0.593$, $p = 0.462$) and CIII latency ($F(1.252, 18.785) = 2.929$, $p = 0.097$).

One-way ANOVAs were used to examine the effects of checkerboard stimulus duration on peak-to-peak amplitude. The amplitude of the baseline to CI was

not significantly different across the 3 checkerboard durations ($F(2,30) = 1.894$, $p = 0.168$). Increasing the duration of the checkerboard stimulus increased the amplitude of the CI-CII ($F(2,30) = 10.922$; $p < 0.001$). T-tests revealed that with the 14ms condition had a significantly greater amplitude than the 7ms condition (t=--5.377, df=15, p<0.001), but the 21ms condition although the amplitude was greater than the 14ms, this was not significant (t=--0.730, df=15, p=0.476). Increasing the duration of the checkerboard stimulus also increased the peak-to-peak CII-CIII amplitude ($F(2,30) = 34.524$; $p < 0.001$). In the 21ms condition there was a significantly greater amplitude than the 14ms condition (t=--2.724, df=15, p=0.016) and the 14ms condition having a significantly greater amplitude than the 7ms condition (t=--5.946, df=15, p<0.001). The same pattern was revealed for the CIII to CIV amplitude ($F(2,30) = 22.115$; $p < 0.001$) with the 21ms checkerboard duration condition showing a significantly greater amplitude than the 14ms condition (t=--3.931, df=15, p=0.001) and the 14ms condition having a significantly greater amplitude than in the 7ms condition than (t=--3.327, df=15, p=0.005).

Pattern appearance/ disappearance responses from grey background

Increasing the duration of the checkerboard stimulus reduced CI latency ($F(2,12) = 11.413$, $p = 0.002$, $\eta p2 = 6.55$). When the checkerboard was presented for 21ms CI latency was significantly shorter than when presented for 14ms (t=3.990, df=6, p=0.007). There was no significant difference in CI latency between the 14 and 7 ms conditions (t=-0.488, df=6, p=0.643). CII latency was reduced when checkerboard stimulus duration was increased ($F(2,12) = 21.802$, $P < 0.001$, $\eta p2 = 0.322$). Simple effects revealed that when the checkerboard was presented for 21ms CII latency was significantly shorter than when presented for 14ms (t=5.279, df=6, p=0.002). When the checkerboard was presented for 14ms, CII latency was significantly shorter than when presented for 7ms (t=2.788, df=6, p=0.032). There were no significant differences across checkerboard durations for CIII latency ($F(2,12) = 0.426$, $P = 0.662$, $\eta p2 = 0.066$) or for CIV latency ($F(2,12) = 2.856$, $p = 0.097$, $\eta p2 = 0.322$). The peak-to-peak amplitudes were not significantly different across all checkerboard durations, baseline to CI amplitude ($F(1.127, 6.759) = 0.499$, $p = 0.619$, $\eta p2 = 0.077$), CI to CII ($F(2,12) = 0.204$, $p = 0.818$, $\eta p2 = 0.033$), CII to CIII ($F(2,12) = 2.389$, $p = 0.134$, $\eta p2 = 0.285$) and CIII to CIV ($F(2,12) = 0.851$, $p = 0.451$, $\eta p2 = 0.124$).