Physiological Studies of Visual Perception

Thesis and Abstract M.Sc. by Research

Jeremy Heath

St Edmund Hall

ABSTRACT

The problem of investigating the neural basis of higher cognitive function is receiving considerable attention with the increasing availability of functional neuroimaging. The aim of this thesis was to investigate how participants perceive a bistable, rotating structure from motion (SFM) cylinder, looking in particular at which areas of the brain are responsible for generating the internal switch that causes a perceptual change. Another aim was to discover how participants with autism, a neurodevelopmental condition thought to affect higher functioning, might differ in their perception of a similar stimulus. This thesis aimed to assess the interplay of bottom-up and top-down processing and the affect autism might have on the perception of multiple rotating SFM cylinders. Quantitative data were collected using Magnetoencephalography (MEG) and psychophysical testing. Participants viewed a continually rotating bistable SFM cylinder, giving responses in the form of a button press, whilst functional imaging was recorded using MEG. They were either presented; an ambiguous SFM cylinder in which participants were able to report perceptual switches, or a stable SFM 3D cylinder in which participants could report stimulus induced switches when the disparity of the stimulus was reversed. The results of this study showed a statistically significant increase in left frontal cortex activity 1180ms prior to the behavioural response to perceptual switches ($p<0.05$ when comparing perceptual switches to stimulus induced switches). When testing participants with autism, a behavioural psychophysics set up was used and participants indicated the direction of rotation of a continuously rotating SFM cylinder. Participants with autism showed borderline statistically significant reduced perceptual durations when viewing a constantly rotating bistable SFM cylinder ($p<0.10$). The increase in activity in the left frontal area was interpreted as evidence of the internal switch responsible for the perceptual change participants reported and could be the neuronal signature for the top-down control of perceptual switches. The reduced perceptual durations seen in participants with autism could be due to a weaker involvement of top-down control leading to a less stable perception, with local instability taking a greater role, however more participants would be required in order to get statistically significant results. Further work is required to localise the brain area of increased activity preceding intrinsic switches, incorporating an increased number of participants. In order to assess how brain function is altered in the autism spectrum, perceptual switching should be investigated in the participants with autism using a neuroimaging methodology.

DECLARATION

I declare in this thesis entitled *'Physiological Studies of Visual Perception'* data were collected from autistic individuals by Dr. Kristine Krug due to the vulnerability of these individuals and the sensitive nature of collecting such data; all other data were collected by the author. The rest of this thesis remains the result of the authors own research except as cited in the references. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

Jeremy Heath

10/09/2010

CONTENTS

ABBREVIATIONS

2D/3D	Two/three dimensional
ADOS	Autism Diagnostic Observation Scale
Autism	Autism Spectrum Disorder
BOLD	Blood Oxygen Level-Dependent
CCW	Counter Clockwise
CW	Clockwise
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
IQ	Intelligence Quotient
LED	Light Emitting Diode
MEG	Magnetoencephalography
MT	Middle Temporal
PET	Positron Emission Tomography
SD	Standard Deviation
SFM	Structure from Motion
SQUID	Superconducting Quantum Interference Device

Chapter 1

1. INTRODUCTION

NEURAL BASIS OF VISUAL PERCEPTION

It is interesting to note that in figures such as the Dalmatian (figure 1.1) how easily our brain allows us to interpret a random assortment of dots into such a complex image. It is nowadays taken for granted that this sort of visual perception occurs in our brain, but this was not always the case. In the 1000s, Islam scholar Ibn Al-Haytham was the first scientist to argue that vision occurs in the brain rather than the eyes (Masic, 2008). The world around us often provides incomplete sensory information, leaving ambiguous images which our brains interpret and thus we perceive the world as a stable unambiguous landscape.

Figure 1.1: Dalmatian sniffing in the park. (Image taken from http://joeltalks.com/web_images/dalmation.jpg 21/06/10)

Optical illusions often arise from the assumptions our brains make in order to create this stable world around us. For example in figure 1.2 (a) and (b) there is no triangle and no sphere; these ghost images are inferred by our brains in order to make sense of the figures. A famous optical illusion, the Necker cube (figure 1.2 (c) ii.) is ambiguous in nature and can be perceived in either of the two possible states at different times. It can be seen either in the up state (figure 1.2 (c) i.) or the down state (figure 1.2 (c) iii.) and, when viewed for a certain length of time, people report that they see the percept change from one state to another state at random intervals. What makes these bistable figures so interesting is the fact that the stimulus does not alter, only perception does.

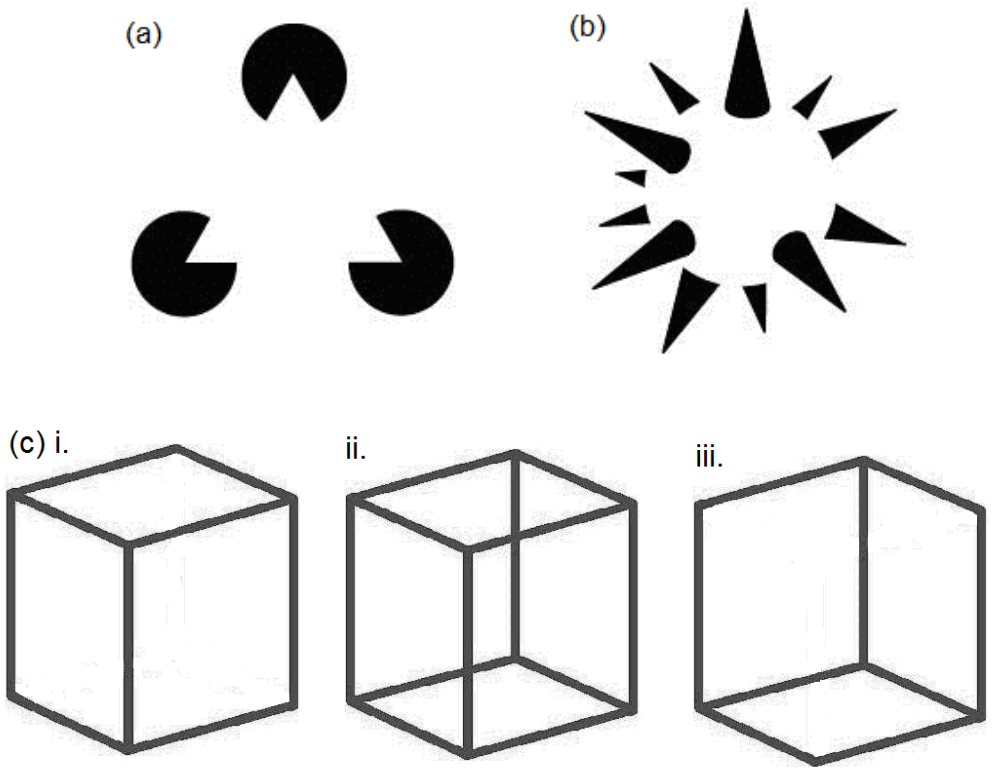


Figure 1.2: Examples of optical illusions: (a) a floating triangle on circles. (b) a ghost sphere. (c) ii. the Necker cube (with i. and iii. showing the two possible perceptual states). (Images (a) and (b) taken from http://sharp.bu.edu/~slehar/Spatial/Spatial.htm 21/06/10).

More complex figures have been created for further research into visual processing. Such figures take advantage of what we know about visual processing and the way we perceive the depth of an image. Objects in the world around us sit in 3D and our eyes only receive images in 2D, yet somehow we maintain this strong perception of a 3D world. This rendering of depth is a very complex task and there are two main cues that allow such a task, namely monocular and binocular cues. Monocular cues are cues that allude to depth that can be derived from the image of one eye alone. These include: kinetic depth, motion parallax, colour changes with depth, perspective and occlusion. Kinetic depth is observed when rotation of an object leads to a 3D appearance and is discussed in more detail later on in this chapter. Motion parallax is the effect seen that near objects appear to move further than far objects when an observer moves his/her head from side to side. We can also infer the depth of objects on a greater scale using colour changes, a mountain in the distance will appear bluer than a nearer mountain. Perspective is a well known effect where as objects move into the distance they appear smaller due to a decrease in visual angle. Finally occlusion is the effect where if an object is closer than another object it will occlude the object behind it.

Binocular depth perception, or stereopsis, is the sense that gives the most vivid representation of depth and is the effect taken advantage of to create 3D cinema. Interestingly it is this sense that must be ignored by artists in order to create a 2D representation of the world around us. Based on recent analysis of many of Rembrandt's self portraits it has been suggested that Rembrandt could have had

a unilateral strabismus leaving him stereo blind (Livingstone et al., 2004). His astute powers of observation may have been due to the fact that he saw the world in 2D, as if the world were a painting with no real depth. Surprisingly, not one of the great early students of optics – Euclid, Archimedes, Leonardo de Vinci or Newton – understood stereopsis, although each had the necessary technologies available. Stereoscopic vision was not discovered until 1838, when physicist Charles Wheatstone invented the stereoscope. Binocular depth perception relies on the computations of small differences in the visual angle when the same object is viewed with each eye. Up until the 1960's depth perception was thought to occur fairly late in the visual processing system, only obtainable after shape and form had been processed by matching these retinal features in the representations from the two eyes. In 1960 Bela Julesz proved this idea was incorrect when he found that stereoscopic fusion and depth perception did not require any such form, movement or colour processing to have occurred, the only clue necessary for stereopsis was a retinal disparity. Julesz demonstrated this fact by creating two identical patterns of random dots with only one difference – that a square area in the middle was shifted horizontally in one copy. When viewed through a stereoscope, or if the two images were fused stereoscopically, if the square in the left image was shifted to the right, the combined image square would appear to float in the air closer to the observer (see figure 1.2.1), the converse also applies.

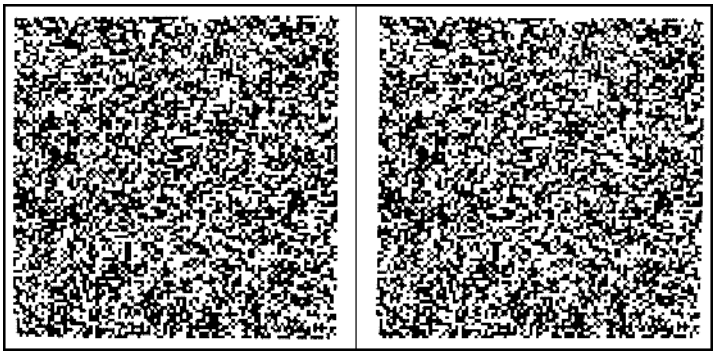


Figure 1.2.1: Example of random dot stereogram such as those used by Julesz. Through free fusion of the image a square will be visible amongst the apparently random assortment of dots. (Image taken from http://plato.stanford.edu/entries/mental-imagery/randdot.gif, 06/01/10)

Binocular depth perception occurs by the assessment of the difference between the images of each eye. Kinetic depth, for monocular depth perception, occurs by the assessment of the difference between the images only taking the images from different time increments rather than retinal disparities. It has been proposed therefore, that these two methods of depth perception are likely to occur via similar processes in a common neuronal pathway (Livingstone and Hubel, 1988; Fang and He, 2004). Structure From Motion (SFM) figures can be used to take advantage of the kinetic depth effect in order to render the perception of an object from the motion of dots on a 2D screen (figure 2.1.2).

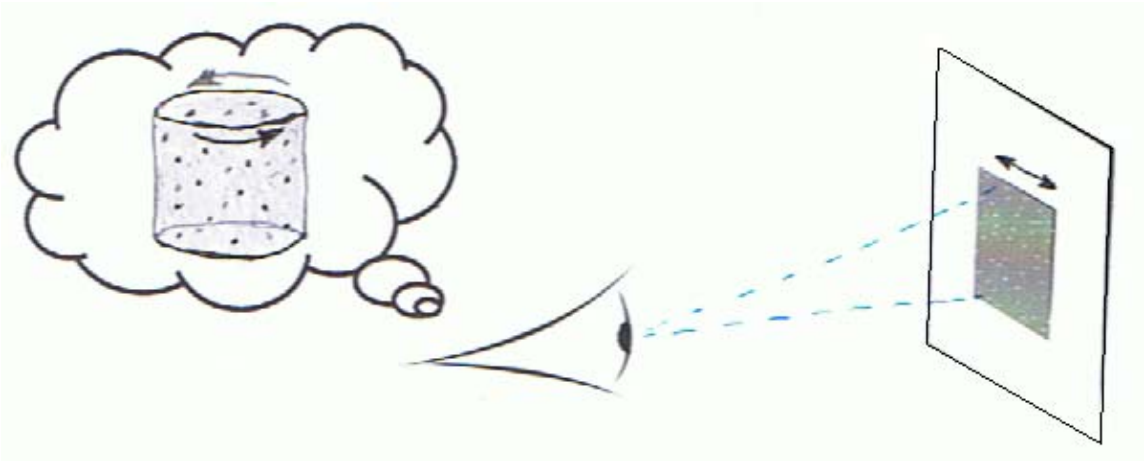


Figure 1.2.2: Observer views two sheets of dots moving in opposite directions and perceives a 3D rotating cylinder due to the kinetic depth effect.

Such figures are bistable, like the Necker cube, and can be perceived to rotate in either direction. Now if these bistable SFM figures are viewed through a Wheatstone stereoscope, a binocular disparity can be added to one layer so as to bring the front surface dots closer to the observer and the rear surface dots further away from the observer. This imposes a third dimension to the image forcing the observer to see the cylinder rotate in only one possible direction, thus rendering the percept unambiguous. Interestingly, participants are unable to tell the difference between objects which are bistable and those which have a binocular disparity added, so long as the disparity increment used is near threshold (Nawrot et al., 1993a); this was shown while participants were still performing above threshold on the disambiguated figures. This discovery advanced research into the perception of SFM figures. Now we have a stimulus which is bistable, with which we can probe perceptual decision making about the direction of rotation. A binocular disparity can be added making the stimulus unambiguous allowing us to check observers' performance. Because the

observer does not detect a difference between these two states, it is an excellent stimulus for probing the neuronal basis of perception.

The stimulus used in this thesis is such a SFM figure: specifically I will use the orthographic projection of a revolving transparent cylinder, which is perceived in 3D. Binocular disparity will be added analgraphically (red/green glasses) or through a Wheatstone stereoscope. Other factors can affect the percept of such a stimulus, increasing the dot density or decreasing angular velocity makes the stimulus more stable resulting in longer durations of perception in one direction so the cylinder is seen to switch at a lower frequency (Brouwer et al., 2006).

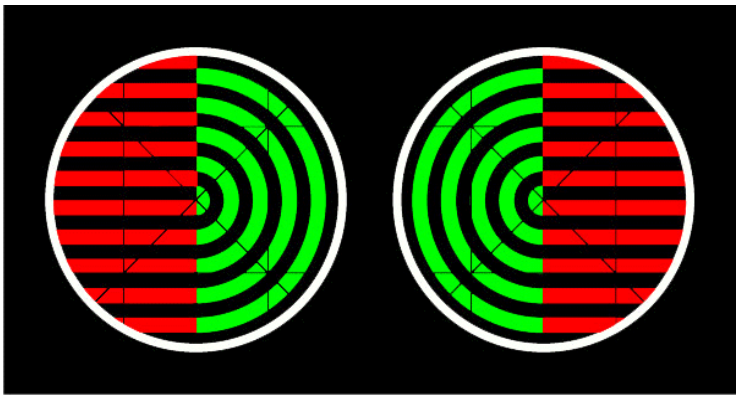


Figure 1.3: Typical binocular rivalry image. Through free fusion of this image one of four percpets may arise, that of green circles, red stripes, or half red stripes half green circles in either orientation. (Image taken from http://www.perceptionweb.com/perception/perc1200/alais.html, 06/01/10)

It is particularly the switch of a bistable figure that has interested neuroscientists because it allows the exploration of the neural correlates of perception. A lot of previous research has focussed on binocular rivalry in exploring perception of visual stimuli. Binocular rivalry is a powerful tool for studying conscious visual

awareness. One figure is presented to each eye and instead of merging the two images, they compete for perceptual dominance (see figure 1.3). During rivalry one object or just a part of that object can be suppressed, leaving the other one to be consciously perceived. The percept can alter every few seconds with no change in the visual stimulus. Therefore understanding the nature of this perceptual change, and where it occurs in the brain, may lead to a greater understanding of conscious visual perception. At present it is argued that the perceptual switch that occurs in binocular rivalry could be down to: (i) a low-level eye-driven mechanism where small flicks of eye movement lead to a new percept being formed; (ii) the switch could occur due to local instability early on in the visual cortex; (iii) the switch could be under higher cortical control with influences such as pattern suppression; (iv) finally an inter-hemispheric switch has been postulated (Sengpiel et al., 1995; Logothetis et al., 1996; Miller et al., 2000; Polonsky et al., 2000; see Blake and Logothetis, 2002 for review). Binocular rivalry as a stimulus does not allow for observer-naive disambiguation of the stimulus because it is obvious to the observer if no binocular rivalry is present in the image. This is a problem as it will not allow an unbiased comparison of the ambiguous and unambiguous states as proposed in this thesis. It is this fact that has led to a greater interest in bistable SFM figures as the tool for probing into the conscious perception of vision and to exactly what neural mechanism lies behind the perceptual switch.

SFM figures such as that of an orthographic projection of a transparent cylinder show spontaneous reversal when viewed for a prolonged period of time, as

mentioned above (Treue et al., 1991). The neural mechanism behind this phenomenon is one that has attracted much interest recently. Using fMRI, Brouwer and Van Ee (2007) looked for evidence of the switch, aiming to predict the direction of rotation a participant perceived by looking at various brain areas. They collected data from 5 participants and succeeded in predicting perceptual states in areas MT, Dorsal Retinotopic areas and two parietal areas, demonstrating activation of higher cortical visual areas reflecting the content of awareness during perceptual bistability as opposed to lower cortical visual areas used to predict perceptual states in binocular rivalry (Haynes et al., 2005). From this they argued that the perception of binocular rivalry differs from structure from motion. The first involves suppression of half of one image, the second is less to do with whether the image is seen or not and more to do with interpretation of a conflict that exists within the stimulus, i.e. that of whether the movement of the dots signifies a clockwise or counter clockwise direction of rotation (Brower et al., 2007).

It is known that area MT/V5 is within the pathway for motion perception (Salzman et al., 1990; 1992) with some aspects of disparity perception also included (Uka et al., 2006). Evidence although still far from conclusive is now leaning away from low-level mechanisms in favour of higher order control over the observed switch when viewing bistable stimuli (Krug 2004; Ngo et al., 2008), but it remains unclear where the perceptual signals in these visual areas originate. In this thesis I aim to investigate the source of perceptual decision signals in the visual cortex using a new neuroimaging technology,

Magnetoencephalography (MEG), in humans. The next section of this chapter will introduce what MEG is and why it was chosen as the preferred method of studying this phenomenon.

MEG FOR DETECTING BRAIN SIGNALS WITH MILLISECOND RESOLUTION

MEG can assist measurement of electrical activity in the brain. It does so via the detection of tiny electromagnetic fields that can be detected outside the head. Many neurons are required to fire simultaneously to produce a magnetic field of great enough magnitude to be measurable (see figure 1.4). The type of data MEG extracts therefore differs from single unit recordings such as those performed in the Rhesus Macaque as it reveals areas in the cortex where many neurons are firing simultaneously in the same orientation over the whole cortex as opposed to recording from just one neuron. This means MEG is selective for homogeneous brain activity.

The magnetic fields produced by the brain were first detected by David Cohen in 1968 (Cohen, 1968). He built on work done with magnetocardiography by extending the technique to the cortex; this required the use of much more sensitive recording material and magnetic shielding. He performed his measurements using an induction coil magnetometer with 10^6 turns and a ferrite core. In the 1970s the incorporation of Superconducting Quantum Interference Devices (SQUIDs), a sensitive detector of magnetic flux, led to a leap in the ability

to detect these minute field potentials giving greater sensitivity and specificity to the devices (Cohen, 1972).

SQUIDs were first invented in 1964 by James Zimmerman (Zimmerman et al., 1970) and one of the devices' most promising uses has been in MEG. They are so sensitive that they can be used to measure fields 100 billion times weaker than the Earth's magnetic field (see figure 1.4) SQUIDs are usually made of a superconducting lead alloy often in conjunction with niobium. These need to be kept very cool with liquid helium in order to retain their superconductive properties. The superconducting alloy is formed into tiny loops of superconductors with Josephson junctions – a separation of two loops of superconductor by a non-superconducting layer so thin that electrons can cross through the insulating barrier to achieve superposition (where each electron moves simultaneously in both directions). This means that if a magnetic field is placed over the superconducting coils it causes a current to flow in both directions. Once this current exceeds the current needed to cross the Josephson junction the circuit becomes resistive and a voltage can be detected across the junction. This voltage is proportional to the magnetic field over time and thus forms our output signal.

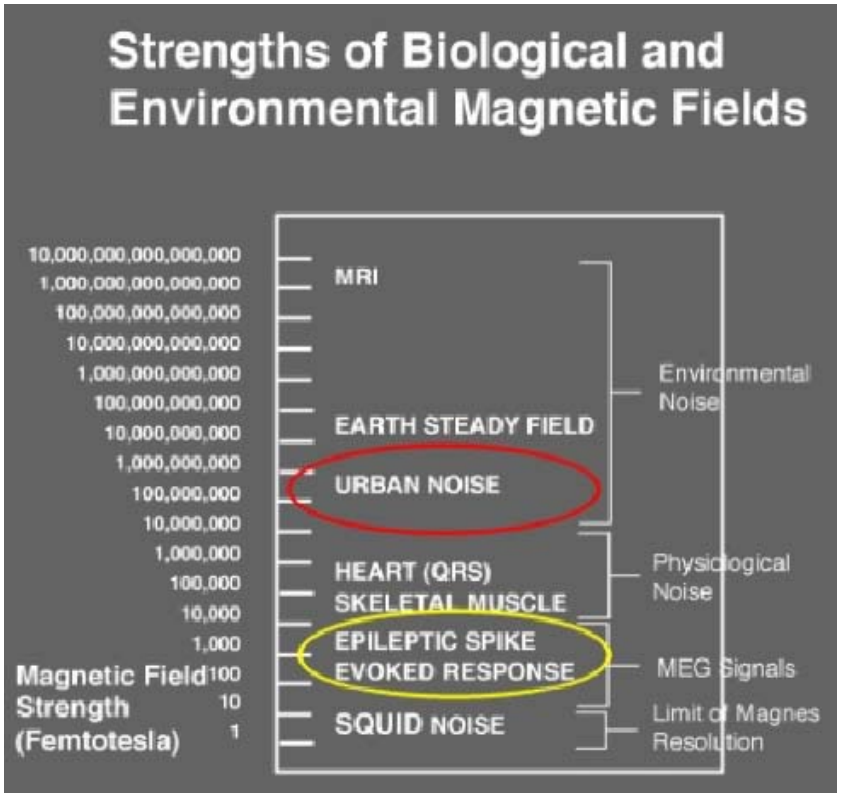


Figure 1.4: showing a logarithmic representation of the magnetic field strength of the evoked responses in comparison to SQUID noise and external noise. (Image taken from http://web.mit.edu/kitmitmeg/MEG_Work_5.jpg, 07/01/10).

MEG has a high temporal accuracy, equivalent to that of EEG, with a temporal resolution of up to a millisecond. It is therefore an excellent imaging technique for transient events such as those of the visual system. Functional neuroimaging methods such as fMRI have a temporal resolution of a couple of seconds and as such would not be very useful in measuring a dynamic event such as binocular rivalry where one percept only lasts a second or two.

MEG is mainly selective for activity in the sulci, comprising two thirds of the cortex, due to its selectivity for tangential sources (fig 1.5). This is another aspect of the device that is worth considering when selecting it for research, as most

activity on the gyri of the cortex will be more difficult to detect. The superposition of the MEG traces onto structural MRI images allowed for better spatial resolution, down to a detail of several millimetres (Hamalainen et al., 1993); without information from MRI, MEG is only really good at localising sources to the nearest lobe.

This method of increasing MEG's spatial resolution was termed source localisation. One method of source localisation looks at the data for one subject as a whole to work out a best fit dipole for each source (see Electrophysiology section below for an explanation of dipoles). A known dipole from the head positioning coils is used as a marker. The locations of the markers are used to define a common coordinate system thus allowing superimposing of functional MEG data onto the structural MRI data. This is a complex and specialised process beyond the scope of this thesis, and involves careful interpretation with a good understanding of the process and assumptions made, particularly when using the method to spatial resolutions much finer than a centimetre.

Modern MEG machines now use hundreds of magnetometers, each with its own SQUID. These are housed in a chamber filled with liquid helium called a Deber. The Deber comprising of a sophisticated non-magnetic (and largely non-metallic) vacuum flask housing the SQUIDs at the superconductive temperatures required for optimal function. The systems are thus expensive to run and as much as 5000L of liquid helium is used per year in one modern scanner to maintain the superconductive properties of all the SQUID sensors. Noise is a big

problem with such sensitive measuring equipment with interference from the Earth's magnetic field, a/c power lines, cars and other electrical and metallic objects which need to be eradicated in order for sensible measurements to be taken (figure 1.4). Great care must be taken to ensure magnetic shielding is adequate to reduce noise to an acceptable level. MEG units are thus housed in their own specially shielded room. Magnetic shielding incorporates expensive Mumetal® and nickel into a Faraday-like-cage forming a barrier with the conductive material. The metals are alloys mostly comprised of nickel and have high magnetic permeability to absorb and redirect as much magnetic flux as possible.

ELECTROPHYSIOLOGY

MEG detects magnetic field created by an electrical dipole. An electrical dipole merely refers to a separation of positive and negative electrical charges. Every electrical dipole has an associated magnetic field when current is allowed to flow between the two charges. This is called a magnetic dipole with a magnitude equal to the current flow times the area of loop within which the flow of current occurred. This associated magnetic field loops anticlockwise around the dipole when viewed from the positive charge (figure 1.5).

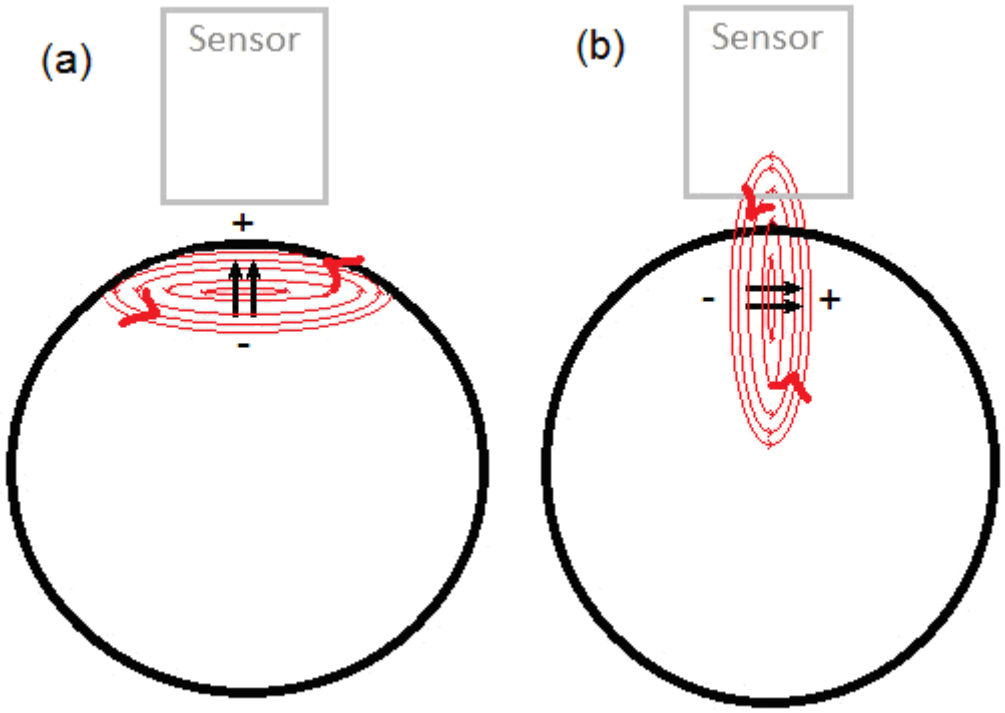


Figure 1.5: Showing the difference between (a) radial (gyral) dipoles and (b) tangential (sulcal) dipoles. Key: two black arrows indicate current dipole pointing from negative charge to positive charge; Red concentric circles indicate magnetic flux, red arrows indicate direction of flux.

Neuronal activity is carried down axons via action potentials. Like any other cell in the body, neurons are selectively permeable to ions such as potassium and sodium. The concentration of potassium is kept high inside cells and the concentration of sodium high outside cells. The sodium potassium pump keeps this concentration gradient set up across the membranes of the neurons; potassium channels allow potassium ions to leak out of the cell as a result of this gradient. The membrane is less permeable to sodium ions in the resting state and any leakage is counter balanced and as such there is no net charge flow. The result is a membrane potential that is more negative inside the cell due to this net loss of positive potassium ions. The voltage is normally around -70mV with respect to the outside of the cell and is termed the 'resting potential'. When a

neuron is activated, excitatory activity causes a change in the sodium channel, increasing the membrane's permeability and depolarising the membrane. If this reaches a critical value, typically around -55mV, the neuron fires an 'action potential' where the membrane becomes more permeable to sodium ions, causing them to rush into the cell. The influx of positive ions creates an inner membrane voltage that is positive and we describe this as a state of 'depolarization'. The voltage reached is typically +10-30mV and is maintained for approximately a millisecond. Then the sodium channels become inactivated again and close. Subsequently potassium channels open to allow a positive ion outflow which brings the membrane back to its resting potential. This excitatory event is propagated down the axon of the neuron until it reaches a pre-synaptic terminal; here the depolarisation causes a release of the neurotransmitter, which in turn can cause a depolarisation at the post-synaptic terminal.

Action potentials could generally be propagated in both directions, but the propagation in the reverse direction is stopped by the refractory period, where the voltage-gated sodium channel will not open again for a period of milliseconds. However there is, momentarily, a passive current flowing in both directions. This appears as a pair of dipoles which forms a quadrupole source which diminishes with the inverse of the cube of the distance from the source; thus creating a minute magnetic field that is singularly undetectable over background noise in the brain at present. The only part in the conduction of electrical signals along the neurons where there is a directional current, and current flow set up in great enough numbers to be detected, is in post-synaptic

dendrosomatic current flow. This occurs after an excitatory neurotransmitter acts on receptors on the post-synaptic dendrites, causing current to spread down the dendrite to the soma (cell body). At the soma, if the excitatory post-synaptic current is large enough to depolarise the cell, an action potential is generated by the neuron which travels quickly down the axon. Such pyramidal dendrosomatic currents are more likely to show parallel synchronous activity as they are situated perpendicular to the cortical surface and hence anatomically aligned; this increases the likelihood of the production of a great enough magnetic flux that can be detected by a magnetometer in the MEG machine (Hamalainen et al., 1993).

MAGNETIC PHYSIOLOGY

MEG is selective for activity within the sulci of the cortex, this section will attempt to explain why this is so. As mentioned above MEG detects the magnetic flux created by an electric dipole from dendrosomatic current flow in pyramidal cells. The magnetic field produced by a radially orientated dipole in a spherical conductor, or concentric spherical shells with different conductions, is zero everywhere outside the sphere as it becomes difficult to place the sensors within the magnetic field (Baule et al., 1965; Grynszpan et al., 1973). The skull behaves like a sphere and as such, magnetic flux created by radially orientated dipoles is undetectable by MEG (see figure 1.5). Tangential dipoles however create magnetic flux that can escape the confines of a sphere thus making it easier to place magnetic sensors within their flux. Pyramidal cells lie within the

cortex, such that the dendrosomatic current flow is orientated perpendicularly to the surface. As such, dipoles set up by the activity of pyramidal cells within the sulci will produce tangential dipoles and so MEG is therefore selective for activity within the sulci of the brain. To show the actual workings when a non-perfect sphere is used such as the human head, a study was devised in 1988 which tested a known dipole's magnetic output within a rabbits head (Melcher & Cohen, 1988). It was shown that the magnetic flux emitted by radial dipoles was less strong, such that magnetic flux of radial dipoles was suppressed by a factor of 6 when compared to tangential dipoles. As such Melcher & Cohen showed that radial dipoles would be too small to detect with the MEG sensors that we have at present and the level of background noise that is encountered even after heavy magnetic shielding.

There are two types of magnetic sensors; magnetometers and gradiometes. Magnetometers are used for measuring magnetic flux. Simple magnetometers consist of coils of wire around a metal core. More sophisticated magnetometers, such as SQUID magnetometers used in MEG recording, are made from very sensitive vector magnetometers, which have the capability of measuring the component of the magnetic field in a particular direction (as opposed to measuring the total strength of a magnetic field – measured by scalar magnetometers). A gradiometer is a device made up from two magnetometers and is used to measure the gradient of the magnetic field, through the assessment of the rate of change of flux. There are two types of gradiometer: Axial gradiometers – not used in this thesis – are devices made from two

magnetometers placed on top of each other in series. Planar gradiometers are devices made from two magnetometers placed side-by-side and connected in a figure of eight configuration. This means that a flux that is equally represented in both coils creates electricity of the same amplitude flowing in opposite directions thus it cancels out, however flux that is stronger in one coil than the other is preserved. This means the planar gradiometers are selective for sources of flux that are closer to one of the two sensors as flux from further away becomes more equally represented in both sensors. As cortical brain activity is what is important in this study only planar gradiometers, selective to shallow sources directly below them, are used.

MEG AND OTHER NEUROIMAGING TECHNIQUES

There are many methods of imaging or recording activity within the brain; from the invasive single unit recordings or intracranial EEG, to non-invasive techniques such as fMRI and MEG. These methods detect or estimate brain activity on very different spatial and temporal scales. Therefore, different methods have to be chosen based on the scientific question researchers wish to answer. Also, the degree of invasiveness varies, with MEG being the least invasive where the participant is free to sit, only restricted by the placement of the helmet over their head. Thus some research methods can only be used in animal experiments for ethical reasons.

In the study presented in Chapter 3, I have investigated the brain events underlying perceptual changes with ambiguous visual images. Previous neurophysiological recordings in visual cortex suggested that the neural processes that include such perceptual changes – during for instance binocular rivalry – take place on a time scale of milliseconds (Blake et al., 2002; Parker et al., 2003). Thus if we looked for transient brain events in higher cortical areas that precede changes in activity in the visual cortex, we could reasonably expect them to be of short duration. Millisecond resolution could only be achieved reliably with MEG, or electrophysiological recordings in animals. However, the latter only allows the detailed study of a small number of brain cells at a time, whereas MEG allows the investigation of the whole cortex. These experiments also required participants that can very reliably report perceptual changes without much training. Therefore, humans seem the most appropriate participants, especially as there is currently no good animal model for autism.

The spatial resolution that can be achieved by our MEG scanner with 102 pairs of orthogonal, first-order planar gradiometers (data from the magnetometers was not analysed) is only within a centimetre or two without further source localization. BOLD fMRI can potentially achieve finer spatial resolution of less than one millimetre accuracy. However fMRI measures functionality through blood flow measurements, an indirect route. It therefore makes the assumption that functionality is proportional to the oxygen requirement of neuronal tissue and as such temporal resolution is poor, making it not ideal as an imaging tool for this thesis.

Other techniques were less appropriate; PET subjects participants to radiation it also has a low temporal resolution of the recorded activation (see figure 1.6). Intracranial placement of electrodes, for example IEEG or single unit recordings would have scientifically been a very robust way of collecting the data with specific mention of single unit recordings as much work has been performed in monkeys using this stimulus to understand visual processing better (Dodd et al., 2001; Parker et al., 2003; Krug et al., 2004). However searching for an internal switch in this way would not be acceptable in human volunteers and would be like looking for a 'needle in a haystack'. Therefore we needed a method that could be instigated globally across the brain to search for this still unfound hypothetical phenomenon. This therefore leaves us with whole brain imaging which will now be discussed in more detail.

When MEG and fMRI are directly compared on how they detected incremental changes in a simple somatosensory task, quantification of evoked responses is possible with MEG, but robust quantification of increasing cortical area of activation is not possible with fMRI (Roberts et al., 2000). MEG has been used in such sensory processing studies such as those studying stages of visual face perception, (Liu et al., 2002) who found face selective MEG responses occurring 100ms after stimulus onset, to those looking for visual sensory processing such as in this thesis (Sterzer et al., 2007; Britz et al., 2009). Such studies show how useful MEG's high temporal resolution makes it excellent for the study of transient sensory neural processing despite its lesser spatial resolution.

It must be noted that MEG is not the 'magic bullet' for imaging visual neuroscience; it is selective for activity within the sulci and for synchronous brain activity. However, as discussed above for the purpose of this thesis these seem the most acceptable assumptions when compared to similar imaging methods. In this thesis I am looking for a theorised higher cortical trigger for a change in visual perception. As such the imaging method used should be able to scan the whole cortex with a temporal resolution of millisecond accuracy. MEG is therefore highly suitable neuroimaging technique for the subject of this research (figure 1.6).

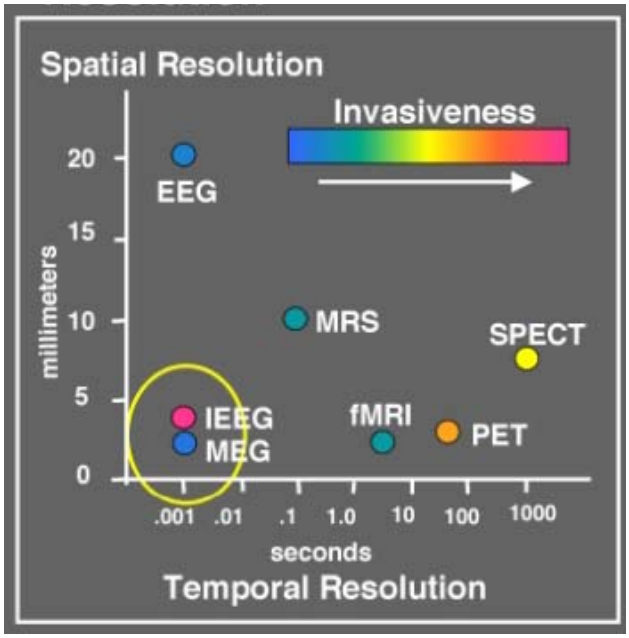


Figure 1.6: Spatial Vs Temporal resolution in various different methods of brain imaging. Note although MEG spatial resolution in optimal conditions has been quoted at 2-3 millimetres (Hamalainen et al., 1993), this finding is likely to be a bit overoptimistic and it is much more reasonable expect to work to spatial resolutions of a couple of centemeters given there are only 204 pairs of detectors. (Image taken from http://web.mit.edu/kitmitmeg/MEG_Work_5.jpg, 07/01/10)

One of the classic issues identified by the Gestalt psychologists in the 1920s is the capacity of our visual systems to make active interpretations of the incoming information. The brain mechanisms that enable this capacity are increasingly revealed by neurophysiological and psychophysical study. Autism is mainly thought of as a behavioural disorder however it is becoming apparent that other cognitive processes can also be affected, for example simple visual processing is thought to be affected whereby individuals seem unable to make the same global or gestalt appreciations of the world (Happé et al., 1996). Study of particular deficits in the visual system can lead to a greater understanding of the processes that are occurring. Autism is a complex and little understood developmental disorder. There has been some research (Happé, 1996) into how simple visual processes are affected and how this might fit into current theories of autism, in particular Weak Central Coherence. This thesis aims to research into this area to test visual perception, hoping to probe the extent of frontal lobe failure and decreased global control of visual processing in autism which will be discussed further in this section.

Autism is a neurodevelopmental disorder that until recently was only characterised by its main symptoms: impaired communication, social interaction and repetitive behaviour. It is thought that autism affects the brain globally and it has been shown that sensory processing is affected (Frith, 1989; Pellicano et al., 2005; Baron-Cohen et al., 2009). Autism was first discovered by Leo Kanner

(1943) and Hans Asperger (1944) simultaneously and independently, both used the word 'Autism' coined by the psychiatrist Bleuler (1916) who described the narrowing of relationships in schizophrenia. When taken to the extreme, the relationship of an individual can be narrowed to the person's own self: *Autos* in Greek meaning self. Since its discovery many scientists and physicians have invented theories in order to help explain how the disorder affects the mind. The three most prominent theories postulated are; Theory of mind (Baron Cohen et al., 1983), Weak Central Coherence (Frith, 1989) and Executive dysfunction (Hill, 2004).

Theory of mind was first tested in the early 1980s (Baron Cohen et al., 1983), the theory hypothesises that individuals with autism will tend to show an inability to predict another person's actions when an understanding of that person's mental processes need to be taken into account particularly when the other person holds a false belief. To show this they used Wimmer and Perner's puppet play paradigm (1983); two puppets, Sally and Anne, are presented and a charade carried out. Sally puts her ball in a basket and then leaves the room. Anne moves the ball to her box. Participants are then asked where Sally will look for her ball. The answer is of course "in the basket" as this is where Sally herself placed the ball and is not aware of it being moved by Anne. However Sally now holds a false belief that her ball is in the basket. It was shown that children with autism (mean age 11 years, mean verbal age 5 years), when compared with typically developed children (mean age 4 years) and those with Down's syndrome (mean age 10 years, mean nonverbal age 5 years), could not impute such false beliefs to the

doll charade; 85% and 86% of typically developed children and those with Down's syndrome passed the false belief charade whereas only 20% of children with Autism passed, $p<0.001$ (Baron Cohen et al., 1983). This was further supported by observations that children with autism had an inability to understand pretence and supported the well known fact that children with autism do not tend to show spontaneous pretend play (Leslie, 1987). An absence of a theory of mind has been widely used to explain some of the complex behavioural patterns in autism and has been successful at explaining the deficits in communication and social interaction with autism. However, it falls short of explaining other features of autism such as the restricted and repetitive behaviour and an often narrow range of interests and activities.

Central Coherence Theory (Frith, 1989; Frith et al., 1994) is another theory that tries to explain the unusual behavioural patterns seen in autism based on a common cognitive deficit. Theory of mind is limited mainly to the triad features of autism (namely; impairment of social interaction, impairment in communication, and restricted interests and repetitive behaviour) and does not help in explaining the non-social aspects of autism, particularly areas where autistic individuals perform better than non-autistic individuals. For example autistic individuals can have excellent rote memory and better than average visuospatial ability. Central Coherence theory proposes that non-autistic individuals process information looking for a meaning or pattern often at the expense of other processes such as memorising the information or a more detailed analysis. Frith & Happé (1994) argued that individuals with autism

show Weak Central Coherence where they will focus on the individual elements often at the expense of understanding the meaning or Gestalt. In essence, Weak Central Coherence describes autistic individuals as not being able to 'see the wood for the trees'. It encompasses not only the deficits and impairments seen in autism but also takes into account the 'islets of ability' seen in some individuals with autism.

It became apparent to neuropsychologists that individuals with autism demonstrated problems with their executive function (Russell, 1997). Executive function is a term typically used to describe functions such as planning, working memory, impulse control, inhibition and the initiation and monitoring of action. Historically it has been thought such functions originate in the frontal and prefrontal areas of the brain. Executive control is not needed for routine actions such as eating or walking but needed when a change in plan occurs such that normal routines can no longer be adhered to. This leads to another theory of autism, that of executive dysfunction (Hill 2004). Interestingly this is supported by evidence that particular differences are seen in the frontal areas of the autistic brain (see below and Courchesne et al., 2007 for review) and executive dysfunction makes an explicit link to frontal lobe failure in autism.

These theories have proven useful for diagnostic and broad spectrum behavioural classification, but have failed to pinpoint the specific brain deficits that underlie the symptoms of the autism spectrum. It has been suggested that autism is a developmental disorder with affected individuals showing an initial

overgrowth of the cortex. This is thought to be followed by an arrested growth period where typically developing individuals 'catch up' in cortical growth, and could even be followed by a degeneration of neurons in certain areas, particularly frontal regions (Schmitz et al., 2007). Casanova et al. (2006) compared 6 autistic brains, aged 4-20 yrs, to aged matched controls and found that developing autistic patients had a greater density of cortical neurons post mortem. There is evidence of inflammation and degeneration particularly in the areas thought to be enlarged most in childhood, the frontal and temporal cortices, the amygdale and cerebellum, and it has been shown that adult autistic patients' brains are smaller in these areas (Courchesne et al., 2007 for review). It is thought that this overgrowth and then possible degeneration of neurons in autistic individuals could cause a loss of interconnectivity within the autistic brain. As such their brains work in a more segregated way with less communication between areas, especially frontal and temporal areas, leading to some of the classical symptoms of autism. A meta-analysis of twelve studies looking at MRI brain volume and three studies measuring head circumference differences in individuals with autism revealed a period of pathological brain growth and arrest in autism in the first few years of life (Redcay et al., 2005). One MRI brain volume difference study showed that children with autism had 10% larger brain volumes than those of typically developed children (Courchesne et al., 2002). Below is shown a diagrammatic representation of what is thought to be occurring during the development of the brain of an individual with autism taken from Courchesne et al., 2007 (figure 1.7). Initially brain size is smaller, there is a pathological overgrowth and arrest with a possible degeneration so

that around the time an individual with autism becomes an adult their brains are relatively the same size or possibly slightly smaller.

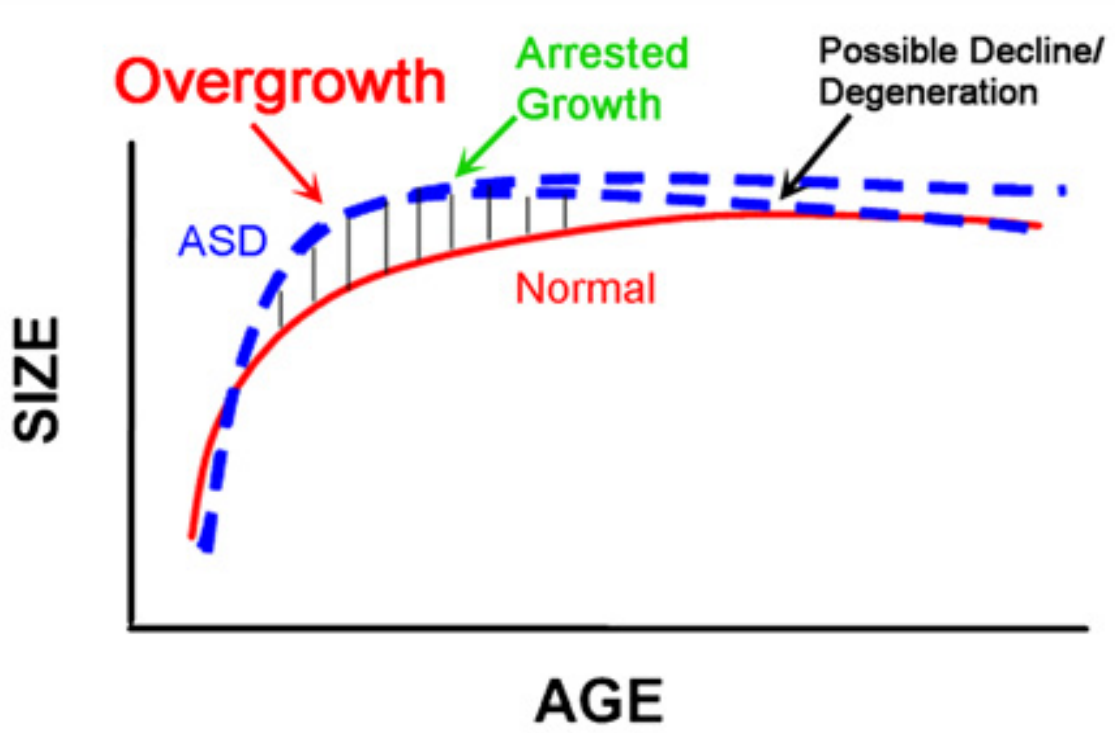


Figure 1.7: Figure taken from Courchesne et al., 2007. Representation of the differing neurodevelopment postulated to occur in autism. Key: ASD – Autism Spectrum Disorder. Scale for age is approximate and roughly 1-20years, size refers to MRI brain volume.

In the second part of this thesis I will explore the effect of autism on perceptual decisions about a bistable rotating SFM cylinder. Two main strategies will be employed in this thesis. To the best of my knowledge no such study has yet explored autism's effect on perceptual duration of a bistable cylindrical SFM. This study aims to see if autism affects the global sensory processing and to what extent stability of the SFM will be affected under continuous viewing. This will

give further insight into how humans perceive such stimuli and may allow some insight into the pathology of autism and its effect on simple sensory processes.

Neuroscience constantly seeks to further the understanding not only of a normally developed cortex but also how brain processes are altered by disorders. For example certain mental disorders are already known to affect simple sensory processes. Work using bistable stimuli has been performed on participants with bipolar disorder and studies have found that their perception of such stimuli can be altered. It is thought that individuals with Bipolar disorder have a slower switch rate termed a 'sticky switch' (Pettigrew et al., 1998). In Chapter 4 of this thesis I will therefore look at how autism affects (i) perceptual switch rates for a bistable stimulus, (ii) global control on visual perception. Grossman and Dobbins (2003) have already shown in non-autistic participants that two bistable SFM figures with aligned axis of rotation tend to co-rotate. If autistic individuals have reduced interconnections of cortical areas, such a phenomenon may not be seen (for a good example of bistable SFM figures co-rotating see http://www.uq.edu.au/nuq/jack/8spheres.html, 08/01/10).

This chapter has discussed the current literature on bottom-up versus top-down control on the perception of reversible figures. This thesis hopes to provide further evidence to the scientific field on the perception of reversible figures, and in this vein the next two chapters will discuss the use of, and subsequently employ, MEG as a tool to look for evidence of top-down control over visual processing. There is little evidence in the literature showing how autism, a

developmental disorder already known to affect simple visual processing (Happé et al., 1996), might affect the perception of such reversible figures. The final part of this thesis will examine the effect of autism on the viewing of SFM bistable rotating cylinder.

Chapter 2

2. MAGNETOENCEPHALOGRAPHY

INTRODUCTION

MEG is a relatively new imaging technique that allows direct functional measurements to be taken completely non-invasively. It was therefore an exciting proposition to be able to perform neurophysiological experiments using such a tool. Due to the novelty of MEG and therefore an unfamiliarity, this chapter will give a step by step example of how this data was collected, identified and analysed; such as to make understanding of the data in the following chapter more easily comprehended and critically evaluated.

Neuronal signals underlying visual processes occur over wide areas of the cortex. In order to study the dynamic of these often transient signals as a person sees and responds to a visual image, we need a method that images large parts of the brain with a temporal resolution on a similar millisecond timescale as neuronal events. MEG fulfils these requirements as stated in Chapter 1 of this thesis. But the measurement of activity maps with MEG is not entirely straightforward. In this Chapter, I will provide a detailed exploration of the necessary transformation of MEG data from raw signals to brain activity maps. Using brain activity I recorded with MEG during motor responses, I will demonstrate how our MEG setup can detect the basic motor programming typical for left and right movements.

METHODS

EQUIPMENT

Neuromag-306 Vector® view system, providing a helmet-shaped array of 102 pairs of gradiometers. Response pad used in-house hardware that involved signalling using fibre optic cables where participants obscured the light with their thumb. The stimulus was projected onto a backlit screen using a Panasonic® DLP™ based projector. A Dell desktop computer was used to display the stimulus using a projector.

STIMULUS

The stimulus program was written by S. Gilson to my specifications specifically for this experiment. The stimulus was displayed at 60Hz using a red-green anaglyph method for viewing depth information. The dots that made up the cylinder were blue and yellow and had a diameter of 0.11° of visual angle; the cylinder had a height of 8.2° and a diameter of 7.8° of visual angle.

Great care was taken that any changes in the visual stimulus would be accurately recorded with respect to collected MEG data. Initially the accuracy was explored of a signal sent from the stimulus programme directly to the MEG record. The accuracy of the timing signal was checked by the placement of a photodiode on the stimulus and the readings the photodiode gave from the screen were

compared to the tags given by the computer program on the MEG trace. It was found that the display programme could not deliver the signals to the computer recording the MEG data in real time. The tags placed on the MEG trace gave errors spanning -81ms to -197ms before the actual event occurred, due to the computer used to display the stimulus programme being incapable of real-time processing. So instead a black box was placed in the bottom right hand corner of the stimulus screen, which turned from blue to white on the same frame the stimulus was altered and remained white for the following four frames; this corner of the screen was obscured from the participants view. This provided a tag which could be placed onto the MEG trace taking up a single channel on the raw data (see later). This channel acted as a digital marker signifying the start of an event which could be identified by the sequence in which they occurred matching up to the run programme. It was found that this method identified the frame on which the stimulus changed with 100% accuracy on the collected data trace. Therefore, we could identify stimulus changes down to the exact frame on which the event started without error (figure 2.8).

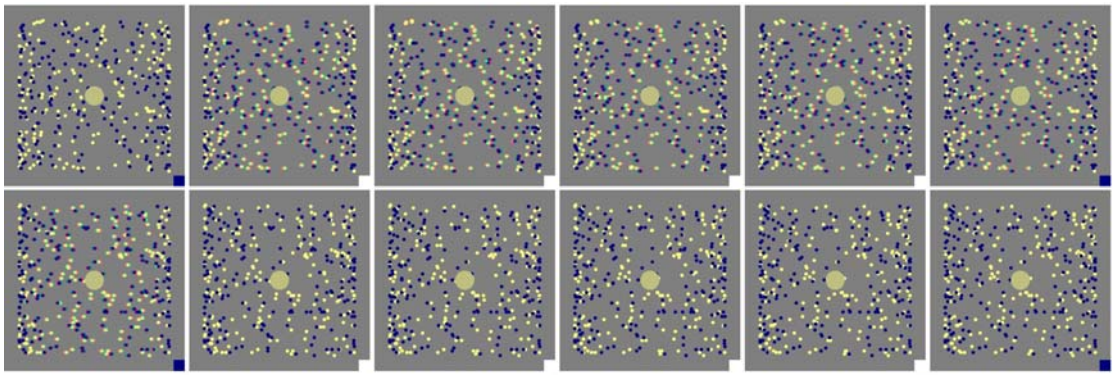


Figure 2.1: Here screen shots of the cylinder stimulus are shown in a stepwise order from top-left to bottom-right, the sequence has been shortened by removing images between the 6th and 7th screen shot where the stimulus keeps rotating with no change in depth information. Each image represents

a single frame presented by the stimulus programme at 60Hz. The stimulus changes from a zero disparity to a clockwise unambiguous stimulus in the second frame, with the red and green dots creating the illusion of depth when viewed through the red green glasses. The blue and white square in the bottom right hand corner of each screen shot can be seen to change on the very frame that the disparity is added. It then stays on for four frames, and the stimulus stays in a clockwise unambiguous state for the next 57 frames before changing back to zero disparity. This is shown in the second line with the first image being the 57th frame in the sequence. It can be seen that the red and green dots disappear on the same frame that the white box appears. The box remains for four further frames to allow the photodiode to capture the change in luminance and print the event onto the MEG trace. . N.B. The fixation circle in the middle of the cylinder was removed for the actual experiment as it would have provided addition depth information.

PARTICIPANTS

Four participants were used to show typical left-right motor responses in the MEG set up, one male (DOM) and three female (IBI, LOM, NEC) all naïve to this particular stimulus sequence. No participant had any known neurological or psychiatric disorder. All participants had normal or corrected-to-normal vision. The participants gave their consent to participate in this experiment. An eye test was then performed with a Snellen chart and a note of any correction of vision was made so that plastic glasses could be provided to be used in the MEG machine. A stereoscopic vision test (TNO stereo test, Laméris, Utrecht) was performed to check that the participant had adequate perception of depth. Only participants that could detect 60 minutes of arc binocular disparities or less were included in the experimentation.

RECORDING

The participant entered the magnetically shielded room and was seated underneath the sensors of the device. The head positioning coils were connected to the MEG machine (see below). The seat of the participant was then lifted up

via a foot pump until the top of their head was just touching the apex of the MEG helmet. Two hand held fibre optic response pads were then given to the participant, one for each hand, to activate the response pads the participant was required to place their thumb momentarily over the beam of red light, thus cutting off the beam.

When the set-up was ready, the door to the MEG room was closed, so the room was magnetically shielded. During the experiment, the participant was monitored from outside the room via a video camera (placed in the room) and an audio link. During recording the MEG trace could be viewed in real-time. First control measurements were taken during which the participant was asked to press the response pads and blink, thus it could safely be assumed that the MEG was recording correctly, and the experiment could go ahead.

HEAD-POSITIONING IN MEG

In order to have an appreciation of the underlying anatomical location of any detected signal the position of the participant's head must be know within the sensor array. This is achieved by setting up a coordinate system relative to the anatomical head position of the subject. Marker coils are attached to set anatomical landmarks on the participants scalp. Electricity can then be passed through these coils which in turn generate a magnetic field, detectable by the MEG machine and later processing of this data leads to an activity map over the participants head, as opposed to that in sensor space. This leads to better

comparison of the data between different trials and different participants also allowing inferences to be made on the cortical source of the signal.

TASK

The motor task involved responding to a set of 6 directions – 2 different directions left and right shown three times each. The set was pseudo-randomly generated, with the restriction that an equal numbers of instructions in each direction be shown. For a trial to be valid the participant would have to identify each reference event correctly. To avoid any directional brain functions in characterising the motor response such as those associated with arrows, each reference event was simply a large 'R' for right and a large 'L' for left in a box of similar size and luminance to that of the stimulus used in chapter 3 of this thesis. These reference trials act as a control condition for the experiment conducted in chapter 3 to demonstrate normal motor programming activity in the participants.

RESULTS

MEG signals were recorded in the four participants DOM, IBI, LOM and NEC during sequences of left and right button presses. In this section I will show the results obtained from performing this motor task.

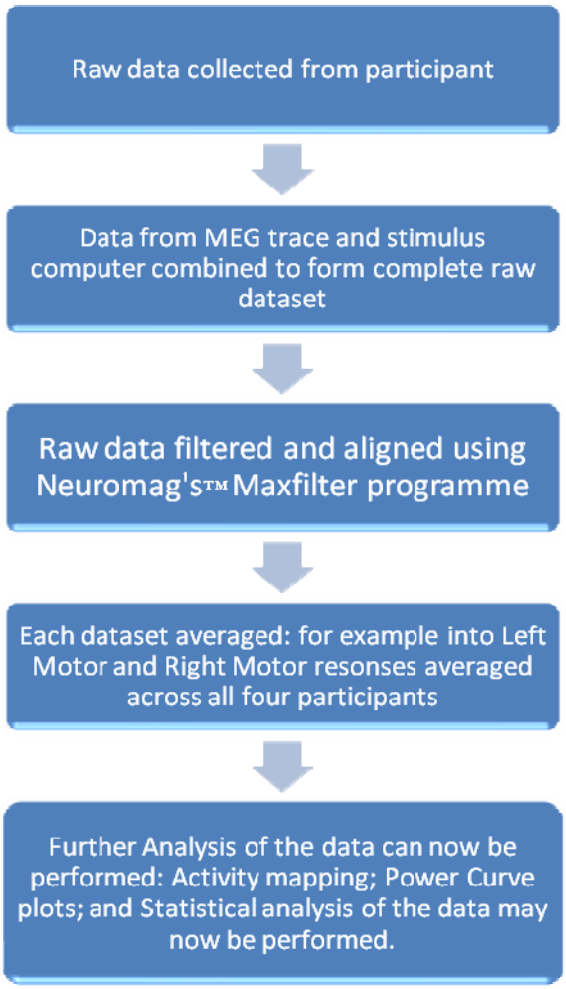


Figure 2.3.1: A flow chart of the order and process of how MEG data is analysed.

I) RAW DATA

The raw data trace is a direct measure of magnetic flux, and hence cortical activity, where magnetic flux is directly proportional to the voltage output of the SQUID magnetometers. The trace (shown below) looks like a long sheet of EEG recordings over 300 channels of data. This data can be interpreted directly, but it is a very complicated and specialist process unsuitable for the material in this thesis. Below is shown an extract from the trace used to typify the motor response taken at a random time over a randomly selected area in signal space. It

can be seen how noisy the raw data looks and the need for epoch selection, filtering and averaging is evident.

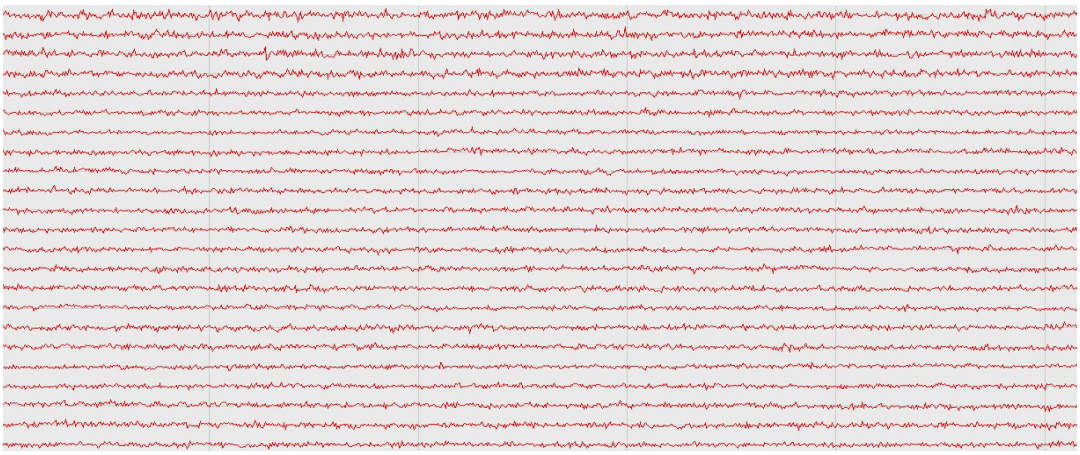


Figure 2.4: Here is a small section of the raw data trace over the parietal region. Each line represents the signal collected from one sensor device. Along the x-axis is time with just over 15 seconds shown (each vertical grey line demarcates three seconds) both magnetometers and gradiometers are shown (magnetometers being every third trace down, their data were not included in the analysis – see chapter 1).

II) EPOCH SELECTION, FILTERING AND AVERAGING

To interpret the data, relevant epochs are extracted from the raw data trace and assigned a label; for example, for the motor signals, data have been extracted from -2000ms before the button press to 2000ms after the button press. The epochs were labelled either as left motor preparation or right motor preparation depending on whether a left motor response or a right motor response occurred. The process of extracting each epoch involved the use of Microsoft™ Excel to create the labels for the epochs. The epochs were then extracted from the raw data using a Perl scrpt, written by S. Braeutigam.

The data contains a lot of noise and artefacts. Neuromag's™ Maxfilter program uses algorithms based on Maxwell's equations to remove artefacts such as sensor and spurious noise; it also acts to align the data over anatomical landmarks rather than with respect to the machine's helmet of coils. Maxfilter performs the removal of artefacts by Signal-Space Separation (Taulu et al., 2005) where it models the brain as being inside an imaginary sphere, the coils to be within a slightly larger sphere and then the outside being everything else. It can then effectively suppress the external interferences from the outside compartment such as electromagnetic pollution, cardiac and muscular activation; artefacts from within the sensor array and imaginary brain sphere can also be suppressed. This is an accepted technique for the initial filtering of MEG signals that has passed peer review (Henson et al., 2009).

Maxfilter was used to align all files to the same head coordinates. The ability to align the data to anatomical landmarks is performed by transforming the measured signals into virtual channels which can be used to compensate for different head positions between participants and also compensate for disturbances caused by head movements during recordings. All the data can be placed over a standardised, common brain. The head coordinates used were based on participant LOMs trial 3, this was decided after careful inspection of the MEG traces for all the participants as her data on this trial allowed a common position that all but one participants coordinates could be aligned to. DOMs data could not be aligned in some cases due to limitations of the algorithms within the program. Instead DOM was centred on approximately the same area space by

aligning to coordinates 0 0 -60 with respect to the centre of the helmet. The data was filtered in the frequency domain based on a fast Fourier Transformation, also known as acausal filtering. A low pass filter was used with the centre frequency chosen to be 30Hz, a roll off of 3dB was used such that at 29Hz the signal was full and at 31Hz the signal was zero (the changes from full transmission to no transmission follows a $\cos^2$ rule). This type of filtering is commonly used to analyse data that is dealt with in the form of epochs, such as that of MEG data (Braeutigam et al., 2001; 2004).

After filtering, it is useful to average all the epochs from different trials together, epochs with identical labels can be averaged together to form a dataset. In this example they were put into datasets for a *left motor preparation* and a *right motor preparation* in response to the instructions presented on the display. The averaging process is useful in minimising any spurious brain activity irrelevant to the studied event, i.e. that of motor preparation. In order to be conserved through the averaging process, an activity needs to be consistently present in each epoch. Any activity spotted is therefore likely to be associated with the event and therefore stimulus. Figure 2.6 shows what the filtered and averaged motor responses from one subject look like. As you can see it looks like lots of 'cut out' sections of raw data centred on an event (i.e. the button press). Each sensor is placed in a position relative to its position on the MEG helmet sensor array. To interpret this data the magnetometers were not considered further, as discussed above, and it would need to be plotted as an activity map (see next section).

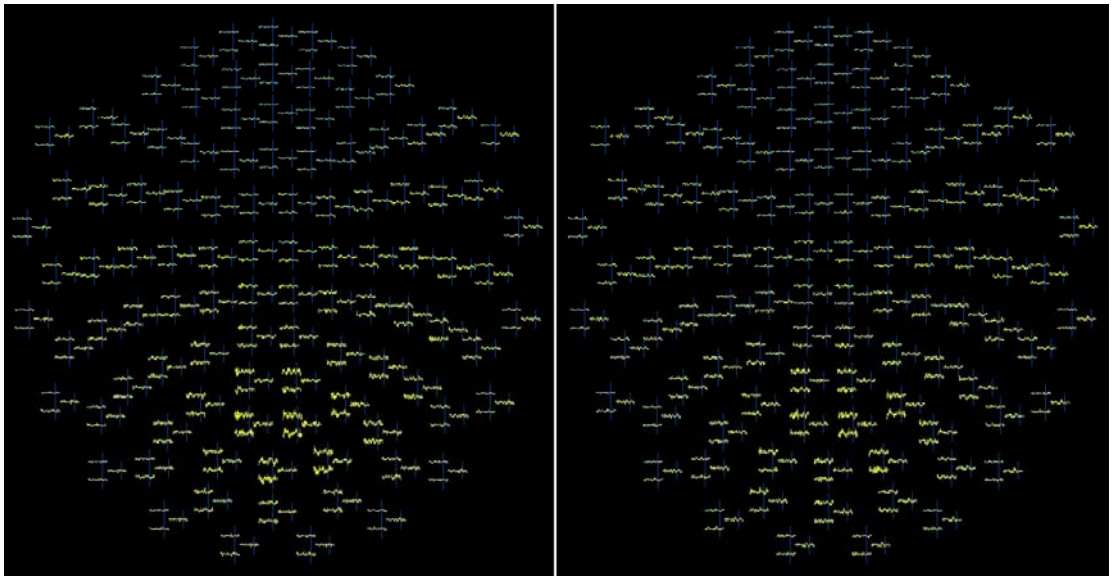


Figure 2.6: Neuromag's™ Xplotter plot of signal over sensor array. For each channel a plot is formed of the averaged epoch over that channel. The y-axis represents activity in femto Tesla; the x-axis is in time from -1500ms to 500ms. Each sensor area is grouped into three data traces two vertically aligned, the gradiometers; and one in the middle of the other two set off to the right, the magnetometer. For further analysis the magnetometer are removed and the two gradiometer data combined to give the response over one sensor area.

III) PLOTTING ACTIVITY MAPS

The functional significance of the above data however is difficult to interpret presented as it is. To make the data more easily interpreted activity maps can be plotted over sensor space. This process requires taking a sampling interval; for the below example steps of 50ms were taken for explanatory purposes only. Each sampled time can be assigned a colour corresponding to its amplitude and plotted in set time increments over the sensor space. This gives a plot of activity with time over the surface of the head; such data is called an activity map plot. However before this is done the magnetometer channels are removed first. Magnetometers respond most to deeper sources and therefore pick up more noise, whereas the gradiometers measure the gradient of the magnetic field and hence are more useful for sensor-space signal mapping (see chapter 1).

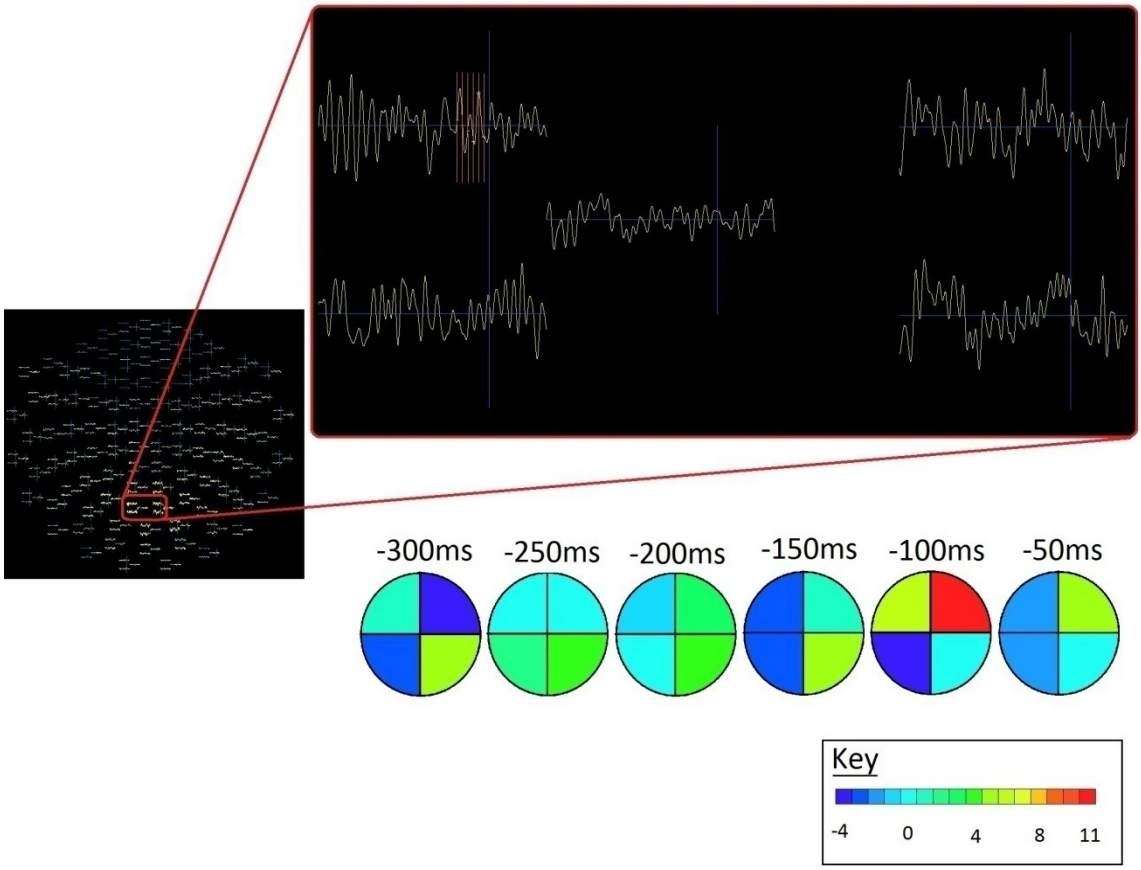


Figure 2.7: This is a simplified demonstration of how activity maps were plotted. To plot the activity map magnetometers are ignored (such as the one in the middle of the group of 5). A sampling interval is then decided upon, in this case 50ms – see the orange lines in the first sensor. At each time point the absolute amplitude of the signal is then assigned a colour according to a key and this is then shaded over the area the sensor was placed and each time interval therefore shows a map of activity over the sensor space (to assess signal strength, root mean square is taken of the combined pair of gradiometers). In this example there are only 4 areas and so the map looks quite simplistic but below are plotted activity maps over the whole sensor array.

The above demonstration is simplified by eliminating several key steps but demonstrates the principle in the overall process. The key steps missed out above are; firstly all the magnetometers are excluded (such as the one in the middle of figure 2.7) leaving only the gradiometers. The gradiometers come as a pair, which both focus on the same area of the scalp. They are orientated orthogonally and as such if the two are combined using Pythagorean theory the activity can be turned into an absolute measure of signal strength. Therefore the next step is that of obtaining a signal strength over that signal space, the

gradiometer pair's signals must hence be combined (by taking the square root of the sum of the square of each signal). The amplitude of the signal can then be assigned a colour and plotted over the signal space – as in the figure 2.7.

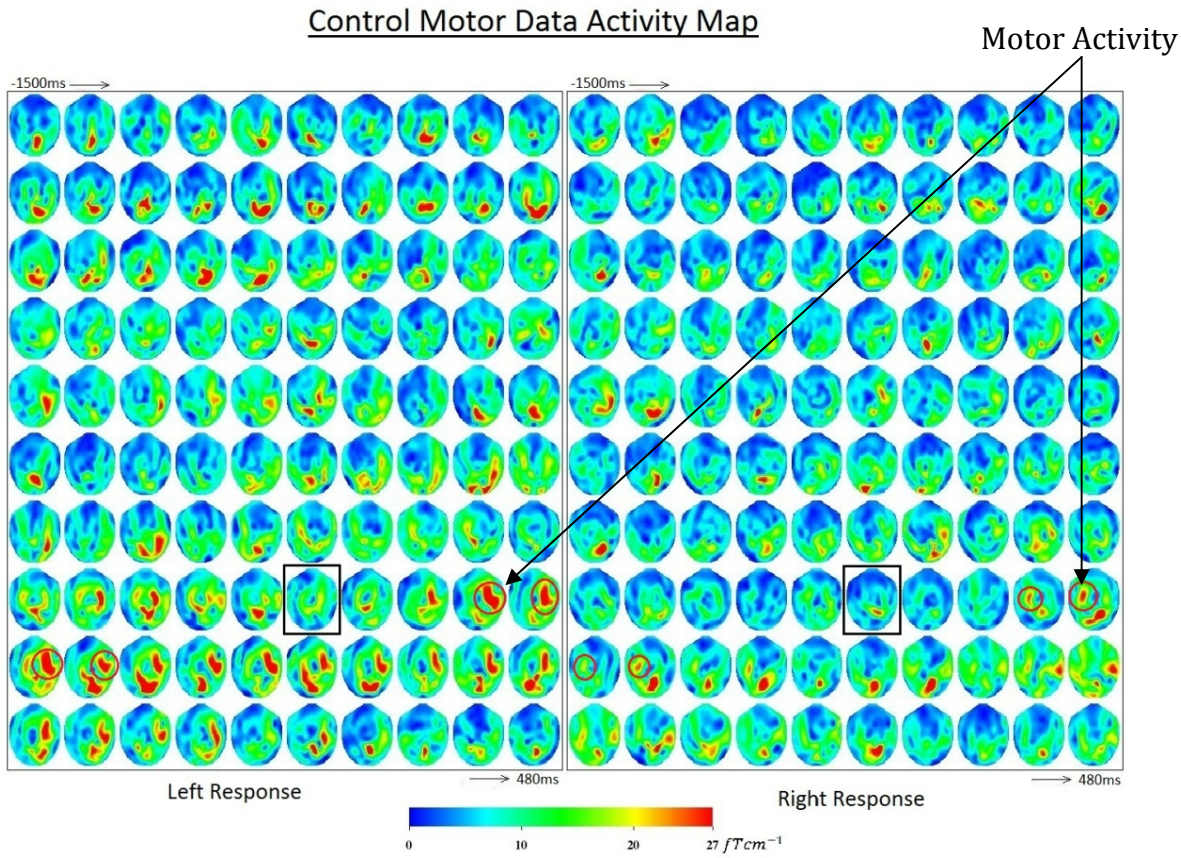


Figure 2.8: Activity map of an average of all participants data showing left and right motor data responses with activity maps orientated with the nose up viewed from above the participant. Plotted from -1500ms to 500ms centred on the participants' response to the stimulus, in steps of 20ms. The top left-hand image of each box represents the activity at -1500ms the bottom-right hand image of each box represents activity at 480ms. The black box is used to indicate the image that represents activity at the time the participant responds to the stimulus. The arrows point to the red circles in the images which indicate the contralateral motor activity associated with the button press.

Figure 2.8 acts as good control data for the experiment detailed in chapter 3. It demonstrates well the movement related cortical potentials in the contralateral cortex (Shibasaki et al., 1980), as indicated by the red circles. The motor activity occurs from around 40ms after the button press showing a direct connection between muscle movement and cortical activity as would be expected with such

a movement, seeing as this is likely to be when maximal muscle contraction occurred: the buttons only needed the participant to obscure the light to be triggered, however participants were instructed to press the button hence, greatest motor activity seemingly post button press.

Prior to a voluntary motor response a phenomenon known as the bereitschaftspotential (or readiness potential) can be observed. This was the final marker to look for to show the motor response recorder in the MEG setup was what we would expect. The bereitschaftspotential is a low frequency response, normally recorded on EEG, seen as an upwards sloping of the baseline preceding the motor response first discovered by Kornhuber and Deeckel in 1964.

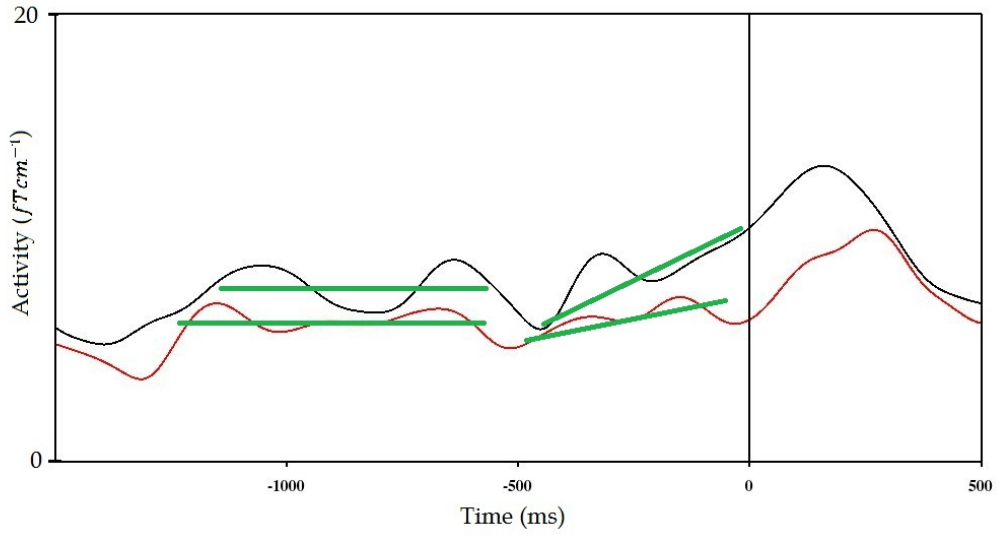


Figure 2.9: Power curve plot of motor data response averaged from all four participants with left motor responses plotted in black and right motor responses in red. Green lines represent baseline activity and the change in baseline with the readiness potential. Strongly filtered with a low pass Fourier filter of 4Hz (roll off 1Hz: see above) to show only the low frequency responses. The x-axis represents time with respect to the participants' response to the stimulus; the y-axis represents activity of the measured signal.

The main features of a bereitschaftspotential can be seen in the figure 2.9 with the baseline changing from level to rising before the motor response. The figure was created by the summation of the square of all the channels activity, the resultant square root was plotted against time. The signal was then heavily filtered to show only the low frequency responses such as that of a bereitschaftspotential (Kornhuber and Deecke., 1964, 1965; Shibasaki et al., 2006 for review).

DISCUSSION

In this chapter I have shown how MEG data is analysed in a step by step process. The motor responses from the data were analysed and a contralateral motor cortical response was shown as expected. Further to this a motor preparation signal was detected (Figure 2.9). This chapter was designed to break down the protocol used in MEG data analysis whilst simultaneously analysing the motor responses of the participants' in order to act as a control for the experiment in chapter 3, thus ensuring the MEG setup was in fact measuring what was expected. This was thought to be necessary in order to familiarise the reader with MEG as it is such a new technology and as such does not appear much in the visual neuroscience literature.

The experiment protocol described above allows good temporal resolution but does not take full advantage of the spatial resolution possible with MEG especially if it is combined with structural MRI data – known as source

localisation. Source localisation was chosen not to be used with this data as the aim was to look for an unknown signal, namely the internal switch. Therefore a broader approach was taken with only the aim of localising the signal down to the nearest lobe, but to get a more accurate time period that future research could home in on.

CONCLUSION

MEG is a powerful yet complex tool which can give remarkable detail in both the temporal and spatial fronts and it does so completely non-invasively. It is therefore a superb tool to use in the study of neurophysiology in humans, particularly that of the visual system where temporal resolution is vital. A first look at the data shows we are getting results that we would expect from standard motor responses to the visual stimuli. This acts as a good control step and foundation for the more complex analysis that will be performed in Chapter three.

Chapter 3

3. PERCEPTION OF A BISTABLE STIMULUS

INTRODUCTION

In this chapter I will investigate the pattern of brain activity preceding reported changes in percept using MEG. I will compare the brain events that precede a switch in reported percept (i) that is intrinsic to the brain and not triggered by a physical change in stimulus (a purely perceptual switch) with (ii) those due to changes in the stimulus (a stimulus induced switch). My aim is to identify activity changes in the brain that are uniquely associated with the intrinsic switch in percept. The time course and location of these neural signals will provide insight into the neuronal signature of the perceptual switching mechanism.

Structure from motion figures allow the reconstruction of an object into three-dimensions through motion cues alone (Wallach & O'Connell, 1953; Ullman, 1979; Treue et al., 1991). The percept of such figures can be bistable, for example in the case of an orthographic projection of a revolving transparent cylinder, which can be perceived as rotating clockwise or counter-clockwise alternatively (Treue et al., 1991). Correlation between MT activity and perceived direction has been shown (Dodd et al., 2001) and it has been theorised that some top down control is responsible for altering the direction of this perception if the stimulus is ambiguous (Krug et al., 2004). It is now believed that control of perception of bistable figures is due to a continuous interaction between low-level and high-level mechanisms (Sterzer et al., 2009; Leopold et al., 1999; Long et al., 2004).

The high-level mechanisms or top-down control could be thought to act as re-orientation of attention such to re-evaluate the current interpretation ultimately leading to a reversal in perception – for the purpose of this thesis this theorised high-level process shall be termed 'an internal switch'.

This 'internal switch' has been proposed to come from either the parietal or frontal cortex (Sterzer et al., 2007, Britz et al., 2009). What still needs to be identified, if we are to accept such a theory, is the 'switching mechanism' itself and how it operates. Sterzer et al. (2007) found an increase in right inferior frontal activation ~800ms prior to MT activation in response to a bistable image. Britz et al. (2009) used EEG to measure participants' responses to a complex Necker cube which was presented for 800ms with a 600ms interval in which the participant was to respond to the stimulus. They found an increase in right inferior parietal activity in the 600ms preceding the presentation of a stimulus which led to a perceptual switch (see Discussion chapter for further discussion of these two studies).

A recent review has recommended further work to be done to add to the findings of several fMRI studies but to use a technique with greater temporal resolution (Sterzer et al., 2009). This thesis aims to do just that, by using MEG to compare two states, namely i) that in which the stimulus evokes the change in perceived direction of rotation – stimulus induced switch; and ii) that in which the stimulus does not evoke the change in perceived direction of rotation – perceptual switch, thus looking to see if there is an 'internal switching' process that occurs in the

perceptual switch that is not expected to occur in the stimulus induced switch. I hope to be able to identify a period in time where this internal switch might be thought to change the perception of the bistable stimulus and show in which region or area of the brain it may be found.

METHODOLOGY

PARTICIPANT SELECTION

Data were obtained from five participants – two male and three females – all naïve to this particular stimulus sequence. One participant had to be excluded because he had difficulty perceiving the bistable stimulus to switch. No participant had any known neurological or psychiatric disorder. All participants had normal or corrected-to-normal vision, and all gave informed consent before experimentation (Helsinki Declaration). The project has ethical approval by Oxford University CUREC.

Participants first took a Snellen test of visual acuity, for which they were asked to read letters off a chart (viewing distance 3m); corrected vision was allowed for and a note of any prescription used was taken so MEG compatible glasses could be made available. The participants' stereoscopic vision was then tested using a TNO chart with red/green glasses, in order to an approximate disparity threshold to be used in the training session (see Obtaining Stereo Thresholds). The final condition for participant inclusion was that they had to respond

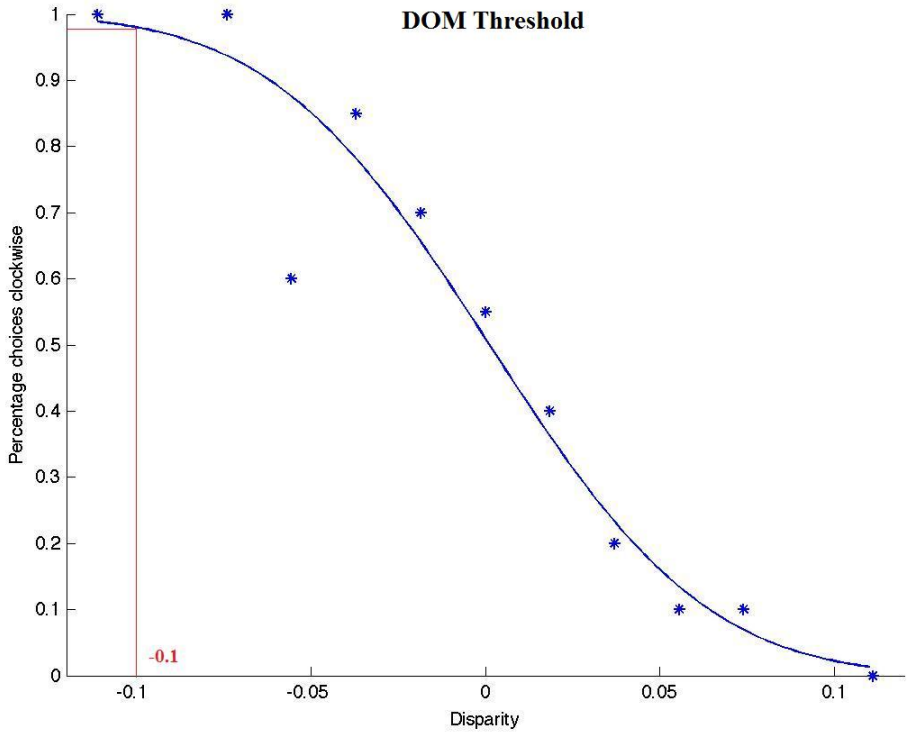
correctly to greater than 90% of the stimulus induced switches during the experiment, otherwise their data were excluded.

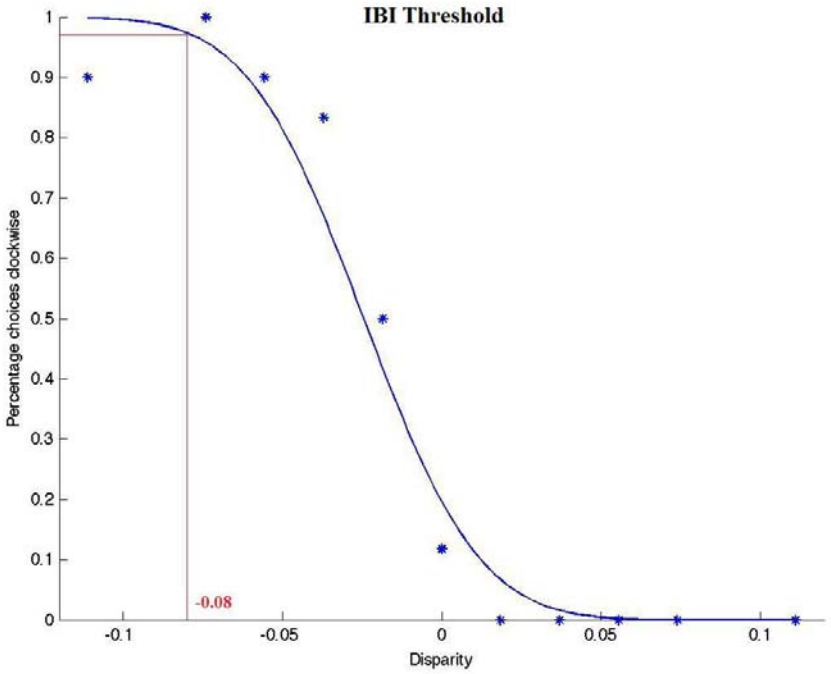
OBTAINING STEREO THRESHOLDS

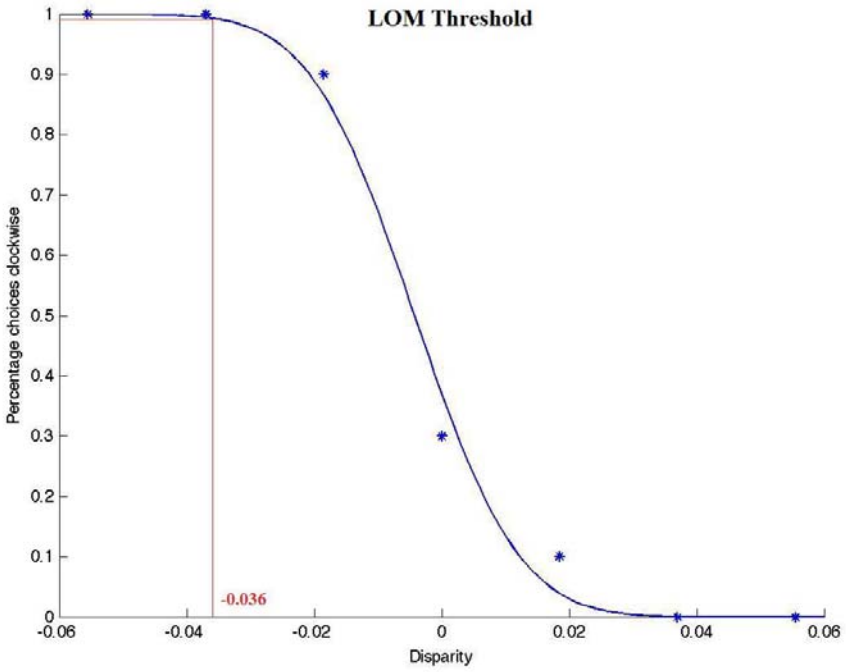
We quantified disparity threshold on the same cylinder stimulus as used in the actual experiments but instead of viewing a constantly rotating cylinder, stimuli were presented for two seconds and then the computer waited for the participant's response before repeating the cycle. This was performed in a dedicated psychophysics set up so as not to use up valuable MEG time. A screen was set up in a blacked out box with the participant 1m from the screen with a refresh rate of 60Hz. The dots that made up the cylinder were 0.11° of visual angle; the cylinder had a height of 8.2° and a diameter of 7.8° of visual angle. The cylinder rotated at a speed of 72° per second. The two main objectives of this session were: a) to find out what disparity was required for the participant to achieve over 95% correct responses, and b) to give the participant some training on the type of stimulus they would encounter within the MEG machine. The disparity for which the participants reported the direction of rotation correctly in over 95% of trials in degrees of visual angle were: DOM 0.1°, IBI 0.08°, LOM 0.036° and NEC 0.1° (figure 3.1).

The protocol for the threshold testing was that the participant was to fix on the fixation dot in the centre of the screen. This was then removed and a cylindrical SFM rotating figure was presented for two seconds. A blank screen was then

presented which waited for the participant to respond before displaying the next stimulus. This process was repeated with different binocular disparities added to the stimulus so that a threshold plot could be obtained (see figure 3.1).




IBI Threshold
Percentage choices clockwise
Disparity
-0.08
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.05
0
0.05
0.1


LOM Threshold
Percentage choices clockwise
Disparity
-0.036
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.06
-0.04
-0.02
0
0.02
0.04
0.06

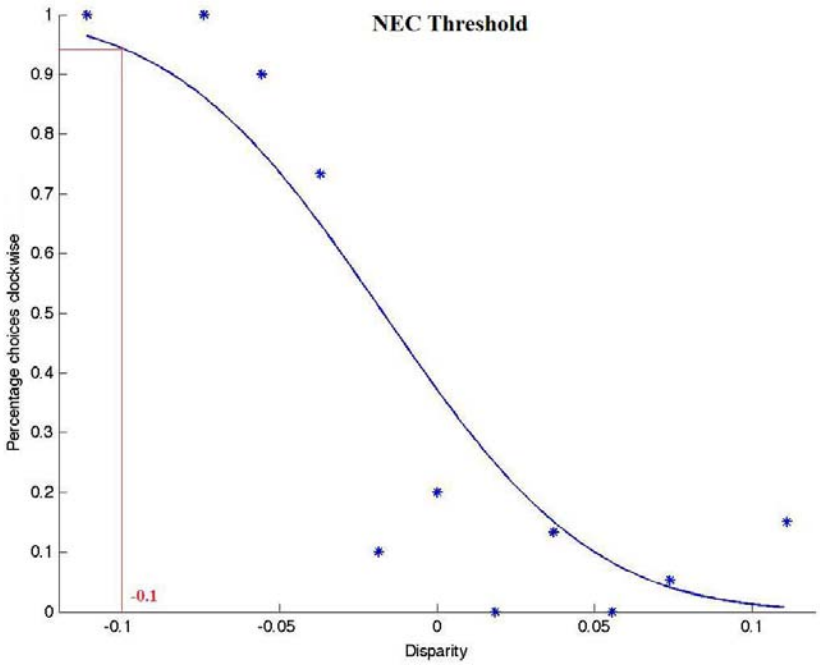


Figure 3.1: showing the psychophysical functions obtained from each of the four participants. The disparity chosen to generate trials with stimulus induced switches for each participant, marked on the x-axis with a red line labelled with the disparity value (the opposite sign cylinder disparity was used for the opposite direction of rotation).

STIMULUS

A Dell PC was used to drive a projector which lit a screen at a viewing distance of 1530mm from the participant. A program, written by Dr. Stuart Gilson to my specifications, was used to project dots onto the surface of a transparent cylinder. The dots were blue and yellow 0.11° of visual angle, the cylinder had a height of 8.2° and a diameter of 7.8° of visual angle. The dots had a sinusoidal velocity profile and the cylinder rotated at a speed of 72° per second. Each dot could be placed closer or further away from the participant in depth using anaglyphic separation viewed through red-green glasses. The stimulus was

programmed such that the depth information would also match the dots progress round the cylinder such that in 3D it followed the contour the surface of the cylinder would follow, in other words the depth information too had a sinusoidal velocity profile. This way, cylinders of differing separation between front and back surface could be created, with cylinders that have smaller separation between front and back surfaces being more difficult to correctly judge their direction of rotation. A cylinder can be presented with no separation between front and back surfaces, these cylinders have no disparity added. Providing disparities used are near threshold, all the cylinders appear the same to the participant (Nawrot et al., 1993a). When viewing the stimulus with no disparity added the cylinder becomes bistable and thus periodically the perception of direction of the cylinder switches. One study, using simlar stimulus parameters for dot density and rotational velocity, has reported cylinder switches at an average interval of around 30s, although they noted this varies widely between participants (Krug et al., 2008).

Triggers from the stimulus program were sent via parallel port to the MEG recording computer to indicate physical switches in the presented cylinder: whether the cylinder was bistable (trigger 5), rotating CW (trigger 9), rotating CCW (trigger 17). This allowed these events to be identified directly on the raw MEG recorded data, for later analysis.

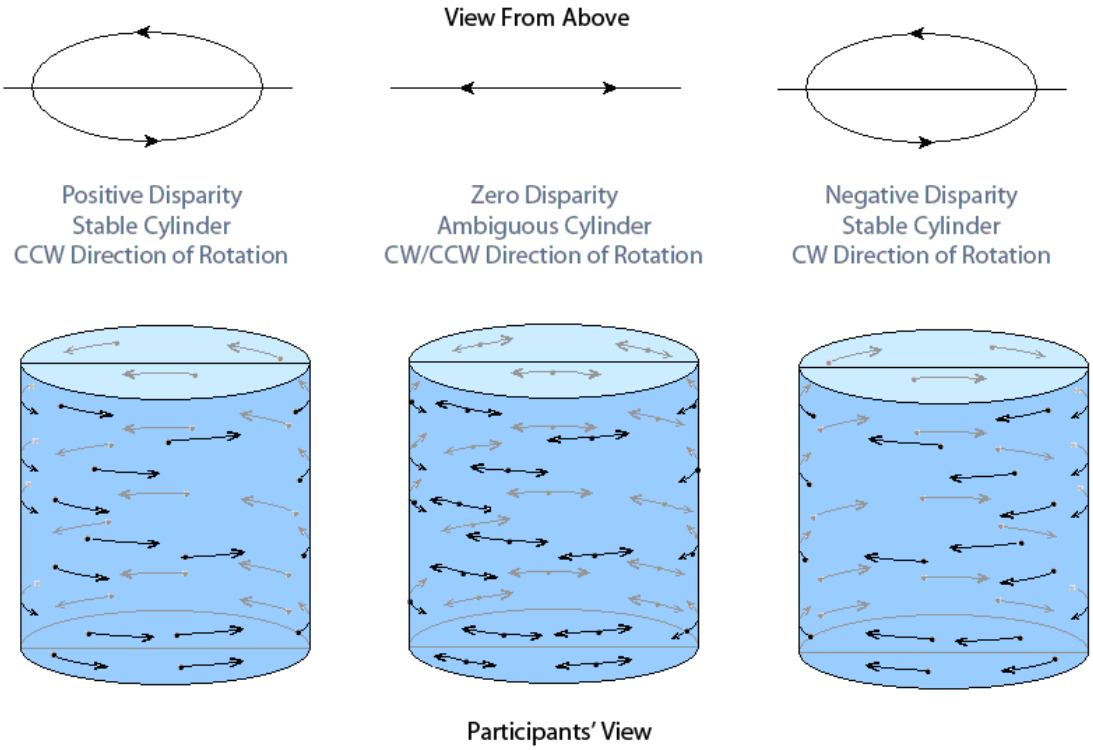


Figure 3.2: the stimulus could take on one of three forms on the left the rightward moving dots were moved closer to the participant whilst the leftward moving dots were moved further away (the converse is true on the right image). This gave a stable cylinder rotating in a CCW direction. In the middle is shown a cylinder with zero depth information added to the dots, this left the cylinder ambiguous as the participant can perceive either layer of dots as being in front of the other. The cylinder can therefore be seen to be rotating in either direction. The images above each cylinder represent an above view of the stimulus here it can be seen what the depth information is doing to stabilise the cylinders on the left and the right.

EXPERIMENT

Participants were asked to wear red/green glasses in the MEG machine with the red glass on the left (the colour scheme used in the nautical world). The participant was monitored using a video camera to ensure adequate concentration and that they were not at any point distressed.

The stimulus was controlled by a series of five text files, each text file corresponding to a trial. These were pseudo-randomly generated in order to make four trials of length 10mins with a total of 76 stimulus events (SIS), 38 in each direction of rotation, where the threshold disparity (figure 3.1) would render the stimulus stable in one direction for several seconds. In the fifth trial (Trial 'E') both cylinder surfaces were at zero disparity rendering the cylinder percept bistable and no change in the stimulus presented occurred. The text file analysis is summarised below:

Trial	Total Length (s)	Total time going right (s)	Number of events going right	Total time going left (s)	Number of events going left
A	600	73	10	73	10
B	600	71	9	71	9
C	600	81	10	87	10
D	600	60	9	60	9
E	500	-	-	-	-

Figure 3.3: Trials A-D were designed pseudo-randomly so that the interleaved stimulus induced switches were of similar proportions and going for equal lengths of time in each direction Total length of the trials was kept to a maximum of 600s. Trial E was completely ambiguous to collect uninterrupted perceptual switches.

(Excluded):	A	B	C	D	E
IBI :	B	A	E	C	D
DOM :	C	D	A	E	B
LOM :	D	E	B	A	C
NEC :	E	C	D	B	A

Figure 3.4: The trials were shown in a different order to each participant and the order was selected using a 5×5 Latin square (Fisher, Frank. 1963). The first participant was excluded from the experiment as he was unable to see bistable switches occurring (see Participant Selection in Methodology).

The first four trials (Trials 'A' through 'D') allowed collection of 76 stimulus induced switches for each participant. A comparison could then be made

between the MEG recorded data for stimulus induced switches and perceptual switches, two seemingly similar events, where the only difference was whether the stimulus induced the switch or the participant internally generated the switch.

ANALYSIS

MEG data analysis is far less standardised than that of the much more widely used fMRI. Careful consideration and planning is essential in designing the experiment and choosing the protocol in which the data is to be analysed in order to best answer the research question. Here the question was to look for differences between perceptual switches and stimulus induced switches by comparing a period of two seconds prior to each event. It would be important to know the switch rate and reaction times (the time taken from stimulus onset to behavioural response) of the participants to ensure the two second epochs being examined were comparable and uninterrupted by confounding events. It may then be possible to use the answer provided by such an experiment to see if it gives evidence for or against an internal switch. The following section gives a brief overview of the meticulous process of MEG data analysis.

The computer programme controlling the stimulus generated a list of its executions so that it could be incorporated onto the raw data produced by the MEG machine. The raw data were arranged onto an Excel spreadsheet and the list generated by the stimulus computer was added to the data – this now

comprised the complete raw data. The perceptual switches and stimulus induced switches were then analysed using Microsoft© Excel. The switch rates of the perceptual switches and the reaction times of the stimulus induced switches were plotted on a log graph so the data fitted a normal distribution. All data outside of two standard deviations were excluded to remove spurious results.

Data were then passed through Elektra Neuromag's™ Maxfilter software (Helsinki, Finland). This acted as a noise filter removing any signals due to artefacts; it then allowed the data to be aligned to fit major anatomical landmarks through the use of the head coordinates obtained from the coils placed on the participants scalp (see chapter 2). The data were then passed through a low-pass filter at 30Hz (see Chapter 2, page 45) to remove gamma band activity as eye movements were not tracked in this experiment.

These data were averaged using Elektra Neuromag's™ Xplotter software (Helsinki, Finland). Averaging assumes that if the same stimulus is shown, then the brain responds similarly. Therefore the signal that survives the averaging process is the signal that interests us most. Xplotter provides graphs of the amplitude of each channel plotted against time. Therefore it allows preliminary viewing of the data that is interpretable by a trained expert. Left and right switches were compared for both perceptual switches and stimulus induced switches, it seemed apparent that there was little difference between the left and right switches. This allowed the data for left and right switches to be averaged together in order to reduce the motor planning signals making the sensory data

easier to interpret. For a more visual representation and further analysis of the data, a program written by S. Braeutigam was used to plot activity maps over a projected brain surface image however spatial resolution on such maps is very poor, localizing signals to the nearest lobe.

For statistical analysis of the data the main aim was to compare the difference in brain activity between stimulus induced switches and perceptual switches. The first step in data analysis was that of a fairly insensitive test of statistical difference, probability spectra, that was used to see if there was any statistical significance in overall brain activation between the two different switches. For this a paired Wilcoxon test was performed comparing all channels in the stimulus induced switches with all channels in the perceptual switches at each point in time. The data was then transformed to fit a Chi Squared distribution by taking a logarithm of the data and multiplying it by minus two (see formula 1). This gave a plot of the logarithm of probability against time.

$$A_{(t)} = \text{prob}(x^2) = \text{prob}\left(-2\sum_{i=1}^{N} \ln z_i(t)\right)$$

Formula 1: detailing the paired Wilcoxon of matched samples and a Chi squared test used in the statistical analysis of data. The paired Wilcoxon test is denoted by 'z', 'N' is the number of channels, 't' represents the time that the statistical test is performed for, and 'x^2' denotes a Chi squared test, 'A' was a global measure of significance, and 'prob' is the significance level of the quantity in brackets. This is a statistical method that has passed peer review (Braeutigam et al., 2001b).

Further analysis of this area in time involved plotting the statistical probability of the difference of brain activity channel by channel to provide a spatial distribution of probability over sites in the brain. This again used the formula set out in formula 1 however the channels were not pooled and a paired Wilcoxon

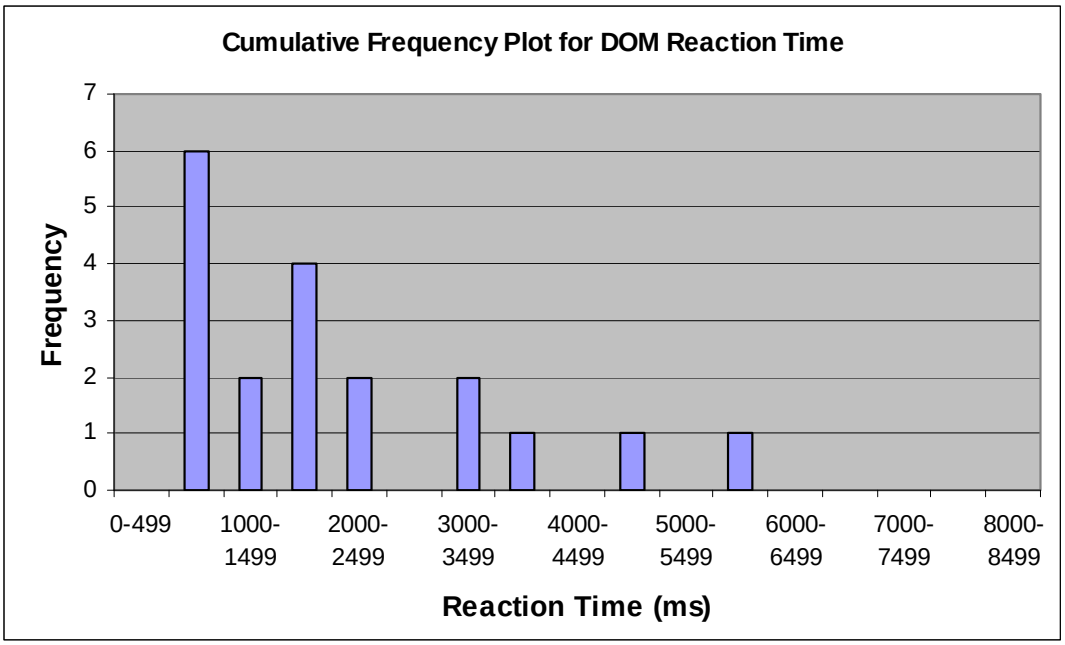
test was performed on all the epochs for each channel at each time point comparing perceptual switches with stimulus induced switches (see formula 1).

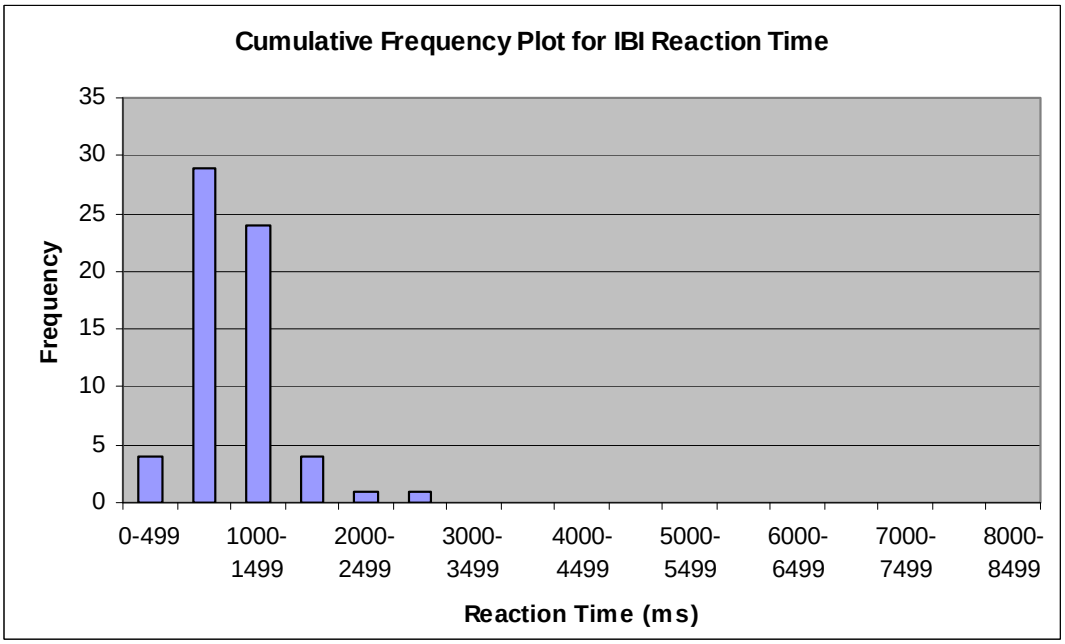
If a statistical difference is found in a spatial distribution plot it is necessary to find out whether that statistical difference corresponds to a signal strength that is greater in the perceptual switches or the stimulus induced switches. This involved combining each pair of orthogonally orientated gradiometers and to plot this signal strength value over signal space. It can then be seen if the area where a statistical significant difference was found shows that difference to be that of greater activity in the perceptual switch state or the stimulus induced switch state.

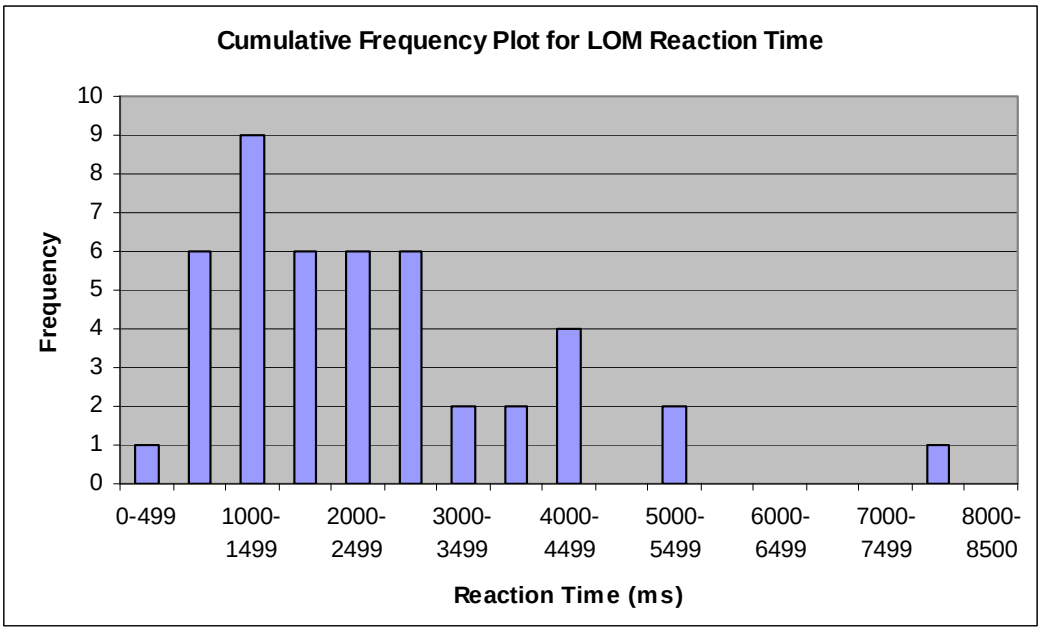
RESULTS

Using MEG, I tested neurophysiological responses from four typical participants to a rotating SFM cylinder. I compared trials where the direction of rotation as defined by binocular disparity changed at intervals and trials where the stimulus did not change but the perceived direction of rotation was bistable. Results are presented as group data, and the individual data will then be closely inspected and analysed to see how well the group data result can be seen in each individual. This allows for thorough scrutiny of the results looking for any bias and to rule out a strong response from one participant dominating the rest, and is thus an important step to take when analysing data from a small participant number.

Reaction time was measured to ensure that there was a common background when comparing perceptual switches against stimulus induced switches between participants. The mean reaction time of participants to the stimulus induced switches were: DOM 1919ms (SD 1603ms), IBI 971ms (SD 442ms), LOM 2370ms (SD 1502ms), and NEC 1993ms (SD 1668ms) (see figure 3.4.1). Data for participants DOM, LOM and NEC were considerably longer than the reaction time data reported in the literature (Treue et al., 1991) only participant IBI's reaction time fitted the expected reaction time for such a stimulus. It must be noted that the task used by Treue et al., was different where the switch was from an 'unstructured' to a 'structured' stimulus, not a change in direction of the stimulus, they reported reaction times of around 1000ms. Although all participants were naïve to this particular set up and were not told the stimulus could be ambiguous, participant IBI had prior experience at viewing SFM cylinders having taken part and run previous experiments. It is for this reason that I suspect her reaction time to be much quicker than the other participants.


Cumulative Frequency Plot for DOM Reaction Time
Frequency
0
1
2
3
4
5
6
7
0-499
1000-1499
2000-2499
3000-3499
4000-4499
5000-5499
6000-6499
7000-7499
8000-8499
Reaction Time (ms)


Cumulative Frequency Plot for IBI Reaction Time
Frequency
0
5
10
15
20
25
30
35
0-499
1000-1499
2000-2499
3000-3499
4000-4499
5000-5499
6000-6499
7000-7499
8000-8499
Reaction Time (ms)



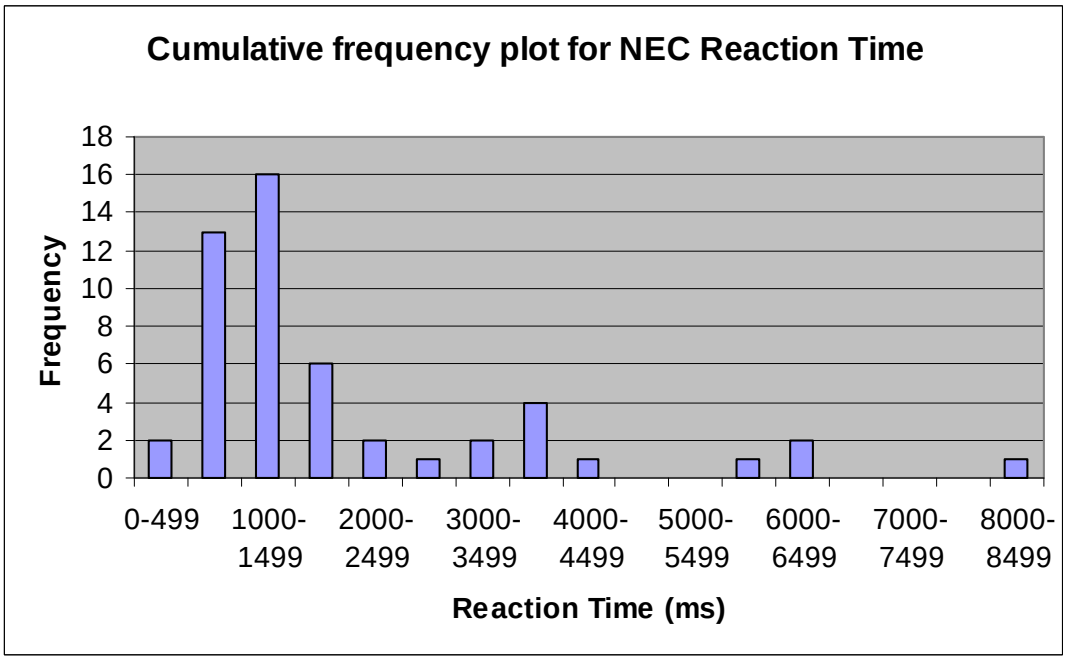


Figure 3.4.1: Reaction time data for participants showing response time in milliseconds on the x-axis and the frequency in number of responses on the y-axis. The x-axis is kept the same across all participants.

Trial E was a purely ambiguous trial where only perceptual switches occurred. Trials A-D had a mix of stimulus induced switches and perceptual switches. For data comparison perceptual switches were taken from trial E only. Stimulus induced switches could only be taken from trials A-D. The decision to take perceptual switches from trial E alone was made to ensure that the number of events of both the stimulus induced switches and the perceptual switches was comparable, thus ensuring the assumptions made when averaging data did not lead to any bias. It also prevented effect of an unambiguous cylinder on the perception of an ambiguous cylinder (Nawrot et al., 1991a).

The data were averaged to create a dataset for each perceptual paradigm using the Xplotter averaging process (see previous chapter); this then gave data that could be passed through statistical filters in order to assess the difference between the two data sets. It was initially performed disregarding spatial information. A probability spectrum was plotted over time in order to first gauge where in time any significant events might occur (see analysis section of this chapter for a full explanation of this statistical process).

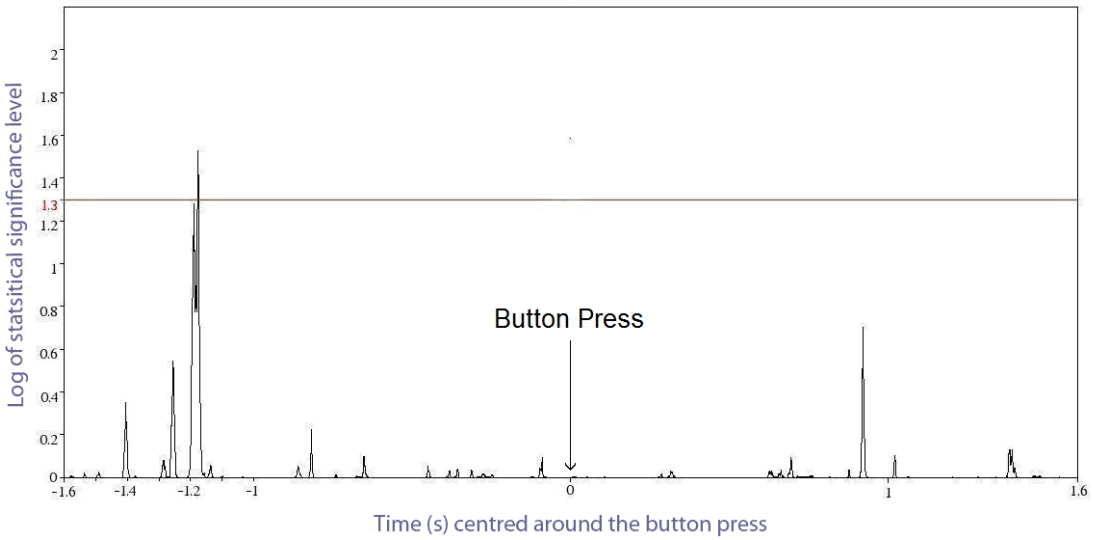


Figure 3.5: Probability spectrum of group data showing the difference in brain activity between perceptual switch and stimulus induced switch from -1.6s before the button press (at 0 seconds) to 1.6s after the button press. The line in red marked 1.3 on the log scale indicates any time period when activity differences cross a significant level equivalent to p<0.05. The y-axis shows the probability A(t) as calculated using the statistical method outlined in the analysis section of this chapter (formula 1). There is clearly one area of statistical significance around -1200ms before the button press (at zero).

A probability spectrum was drawn to compare the brain's activity during perceptual switches and stimulus induced switches, there was one time period at -1210ms to -1150ms before the button press which showed significant differences in activation (Figure 3.5). No significant differences in activity were found after the button press. This indicates that the motor activitythat has made it through the averaging process is similar between perceptual switches and stimulus induced switches.

It is purely the time period around -1180ms where brain activity differs between the two conditions. A close up of this peak is shown in Figure 3.6, focussing on the time period from -1400ms to -1000ms before the participants' response. The peak lasted from -1210ms to -1150 seconds before the button press reaching a

maximum of 1.53 on the log scale, this is equivalent to better than 3% significance.

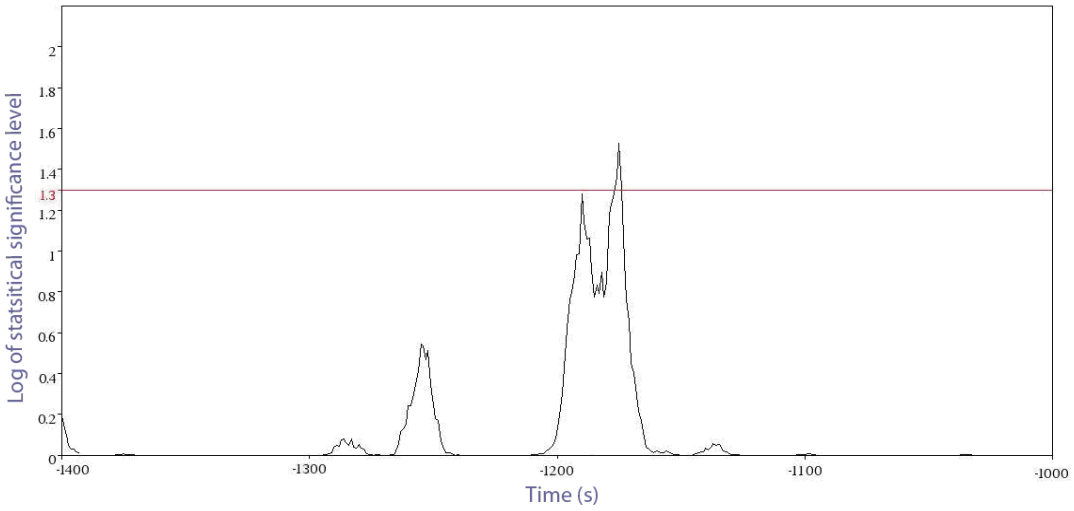


Figure 3.6: shows a close up of the peak in difference between perceptual switch and stimulus induced switch at -1.18s before the button press.

Therefore the data collected showed a statistically significant difference in brain activity between stimulus induced switches and perceptual switches. The next step was to gather some spatial detail from the data at the time found to have a significant difference between the two datasets. This now involved comparing data sensor by sensor using the same statistical method described above. The data could then be plotted with colour to give some spatial information localizing a candidate region to the nearest lobe.

Data were plotted from -1220ms to -1145ms in steps of 5ms averaged across the four participants. The resultant plots were checked in sensor space for areas of significant activation differences ($p<0.05$) looking around the previously identified time period of interest (around -1180ms). Significant activation

differences can predominately be found over the left frontal cortex emerging from -1195ms (figure 3.7). The extent and statistical significance of the activation difference became stronger up to a peak around 1180ms and then fades after 1165ms.

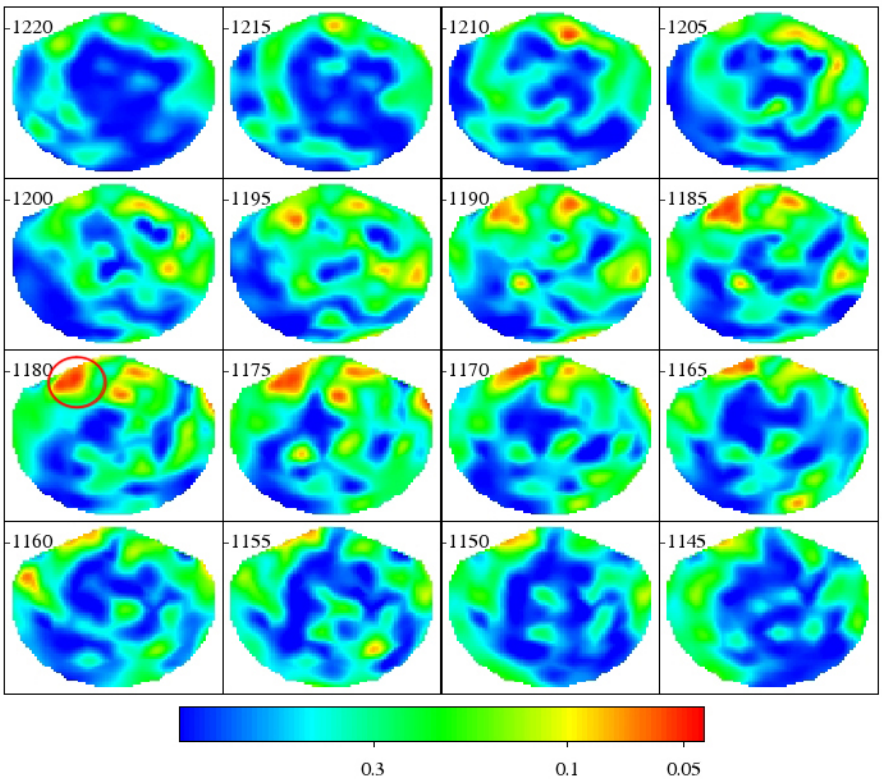


Figure 3.7: Spatial Distribution of Probability over sensor space in the time during the main peak. This is a view from above the sensors with the nose of the participants at the top of the image. Red indicates a statistical significance p>0.05 as shown on the key. The red circle in the image at -1180ms draws your attention to the area of statistical significance in the left frontal cortex.

A power plot over sensor space was then draw where signal strength was calculated taking the square root of the sum of the square of each pair of orthogonally orientated gradiometers (figure 3.8). This now allowed comparison of the two states to see in which state this statistically significant difference in activity was greatest.

Perceptual Switches Stimulus Induced Switches

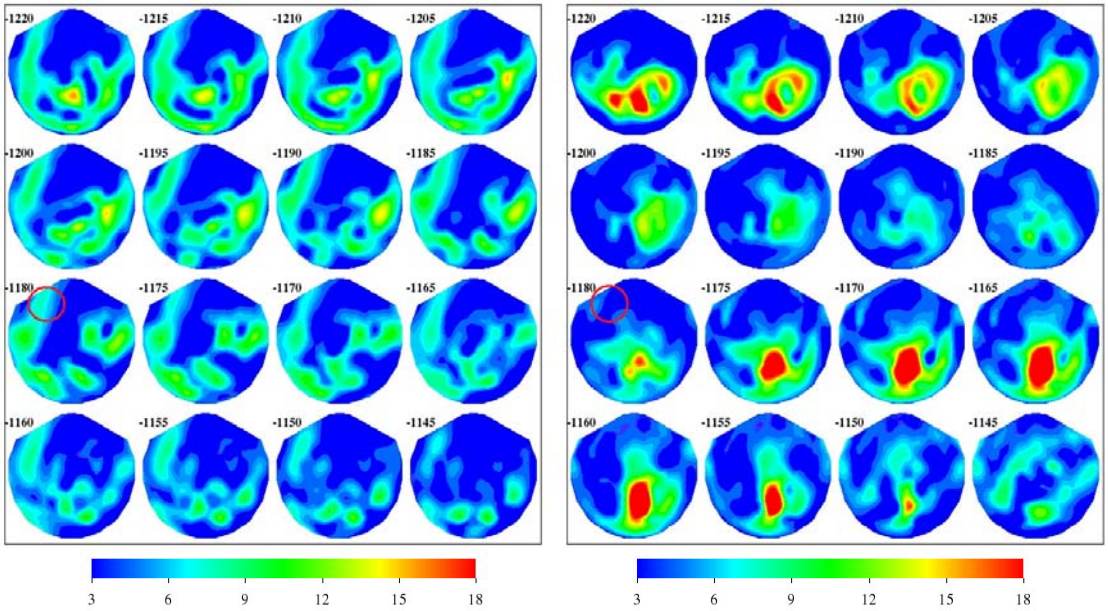


Figure 3.8: Local power plots based on grand mean responses corresponding to probability plot 3.7. It appears that there is a marked increase in occipital lobe signal strength in the stimulus induced switch state from -1175ms however when referring back to figure 3.7 it can be seen that this signal strength difference does not reach statistical significance. The red circles drawn on the figure are superimposed from figure 3.7.

There is greater signal strength in the perceptual switches than in stimulus induced switches at -1180ms over the left frontal cortex. For a more accurate representation of the difference in signal strength a plot was made where the stimulus induced switch signal strength was subtracted from the perceptual switch signal strength (figure 3.9). It can be seen clearly that there is indeed greater signal strength, one of around 4fTcm^{-1}, in the left frontal cortex at -1180ms.

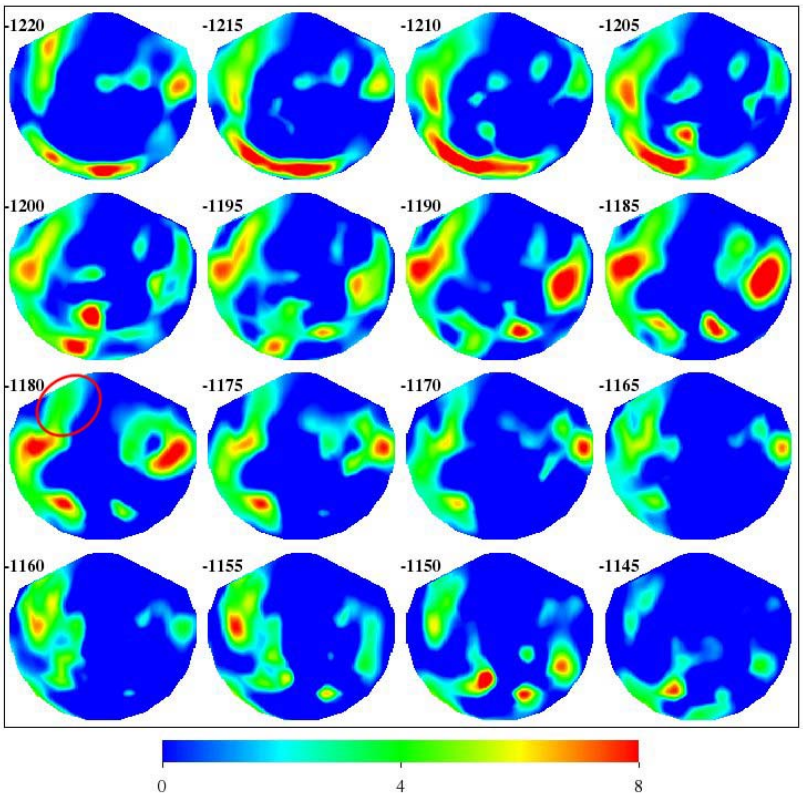


Figure 3.9: Power difference plot showing stimulus induced switches subtracted from perceptual switches. Note that all differences more negative than zero appear blue and as such the occipital lobe increase in signal strength seen in stimulus induced switches in figure 3.8 appear blue. This figure acts merely as an aid to see the value of the difference in signal strength in the area of interest at -1180ms that was statistically significant. It can be seen that there was a 4fT increase in signal strength in the left frontal lobe at -1180ms when comparing perceptual switches to stimulus induced switches.

In summary, a significant difference in the group data at 1180ms before the participants' response was found between the perceptual switches and the stimulus induced switches. Next, I assessed whether the significant events identified in the group data could also be found in the data from each of the individual participants.

It was shown above that there was a statistically significant difference in the activity between perceptual switches and stimulus induced switches in the left frontal cortex at -1180ms before the behavioural response. This difference in activity corresponded to a greater signal strength in perceptual switches over stimulus induced switches in the left frontal cortex at -1180ms. The next step is to see in how many of the four participants this difference can be seen on an individual level and if this difference still holds statistical significance. A probability spectrum plot was drawn including the group data and each of the individual's data (figure 3.10).

In the context of comparing the difference in activity levels of the same individual there is likely to be more background brain activity that is identical trial to trial in each of the two states, namely perceptual switches and stimulus induced switches. The levels of significance are therefore likely to be much greater and the data is more noisy. The main issue was finding the relevant peak in the probability spectrum that correlated to the event that was seen in the group data analysis. This was achieved by comparing the spatial statistical data (figure 3.11 and 3.12) to the probability spectrum (figure 3.10) in order to find a peak that had similar features in space, time and character to the significant peak shown in the group data. These peaks were more obvious in participants DOM and NEC due to the fact that they occurred at a similar point in time to the group data; participant IBI appears to have her peak shifted slightly at -1170ms. For

participant LOM the peak that was most similar to the group data peak was found to be much closer to the button press than expected (see below and figure 3.11).

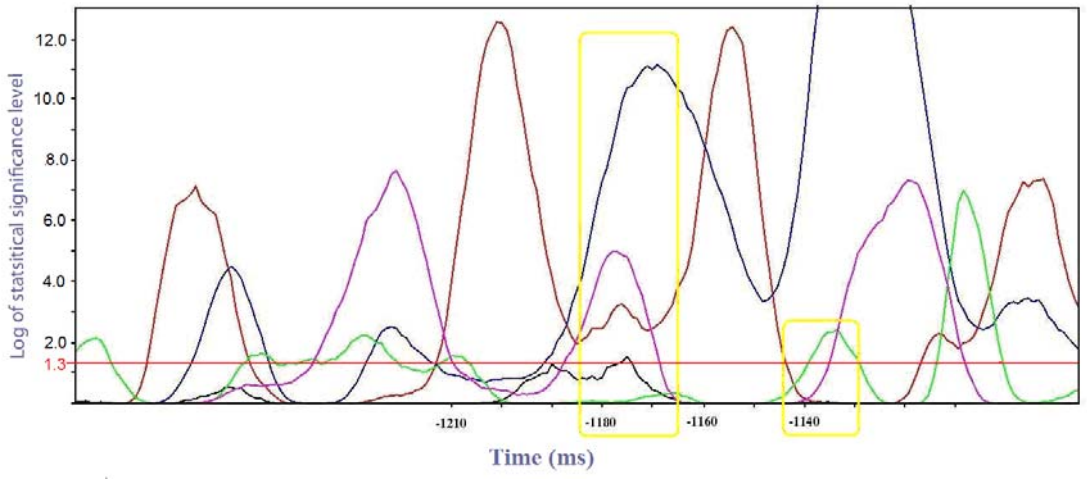


Figure 3.10: Individual and group data probability spectrum plot centred around -1180ms. Black-Group data; Red-DOM, Navy Blue-IBI, Green-LOM, Magenta-NEC. The yellow boxes are placed to illustrate the peaks of interest.

Participant LOM had two candidate peaks, one at -1140ms and one longer peak from -1300ms to -1200ms. To discern which peak signalled activation difference in the left frontal cortex and thus the peak most likely to be associated with the group data result spatial probability plots were drawn and the two peaks, one at-1120ms and one at -1140ms, were examined. Using figure 3.11 it can be seen that the peak from around -1300ms to -1200ms is due to activation in the occipital cortex. However the peak at -1140ms is in the left frontal cortex. Figure 3.12 shows probability data plotted over sensor space for all participants during the relevant time period.

Participant LOM

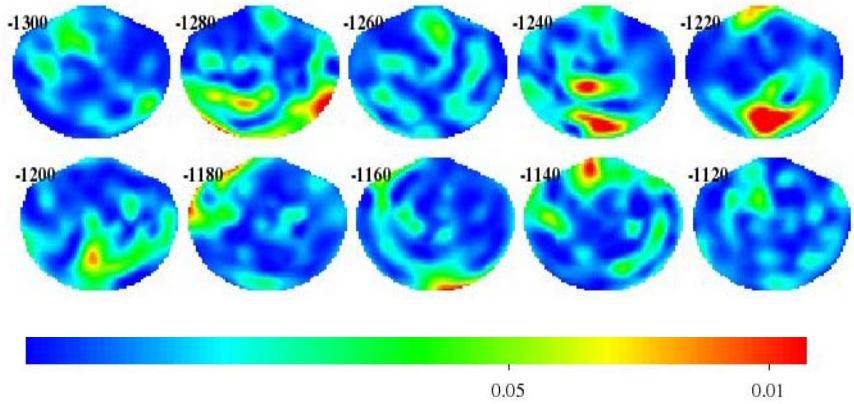


Figure 3.11: Spatial distribution of probability of participant LOM used to identify which peak in the probability spectrum (figure 3.10) corresponded to left frontal cortex activation.

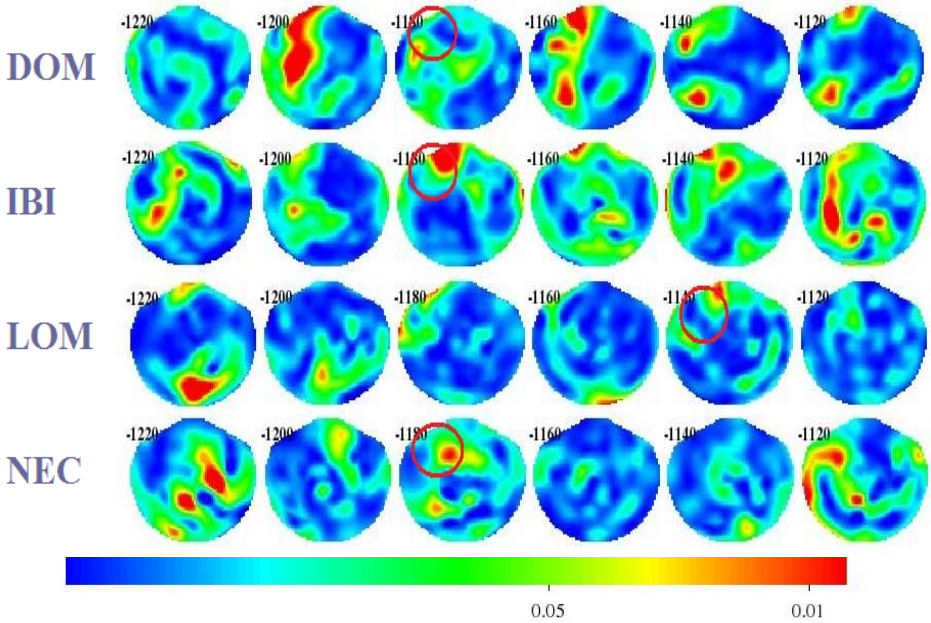


Figure 3.12: Spatial Distribution of Probability plot of individual statistical data. Each participant's data is represented on a different line; red circles are used to signify areas of interest. The time scale was chosen as a common scale in 20ms intervals. Participant IBI's response really was at -1170ms where the significant peak is fairly consistent with the one shown at -1180ms but may expand a little.

Next power plots were taken over sensor space where the strength of the signal was calculated by taking the square root of the sum of the square of the pair of orthogonally orientated gradiometers (Figure 3.13). The stimulus induced switches were then subtracted from the perceptual switches, as performed in the

group data. Figure 3.14 shows the result of the subtraction and it can be seen there is a difference in left frontal cortex activation in all four subjects, however when overlaying the activity data plots onto the probability plots it can be seen that the significance levels only reach 5% ($p<0.05$), the same statistical significant level as found in the group data.

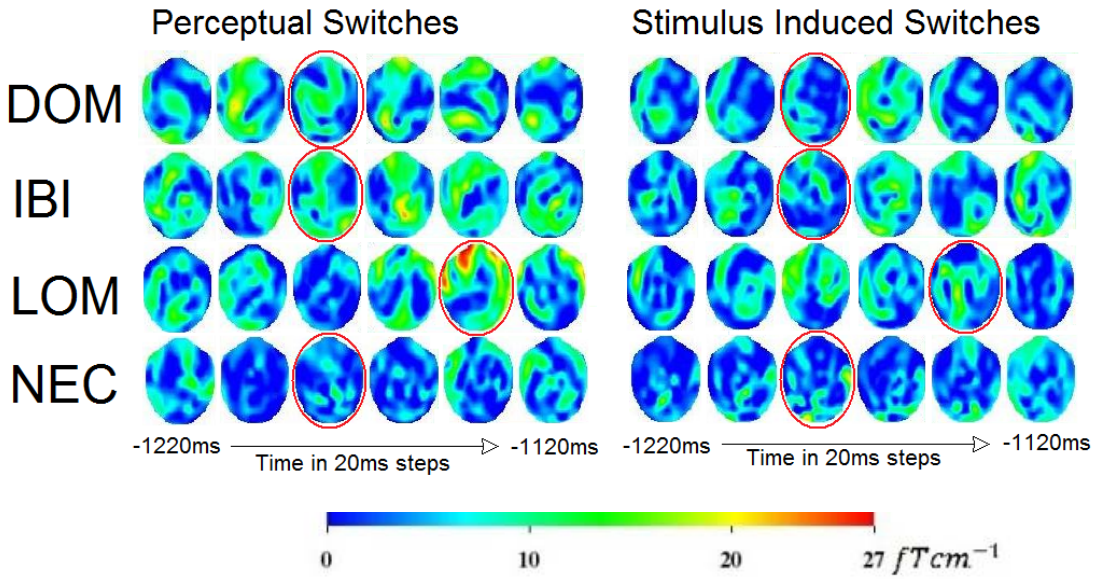


Figure 3.13: Local power plots based on individual responses corresponding to probability plot 3.12. Red circles were placed around peak in individual statistical probability.

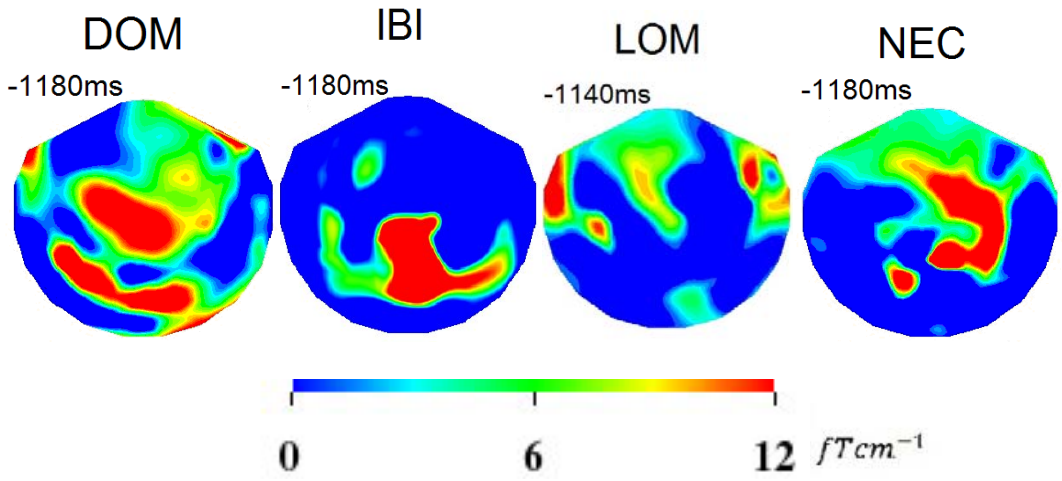


Figure 3.14: It can be seen in figure 3.13 that there is an increase in the perceptual switch signal strength when compared to the stimulus induced switches at the time of the peak in individual statistical probability that fitted with the group data. This figure is a plot of the stimulus induced

signal strength subtracted from the perceptual switch signal strength to make the difference more obvious to the reader. It can be seen that over the area in the left frontal cortex signal strength differences reach 6fTcm^{-1}. To avoid an overcomplicated and confusing figure the colour range was taken from 0fTcm^{-1} difference up to 12fTcm^{-1}, any number less than zero would therefore show as blue thus ignoring differences where stimulus induced signal strength was greater than perceptual signal strength. These differences can be seen in figure 3.13 and figure 3.14 is intended purely as an aid to focus on the relevant difference that occurred over the left frontal cortex making. The reader is encouraged not to take this figure on its own but use it as an aid to interpreting figure 3.13.

Therefore there was a statistically significant increase in signal strength at 1180ms before the behavioural response in perceptual switches when compared to stimulus induced switches that was seen in all four participants ($p<0.05$).

DISCUSSION

This experiment was designed to study the neural basis of perceptual decision-making, in particular to probe differences in brain activity between two different types of perceptual switching; stimulus induced switches and perceptual switches. The main finding was that in the perceptual switches there was increased left frontal sensor space activity at -1180ms before the button press which was of statistical significance ($p<0.05$). This could be the neuronal signature of an internal switching mechanism, which governs changes in the perceptual appearance of bistable figures. The brain region identified warrants further exploration in this context.

Firstly it must be examined whether there are ways to explain the data without such a hypothesis. It is unlikely to be a spurious point, as although the participant number was low the epoch count was high and shown to be reproducible given the statistical significance obtained ($p < 0.05$). However it

could be argued that, due to the very narrow peak in significance level and further that the individual statistical probability plot (figure 3.10) showed an oscillatory nature, the statistically significant result was the result of beta-wave activity falling into phase across the participants at -1180ms before the button press. The author therefore recommends the reader to take caution when interpreting the data presented in this chapter and further analysis of the frequencies of the oscillations is required. It must be noted therefore that a further step of analysis of this data could include separating the data into the different frequency bands as often performed when analysing EEG data.

Due to the frontal location of the activity the response is unlikely to be linked to direct visual processing, which would occur in the classic visual areas, as the frontal lobe is one of the few lobes in which no visual processing is thought to occur. As left and right switches were averaged together any eye movements in the perceived direction would have been cancelled out. Motor preparation is unlikely due to the location of the activity, furthermore typical motor preparation responses are exampled in Chapter 2, and none of the features typical for motor preparation are seen in the activity change 1180ms before the behavioural response. Being frontal brain activity the activation could be an eye blink response, however eye blink activity would be bilateral (or possibly central). Seeing that all our participants did not wink a second before altering their perception of the ambiguous cylinder (no winking was seen through the video link to the MEG scanner) this activity is unlikely to be that of an eye blink.

In the study of visual neuroscience scientists have come up with many different methods of testing perceptual responses. This study adopted the use of a SFM cylinder that was capable of producing perceptual and stimulus induced responses without the subject being able to differentiate between the two. The SFM figure chosen is part of a group of stimuli known as bistable ambiguous figures. Such figures have undergone extensive investigation by neuroscientists over the last century (see Long and Toppino, 2004 for a review). Correlations between neuronal firing in area MT and reported direction of rotation was first shown in Rhesus Macaques by Bradley et al. (1998); further to this work, it has been shown in monkeys that the observed effect is not due to artefacts such as eye movement, behavioural bias or attention to spatial location (Dodd et al., 2001). . An interesting fMRI study (Brower et al., 2007) was able to predict which state of ambiguity the participant was in looking at a variety of dorsal visual areas and area MT. Krug et al. (2004) when testing choice probabilities in correlated and anti-correlated stimuli found that MT neurons with high choice probabilities for a cylinder stimulus had reproducible, selective responses to an anti-correlated stimuli as well. This is not what would have been expected because neurons high up the ventral stream do not respond to anti-correlated stimuli as they do not give a consistent usable binocular depth percept. Showing that perception of these bistable SFM is not yet complete by area MT. As such a top-down mechanism could be at play when an ambiguous SFM cylinder is perceived to switch direction of rotation. This is interesting when trying to determine the role of the signal detected in this study. Top-down control over visual processing has mounting evidence in the scientific literature as described

above. This left frontal brain activity could be higher centres in the frontal cortex sending modulation information to area MT in order to manipulate the perception of such ambiguous stimuli.

There have been two significant studies that look at how processing of reversible figures occurs, in particular looking for evidence of top-down control. However, they did not use SFM figures like the experiments in this thesis. Britz et al. (2009), the more recent of the two, used a complex Necker cube reversible figure which was displayed for 800ms before the participant was given 600ms in which to respond to the figure, this procedure being repeated many times. Using EEG they considered how the brain state prior to a perceptual switch might lead to the switch occurring. Their main finding was of right inferior parietal cortex activity which was significantly more active before a perceptual reversal. In addition to their main finding they discovered bilateral activity in lateral prefrontal regions that did not reach statistical significance, which occurred at 2 intervals of 136-158ms and 306-331ms before the perceptual switch. The second study of note was that of Sterzer et al. (2007). Here the stimuli used were two dots that switched between the four corners of a square at 4Hz. In the ambiguous percepts the dots were in opposite corners and switched to the other two opposite corners. In the stable percept the dots were vertically or horizontally aligned and switched to the opposite side of the square (see Figure 3.11). Participants were then asked whether the dots were moving horizontally or vertically. They found right inferior frontal responses that occurred during the ambiguous trials 784ms +/- 200ms before the behavioural response.

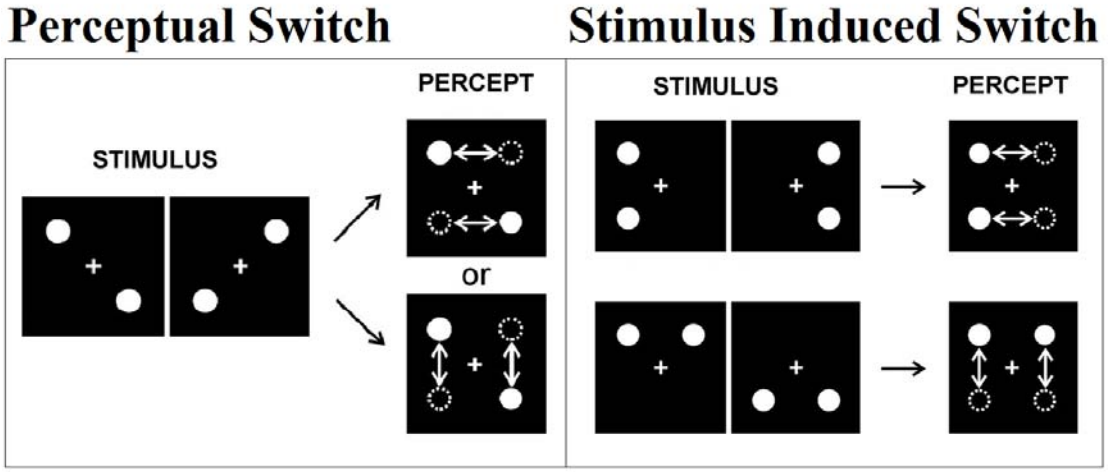


Figure 3.11: taken from Sterzer et al. (2007), figure showing stimulus used by Sterzer et al. (2007).

The study in this thesis implicates activation in a left frontal region at 1180ms before the behavioural response. This highlights a different brain region at a different time than both the studies above. Britz et al. (2009) find a parietal activation greater in the 600ms preceding the stimulus switch. However their method only allows for measurements of brain activity within this 600ms time period. Sterzer et al.'s (2007) main finding was that of right inferior frontal activation, which occurred on average 784ms +/-200ms earlier during perceptual switches than stimulus driven switches when compared to MT activation. Temporally this result is different to the result in this thesis however, there are considerable temporal errors associated with BOLD fMRI imaging in relation to cortical activation. The main problem in comparing their results to the result presented in this thesis is the fact that they found right frontal activation whereas this thesis found left frontal activation. Sterzer et al. (2007) also reported left frontal operculum activity when comparing perceptual Vs stimulus driven switches (p=0.01). The reason this wasn't reported as a main

result was due to the fact there was no significant latency difference detectable between left frontal operculum activity and MT activity. The timing of results from Sterzer et al. (2007) must be taken with caution due to the errors associated with BOLD fMRI where the assumption is made that blood oxygen levels correlate to activation of that brain region. This is a safe assumption to make as metabolically a brain region requires oxygen with increased activation levels however the time errors that are associated with such assumptions make BOLD fMRI only accurate to the nearest second or two (see Chapter 1 figure 1.6). It must also be noted that Sterzer et al. (2007) had a different reference point from the one used in this thesis, namely that of MT activation. Although it might seem our result is several hundred milliseconds before theirs; i) their result is correlated from a reference point of area MT activation whereas results from this thesis are correlated from the motor response (button press); and ii) they point out in their discussion that although they are probing down to milliseconds the technique they are using (BOLD fMRI) allows for errors of up to 200ms, therefore the two studies are not directly comparable. Other studies have requested that further work be done on this phenomenon using a method with much greater temporal resolution (Sterzer et al., 2009) and the study laid out in this thesis has set out to do just that.

Further evidence that a left frontal region could be responsible for perceptual switches was found in a study by Heekeren et al. (2004). When looking at decision making processes they found activation in the left dorsolateral prefrontal cortex (DLPFC). Participants were asked to discriminate between a

face and a house; the images had varying amounts of noise added so as to make the task more or less difficult. The task was made to follow on from previous experiments (Shadlen et al., 1996) and fulfilled the two criteria put forward by Shadlen et al. (1996) for a model of perceptual decision making: the region showed greater activity when the trials were less difficult (less noise were added making the images easier to see), and the activity was correlated with the absolute difference between the signals of face- and house- selective regions (Heekeren et al., 2004). It seems this region has been attributed to simple decision making processes, for example another PET study found left posterior DLPFC activation when participants were asked to perform simple decision tasks e.g. to point to the stripes if they saw a red cue (Petrides et al., 1993). It seems this prefrontal region has general decision making roles and it could act further as top-down control to alter perception to another interpretation of an ambiguous stimulus.

The reaction time data in this study was longer than expected (see Results section above): this led to an advantage when analysing the results. When comparing perceptual switches with stimulus induced switches the perceptual switches are compared over a common background. This is because the signal detected in this study was found at 1180ms before the button press. As three of the four participants took over 900ms longer than this to react to the presentation of a stimulus with a disparity added, they were viewing a constant stimulus during the period a signal was found in the perceptual switch. If however the reaction time of the participants matched with the reaction time

data found in the literature the stimulus induced switch data would have been inconsistent and therefore would have provided a poor background state to compare the perceptual switches too. It would have been unlikely that any statistically significant difference would have been found at the time presented in this study

This observation adds more validity to the results presented in this thesis as at the time of increased brain activity a further variable has been reduced for participants DOM, LOM and NEC. As this experiment shows, the fact that a comparison can be made whilst a constant background state was present in the stimulus induced switch data leads to the ability to make a more poignant interpretation of the data. Further research into this area could aim to include participants with increased reaction times in order to achieve a better comparison of perceptual switches and stimulus induced switches when taking into account that the signal they might detect could be as far before the behavioural response as 1180ms.

The reaction time data for the participants was varied, and exposure to SFM cylinder experiments seemed to decrease the reaction time of one participant (see Results section). In contrast to the difference in reaction time data the timing of the activity suggesting perceptual switching seemed remarkably similar between participants, however it must be noted that individual data analysis was guided by the group data analysis looking only in a narrow time window. I suggest that the consistency seen in the perceptual switch response at

around -1180ms in the individual data could be due to the fact no training is necessary to see spontaneous switches and so the timing of the 'internal switch' matches more closely to the reaction time one would have expected. It would be interesting to take this further and compare reaction data and perceptual switch data in trained and untrained participants.

It would be ideal if it were possible to perform single unit recordings of the activation found in perceptual switches at -1180ms. However when looking for a target brain region whole brain imaging has the advantage of taking into account activation of all neurons. This study has found such a target brain region and time in which to look for this 'internal switch'. With further study being performed in our laboratory, source localization would lead to a better understanding of the brain activity found. It would also be important to continue this work with more subjects. With the greater knowledge of this response and a more accurate result plotted from many participants, source localization or even single unit recordings in primates could lead to a greater understanding of how our brain perceives ambiguous perceptions in the world. It might even be possible to stimulate such an area in order to generate spontaneous switching and this would be a very exciting prospect indeed.

CONCLUSION

In conclusion, there is increased activation of a frontal area in the brain during participant induced switches that is not present during stimulus induced switches ($p < 0.05$). This could be the top-down control predicted (Krug et al., 2004) as responsible for generating the internal switch that causes the well described phenomenon of bistability of certain stimuli. This is an exciting spatial and temporal target needing further work and MEG is an excellent tool for probing into behavioural neuroscience such as this.

Behaviourally lesion experiments have lead to the understanding that perceptual alternations of bistable stimuli are slowed in patients with focal damage to pre-frontal areas (Windmann et al., 2006). To further this work source localisation could be performed to accurately locate the implicated area; an experiment could then be performed using patients with frontal lesions such as those used by Windmann et al. (2006) selecting for those who have damage to the implicated area found using source localisation. Their responses could then be compared to controls using MEG. People with Autism Spectrum Disorder are thought to have a form of frontal lobe failure as well as less global connectivity between different areas of the brain and in the next chapter of this thesis I will look to see how this might affect their perception of a bistable stimulus using a behavioural psychophysics set up.

Chapter 4

4. AUTISM AND VISUAL PSYCHOPHYSICS

INTRODUCTION

This chapter will discuss the results from two psychophysical experiments performed to test the effect of autism on visual processing. Theories have been developed over time to try to explain exactly what makes people with autism different. Theories such as 'theory of mind' (Baron-Cohen et al., 1985), provide some cognitive underpinning to the deficits of individuals with autism in making inferences specifically to do with mental states, characterised by an inability to understand pretence (see Jarrold, 2003 for a review). More recently, 'Weak central coherence' theory has been proposed to account for differences in simple sensory processes (Frith, 1989; Frith et al., 1994), a common example being that autistic children find great ease in detecting embedded figures (Shah et al., 1983). This chapter hopes to look for a difference in how autism might affect the viewing of a SFM cylinder.

Autism is a developmental disorder characterised by an initial overgrowth of neurons in the first few years of life, there is then a degeneration of neurons from the age of 10-20yrs. This degeneration process is thought to occur mainly in the frontal and temporal cortices, the amygdale and cerebellum such that inflammation and degeneration is seen in adult autistic people such that these areas are smaller (Courchesne et al., 2007 for review; this is discussed in more detail in chapter 1). The previous chapter of this thesis found that the frontal

cortex is important in the process of ambiguous switches. Therefore if autistic individuals have an altered structure of their frontal cortex it is likely to have an effect on the top-down control governing perceptual alterations of the stimulus.

Frith and Happé (1994) propose a theory of central coherence in autism that encompasses not only the social and behavioural aspects of autism but also includes some of their increased ability on embedded figures tasks (Jollife et al., 1997; Shah et al., 1983) hence looking at autism not as a disability but as a different way of information processing. Jollife and Barron-Cohen (1997) found that there was a trend for individuals with autism to draw figures in a more fragmented way using more lines than non-autistic adults. It has been suggested that individuals with autism see the world differently (Dalferth, 1989) focusing on the individual elements of an image rather than the whole gestalt. It is known global appreciation of motion is impaired in autistic children (Milne et al., 2002; Pellicano et al., 2005), requiring a higher percentage of dots to be moving coherently in order for the global appreciation of motion to be identified correctly. It is this impaired global appreciation of vision that the second set of experiments aims to test; Grossman and Dobbins (2003) found that such a global appreciation of vision can be seen in the general population where bistable stimuli with aligned axis of rotation will tend to co-rotate. If autistic individuals have a lessened global appreciation of vision this effect should be reduced.

HYPOTHESES

Individuals with autism have differently developed cortices, especially the frontal and temporal lobes (Courchesne et al., 2007). This could affect the top-down mechanisms thought to govern perceptual switching, leaving more control to bottom-up mechanisms such as local instability, therefore it is expected that the average perceptual durations for participants with autism would be shorter than those of typically developed participants. With weak central coherence, global processing in vision in individuals with autism should be weakened. Thus in the second set of experiments it is hypothesised that participants with autism will report less co-rotation for ambiguous cylinders than typical individuals.

METHODOLOGY

ETHICAL PERMISSION

All procedures were performed after obtaining NHS ethical permission (reference number: MSD/IREC/C1/2007/59). All participants gave informed consent before experimentation and were debriefed.

PARTICIPANT SELECTION

Data were obtained from 10 participants with autism, which were age, gender and IQ matched to 7 control participants. Participants with autism were

recruited through adverts or were invited to participate based on their previous contact with Oxford or London researchers. All participants in the autism group had previously been diagnosed on the autism spectrum. Control participants were recruited from Oxford city using poster advertisements (Figure 4.1).

Due to exclusion criteria and the complexity of the task, some of the autistic data could not be used in all the trials and they were matched to the concurrent controls as best could be done (shown in table 4.7 and table 4.12). The control participants had no known psychological or medical disorders. ADOS scores and IQs were taken by trained persons (Dr. Pellicano and Ms. Cicmil). Vision was tested using a Snellen chart with a requirement; participants had normal or corrected to normal vision. Stereoscopic vision was tested using a TNO chart (Laméris, Utrecht) with a requirement that participants were able to distinguish a binocular disparity of 60 minutes of arc.

	Cylinder Speed		Participants with Autism			Control Participants	
	Exp. 1	Exp. 2	Age	IQ	ADOS	Age	IQ
A	n/a	300	32	130	8	30	n/a
B	90	n/a	17	n/a	n/a	n/a	n/a
C	150	60	17	131	9	18	n/a
D	90	300	47	137	7	52	130
E	90	180	22	136	17	21	138
F	90	300	30	125	7	26	123
G	90	90	31	103	n/a	n/a	n/a
H	90	90	35	101	8	26	134
J	18	18	25	128	9	26	118*
K	90	90	36	114	9	n/a	n/a

*Table 4.1: Cylinder speed, Age, IQ and ADOS data for all participants in this study. *held back by non-English mother tongue. Cylinder speed was kept as consistent between participants as possible however the difficulties experienced with autistic participants viewing such complex stimuli meant the speeds had to be adjusted in a minority in order for them to perform acceptably on the task.*

Before they were allowed to take part in the experiment a trial run was undertaken where the participant viewed many SFM cylinders of different disparity increments. This had three main aims: a) as a further exclusion test to ensure the participant could see the stimulus and thus participate in the experiment, b) to get a threshold reading for the binocular disparity to be used in the stimulus parameters (see below), c) to get the participants used to the stimulus. In order to estimate each participant's stereo threshold they were shown unambiguous cylinders with varying amounts of binocular disparity added to specify a particular direction (trials of 1.5 seconds duration). The lowest disparity at which the participant judged 95% of trials correctly was selected as an estimate of the stereo threshold of the participant for use when unambiguous trials were required in the stimulus. If a participant could not reliably judge the direction of rotation at the largest disparity displayed then they were excluded from the study. This allowed confidence to be placed in the ability of the participants to report the stimulus correctly.

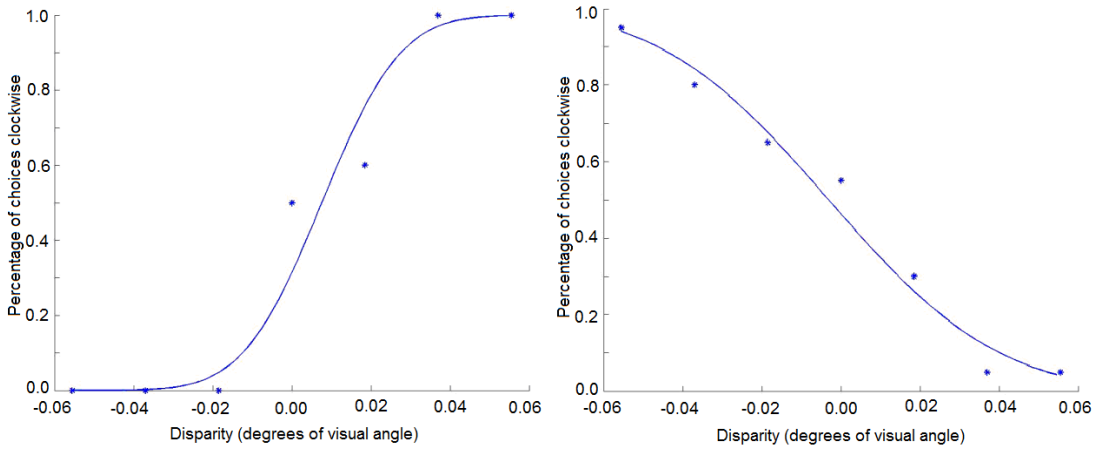


Figure 4.2: example of threshold plots showing one normal response on the left and one reversed response on the right. The reversed response is a unusual phenomenon reported in Carew's

dissertation. Due to the reliability in the performance of the participants with reversal of perception their data was allowed in the final analysis.

APPARATUS AND STIMULI

A Dell Dimension PC was used to power two cathode-ray tube monitors placed side by side in a Wheatstone stereoscope configuration (see figure 4.3). The screens were placed at a viewing distance of 2530mm when viewed through the mirrors. Stereo separation was achieved by splitting the three-channel colour video signal such that the green signal drove one monitor and the red signal the other with the image on each monitor being set to black and white only.

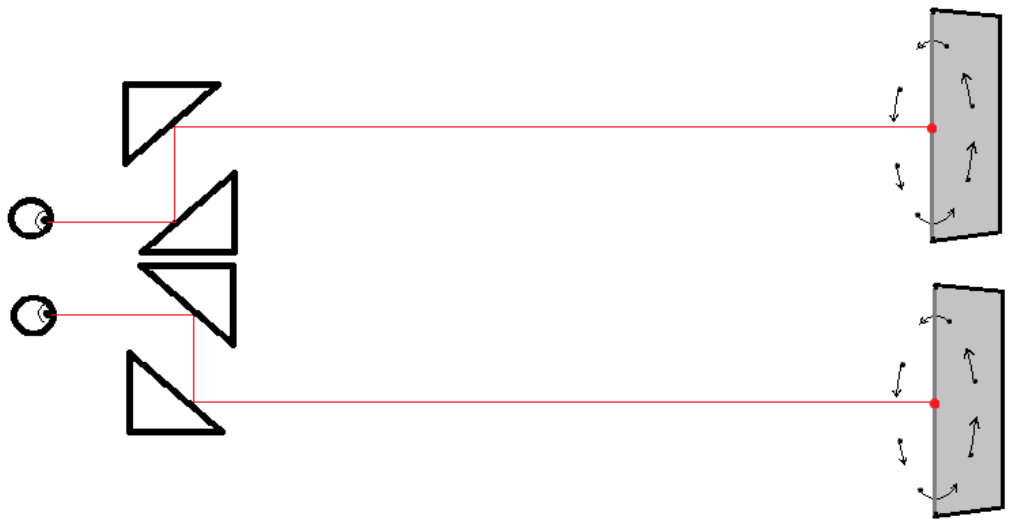


Figure 4.3: Birds eye view representation of the Wheatstone stereoscopic set up used in this experiment with the triangles near the participants eyes representing mirrors and the grey boxes on the right with spinning cylinders representing the left and right monitors used for presenting the stimulus to the participant in three dimensions, note the cylinders on the screen are 2D moving images which when fused by the participant form a 3D perception.

The stimuli used in these experiments were a combination of orthographic projections of white dots placed at random locations on the surface of a transparent cylinder which was rotating around its principle axis. The background was a uniform grey and the stimulus produced the impression of a three dimensional rotating cylinder much like if you were to watch a Coca Cola can rotating on a string from the ring pull (see figure 3.2). For each cylinder the dots were assigned a new random location on the surface of the projected rotating cylinder and in each frame 1% of the dots were re-drawn at random to help prevent tracking of dots, the refresh rate was 60Hz.

A Wheatstone set up allows a separate image to be presented to each eye (figure 4.3). The two images are identical apart from the fact that one image can be shifted horizontally by a certain degree to add a binocular disparity. Such a binocular disparity is interpreted as the image having a depth component to it. Our Wheatstone configuration allowed binocular disparity to be added and a different disparity could be added to dots moving leftwards to those moving rightwards. At zero disparity all dots were in the same depth plane and the cylinder is seen as such due to monocular depth cues such as those used in structure from motion. In this configuration the cylinder is ambiguous and bistable. If a near depth cue is added to all leftward moving dots and a far depth cue is added to all rightward moving dots then the cylinder is seen to rotate in a clockwise direction, the converse is true for counter clockwise rotation (see figure 3.2). To fit in with how the dots would naturally move across a cylinder

surface the disparity added had a sinusoidal velocity profile with maximum displacement at the centre of the cylinder.

I) PERCEPTUAL DURATIONS

It was important to try to keep dot-density and rotational velocity consistent between participants as this is known to have an effect on perceptual durations of SFM figures (Brouwer et al., 2006). 530 dots were used to make up the cylinder the cylinder was rotated 90° per second for all participants except AC (150° per second) and AJ (18° per second): these changes in speed of rotation were made as these two participants were having difficulty seeing the cylinder at 90° per second and altering the rotational velocity was the only way to allow them to take part in the experiment. Note matched controls (CC and CJ) were run at the same cylinder speed as their corresponding autistic participants in order to diminish any effect this might have on the results. Dot size was 0.05° of visual angle, cylinder height was 4.4° and cylinder width was 5.4° of visual angle.

Each trial lasted for a period of 4 minutes with a one minute break in between each run or longer if the participant required, a minimum of 6 trials was performed on each participant. The cylinder was mostly ambiguous but the computer program inserted a few events lasting nine seconds where a binocular disparity was added rendering the cylinder unambiguous. A correct response involved identification of the direction of the stable percept within the 9 second window it appeared on the screen. Half the time this would involve no button

press if the direction of the stable percept was in the same direction as the participant's previous percept. These events were put in place to monitor the participants' attention to the task; participants who correctly identified most of the events were taken to be attending to the task (generally 75% or more but in the case of some participants, where there were too few events to warrant a meaningful conversion into a percentage, a majority was deemed acceptable). The disparity used for these events was calculated from the participant's threshold data where the participant was able to correctly identify 95% of the cylinders at that disparity. Participants were kept naïve to the parameters used and were only told that they were viewing a cylinder that would alter its direction of rotation from time to time. It is known that an unambiguous stimulus can influence future decisions made on subsequent ambiguous stimuli (Nawrot et al., 1991a) so the first response immediately after the unambiguous event was excluded.

II) GLOBAL INFLUENCES ON PERCEPTION OF SFM PROCESSING

Participants were asked to fixate on a small white fixation point in the middle of the screen. A pre-cue arrow would emerge from the fixation point and indicate the cylinder on which to respond to first. It could point in either direction and its direction was altered pseudo-randomly from trial-to-trial. After the arrow disappeared two cylinders would appear either side of the fixation point for 1.5 seconds (Figure 4.6). A blank screen would then be left and the participant would indicate the direction of each cylinder starting with the cylinder indicated

by the pre-cue arrow. The cylinders were either ambiguous or unambiguous. The unambiguous cylinders could be made to rotate in either the CW or CCW direction. Participants were to indicate direction of rotation by a left or a right mouse button click depending on the direction of the front surface of the cylinder so a left click would indicate CW rotation and vice versa. The two cylinders presented on the screen were independent of each other such that two unambiguous, one unambiguous and one ambiguous, or two ambiguous could be presented.

This process was then repeated a minimum of 360 times, this gave at least 40 trials where both the cylinders presented were ambiguous (figure 4.12). A brief description of the trial giving information about the number of cylinders that were to be presented, and when and how to respond to them, was contained in an information sheet given to each participant before the experiment. We were careful not to tell them that any of the cylinders would be ambiguous, therefore keeping the participants naïve to the goals of the research.

Number of dots was 125; cylinders were rotating 90° per second in all participants except AA and AF (300° per second), AC (60°s per second), AE (180° per second) and AJ (18° per second). These values were altered to aid the participants viewing of the stimulus. Note matched controls (CA, CC, CE, CF and CJ) were run at the same speed as their corresponding autistic participants. Dot size subtended 0.05° of visual angle; cylinder height was 1.1° and width 2.0 of visual angle°. Disparity was taken from the participants' threshold plot (Figure

4.2) where participants could be seen to be performing to an accuracy of greater than 95%.

Trials generally lasted 5-10 minutes and participants were encouraged to take breaks when they were tiring. Participants were informed that trials could be stopped at any given point should they tire without any information being lost. This experiment investigated the participants' responses when two ambiguous cylinders were presented, however participants were monitored on accuracy of responses when both cylinders were unambiguous.

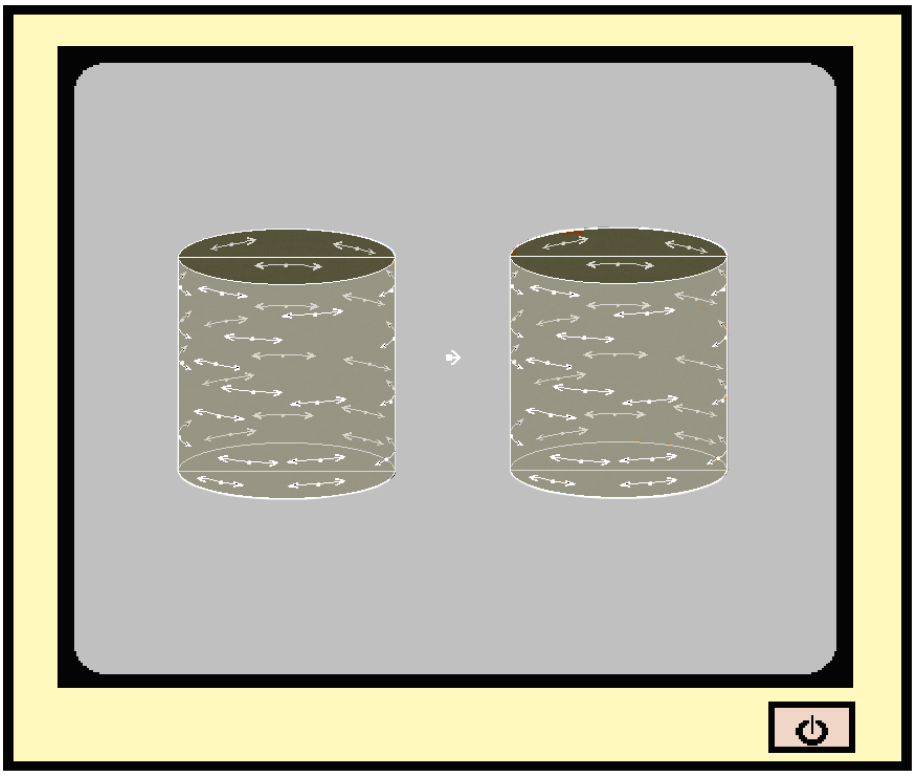


Figure 4.6: Diagrammatic representation of participant's view of stimulus, cue arrow disappears before presentation of the two stimuli which can be in any of the three conditions demonstrated in figure 3.2.

ANALYSIS

For experiment 1, data was imported using Perl programming language and analysed with scripts written specifically to deal with this data. The text files were then modified to be imported into Matlab (The MathWorks Inc.™) for data analysis. For experiment 2, data was imported into and analysed in Matlab (The MathWorks Inc.™) where most of the statistical analysis was carried out. Data was fist analysed for the number of correct responses the participant was able to give and this result was used as inclusion criteria (see above for inclusion/exclusion criteria). Data for the purely ambiguous trials was separated and a program was written to determine whether the participant had perceived the two bistable cylinders as co-rotating or rotating in opposite directions. Finalized data for both experiments were imported into Microsoft© Excel spreadsheet where statistical analysis could be performed. A Mann-Whitney U statistical test was used to test for a significant difference between the two datasets where a significant result was taken if the significance was less than 5%.

RESULTS

(A) PERCEPTUAL DURATIONS

The average duration a percept was stable for when viewing a continuous ambiguous SFM was measured in this experiment. For accuracy it was important that participants were fully attentive to the stimulus, therefore the participants

were expected to get a majority of the disparity events added to the stimulus (see Methods section). Due to the small number of disparity events recorded in some participants a clear majority was acceptable, otherwise participants were expected to get 75% of disparity events correct to be included in this experiment (table 4.7).

Autistic Participant	Perceptual Duration	Number of perceptual switches	Age	IQ	Number of correct responses to disparity events	Total number of disparity events
B	4.6	36	17		0	0
D	2.8	1154	47	137	77	77
H	23.6	23	35	101	2	3
J	44.9	27	25	128	7	10
K	16.4	126	36	114	17	20

Control Participant	Perceptual Duration	Number of perceptual switches	Age	IQ	Number of correct responses to disparity events	Total number of disparity events
A	45.5	24	30		5	6
C	56.6	23	18		4	5
E	8.8	133	21	138	22	24
H	122	12	26	134	1	1
J	91.7	7	26	118	4	4

Table 4.7: Table showing the number of disparity events that the participant responded correctly to (Correct), the total number of disparity events that were presented to the participant (Total), the mean perceptual duration for each participant (Perceptual Duration) and the Age and IQs of the participants.

Four autistic participants were excluded as they did not meet the inclusion criteria for the experiment; one control participant failed to see the bistable cylinder switch and so could not be included (excluded participants are not shown on table 4.7). Participants' with autism had a mean age of 32 years (range 17-47, SD 11.4), IQ of 120 (range 101-137, SD 15.8); control participants' mean age of 24 years (range 18-30, SD 4.7), IQ of 130 (range 118-138, SD 10.6) – IQ data could not be retrieved from participants A and C as they were not available after initial experimentation to come back for an IQ test. Mean perceptual duration for autistic participants was 18s (Range 2.8-44.9, SD 17.0). Mean perceptual duration for control participants was 65s (Range 8.8-122, SD 43.5). This leaves a difference between the means of 46.5s (see figure 4.8).

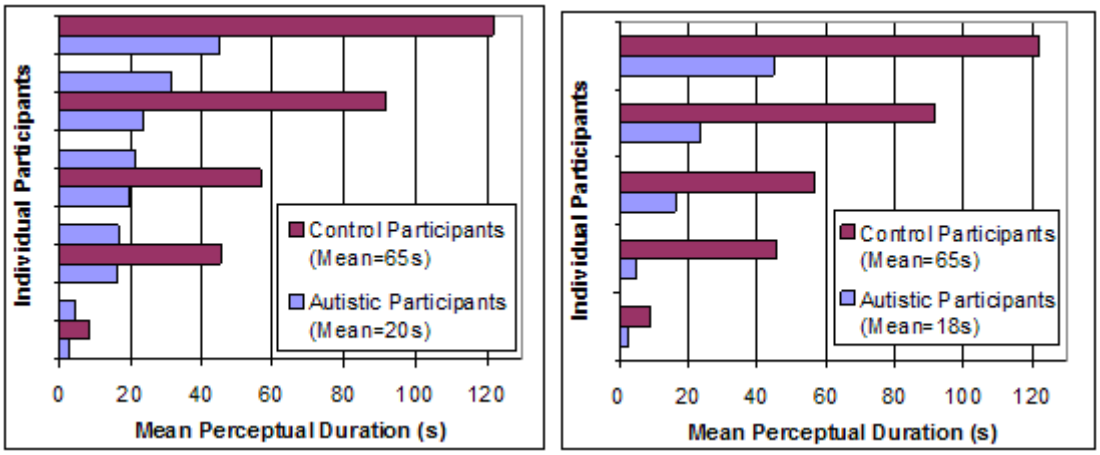


Figure 4.8: The distribution of mean perceptual durations; all participants shown on the left, participants who scored greater than 75% or equivalent are shown on the right.

A two tailed Mann-Whitney U test was performed on the data to see if there was a statistically significant difference between the lengths of the percpetual durations between the two participant groups. The hypothesised difference was

zero; therefore a p-value of less than 0.05 would be sufficient to reject the null hypothesis. The results were compared to a statistical table and it was found that the difference between the two participant groups was statistically significant to 10%. However they were not statistically significant to less than 5%: the difference was not statistically significant enough to reject the null hypothesis. It could be argued this result was borderline significant as the result of the rank sum was 18 and it needed to be 17 or less to reach 5% significance.

Further analysis of the data is important to ensure this result is not biased in anyway by the selection of participants. Three graphs were therefore plotted: one of participants' age against their perceptual duration; another of participants' IQ against their perceptual duration; and a final one to check to see if the extent of the participant's autism disorder had an effect on the result so a graph was plotted to compare ADOS against perceptual duration. No correlation is seen between age, IQ and perceptual duration (Figure 4.10), and no correlation is seen between ADOS and perceptual duration (Figure 4.11).

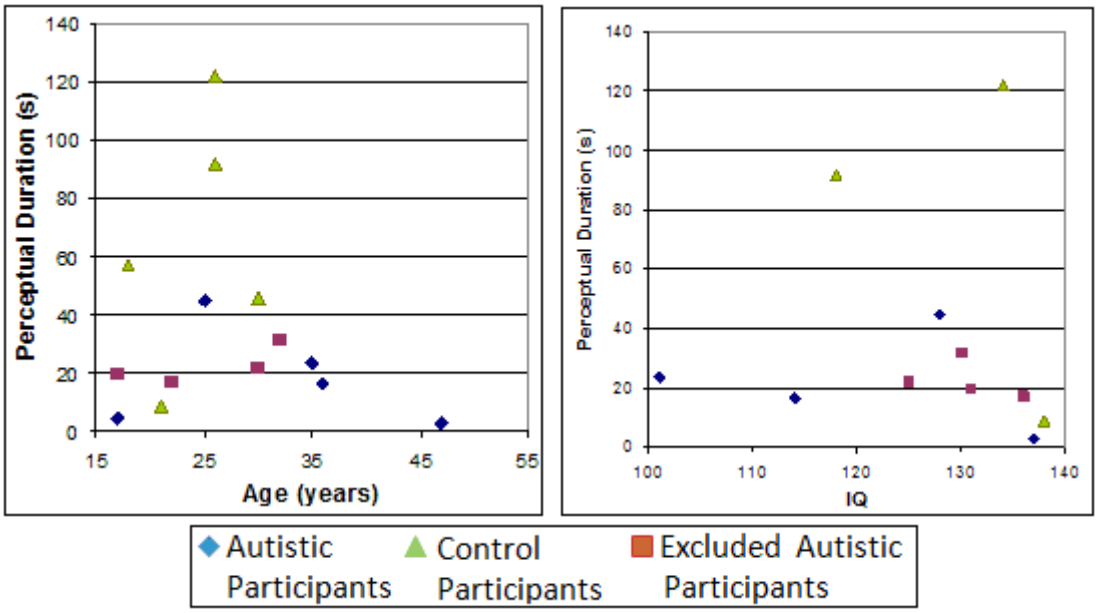


Figure 4.10: Showing scatter plots of IQ and Age against Switch rate showing no correlation between the two and emphasizing the split between the control participants, having longer switch rates, and the autistic participants.

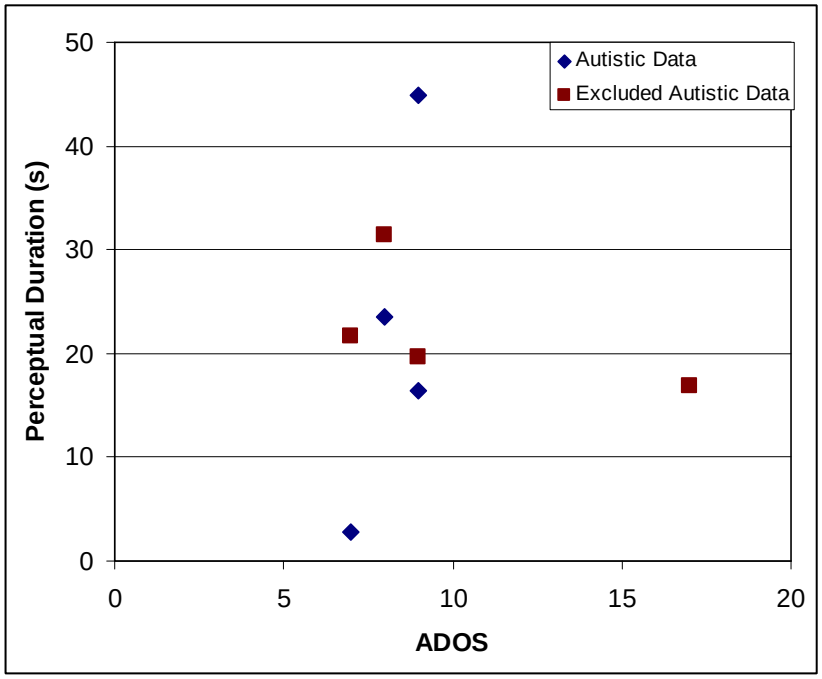


Figure 4.11: Plot of ADOS Vs Perceptual Duration of the autistic participants whom we had ADOS scores from.

In this second experiment participants were asked to give a response to both cylinders presented. Their responses were to be ordered as dictated by the appearance of a cue-arrow before the onset of the stimulus. Participants were excluded if they did not identify 75% or more of the unambiguous cylinders. Six autistic participants and 7 control participants had data that could be included in this experiment. Mean age and IQ for the autistic participants were; 32 years (range 17-47, SD 10.2) and IQ of 124 (range 101-137, SD 13.4); for the control participants mean age was 28 (range 18-52, SD 11.1) with a mean IQ of 131 (range 118-138, SD 8.1), see figure 4.12.

	Autistic Participants				Control Participants		
Participant	% Correct	% Co-rotating	No. Trials		% Correct	% Co-rotating	No. Trials
A	95%	71%	70	A	90%	74%	50
C	4%	73%	30	C	94%	84%	50
D	94%	97%	60	D	98%	83%	40
H	87%	58%	50	E	100%	88%	40
J	24%	78%	40	F	100%	83%	40
K	98%	83%	48	H	76%	88%	50
Mean		77%		J	99%	100%	50
E	54%	95%	20	Mean		86%	
F	66%	68%	40				
G	63%	70%	40				
Mean (all)		77%					

Figure 4.12: Table showing the percentage of unambiguous cylinders the participants were able to identify correctly (% Correct). The percentage of bistable cylinders they reported to be rotating in the same direction (% Co-rotating). The number of trials in which two ambiguous cylinders were shown on the screen. Autistic participant C was consistently seeing the stimulus in reverse as demonstrated in figure 4.2. The reason for this is unclear. But because of the consistency of participant C across different experiments the percentage correct of 4% was corrected to 96% for that particular participant. Autistic participant B did not get round to performing this experiment.

The autistic participant group sees on average 9% fewer ambiguous cylinders co-rotating than the control participant group, but this result was not statistically significant. A Mann-Whitney U test was performed on the data to see if there was a difference between the number of cylinders seen to co-rotate between the two participant groups. The hypothesized difference for the test being zero and therefore a significance level of less than 5% would be sufficient to reject the null hypothesis. When compared to a statistical table the two tailed test was only significant to 20%, therefore the difference is not statistically significant to reject the null hypothesis.

Further analysis was performed to check for other participant factors that might have affected the results. Thus I compared age, IQ and ADOS to the percentage of ambiguous pairs of cylinders (percentage co-rotating) perceived to be co-rotating. For all participants there seems to be no correlation between age and ADOS on the percentage co-rotating. For the control participants there also seems to be no correlation between IQ and percentage co-rotating (Figure 4.14). However for autistic participants there is a weak positive correlation; 44% of the variation in IQ was related to the variation in percentage co-rotating ($R=0.66$, $R^2=0.44$), see figure 4.14. This result was tested for leverage by the removal of the subject with an IQ of 101; on removal of this participant the R^2 value dropped to 0.04 therefore the correlation seen was due to participant selection bias.

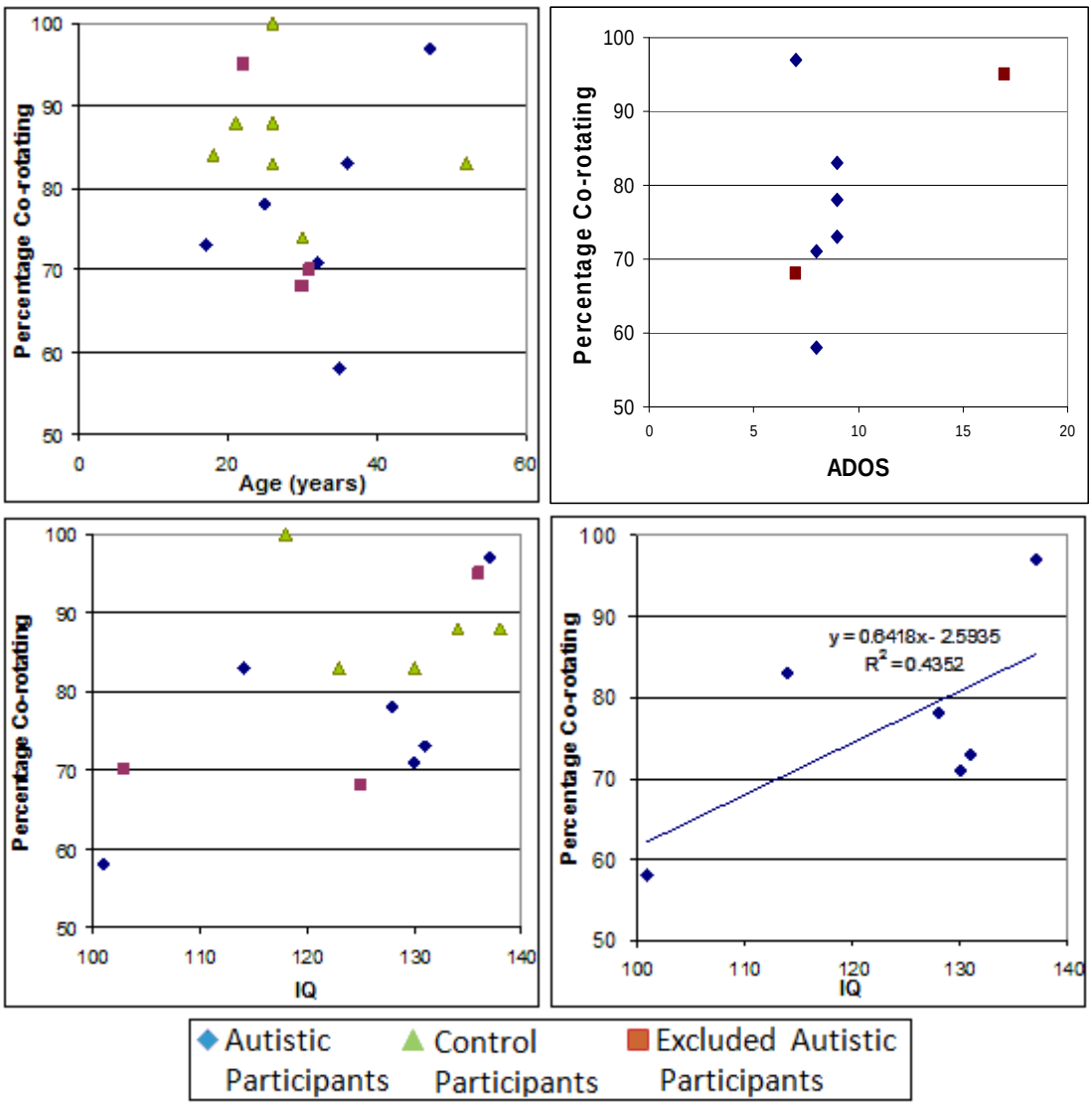


Figure 4.14: Plots of Age, ADOS and IQ Vs the percentage of pairs of ambiguous cylinders seen to be rotating in the same direction.

DISCUSSION

This study examined the effect of autism on the perception of a SFM rotating cylinder. When looking into perceptual durations, it was found that participants with autism do not have a statistically significantly shorter perceptual duration than those of typically developed individuals, however given the small number of participants it could be argued the result was borderline significant ($p<0.10$).

The second experiment was designed to study global influences on visual perception across the visual field, which is evident in the phenomenon that two ambiguous bistable stimuli tend to co-rotate (Grossman et al., 2003). If proposed weak central coherence in autism is evident there may be an effect on this phenomenon. Unfortunately the data did not allow for the rejection of the null hypothesis, as no statistical significance was found when looking for differences in global influences on the perception ($p<0.10$). But the data set was too small to draw firm conclusions. A weak correlation ($R^2=0.44$) was found between autistic participants' IQ and percentage of ambiguous cylinders seen to co-rotate however when assessing for the affect of leverage it was found this significance was only seen when one participant was not excluded: therefore this correlation is an effect of participant selection bias.

In experiment one and two, only 10 and 13 participants could be included respectively. Thus it is difficult to draw firm conclusions about the data and further work must be considered with greater participant numbers. Some difficulty was encountered in this study when running such an experiment on participants with autism. For some participants, it was a surprisingly difficult stimulus to see and it was necessary, in some cases, to alter the rotational velocity of the cylinder in order for the participant to achieve a stable percept (Figure 4.1). It is already known that rotational velocity influences perceptual durations (Carew O, 2008 dissertation; Brouwer et al., 2006). In this experiment it was necessary to alter the rotational velocity in two autistic individuals. To diminish the effect this might have on the results, matched controls were run at

the same rotational velocity as their counterpart autistic participant was run at (see methods). Krug et al. used a cylinder rotational velocity of 90° per second and found control participants to have a mean perceptual duration of 33.5s; it is interesting to note that this is almost double the mean perceptual duration of participants with autism in this experiment (who had a mean perceptual duration of 18s). Further work might endeavour to use more participants with autism, with a much tighter control over the range of cylinder speeds used.

There is some considerable difficulty encountered when performing such complex behavioural psychophysics experiments on participants with autism. Firstly only high functioning autistic individuals were used in this experiment with a mean IQ of 120, even still not all the subjects were able to attempt both tasks and for some the rotational velocities of the cylinder needed to be altered for a stable percept to form; even still there was a high exclusion rate of the autistic participant group. Participants with autism often require that the experimental procedure is laid out in specific detail and that it follow the pre-agreed plan exactly, or the whole affair can become distressing. It is therefore very difficult to experiment on such a group of individuals and it was for these reasons that a greater number of participants was difficult to run. In the first experiment control participant D was not able to see the bistable cylinder switch. The experiment was altered for her to encourage a switch by increasing the number of directional events to 50% of presented cylinders in the final two runs. This led to her correctly identifying the switch but concurrently no further changes in perception was seen. The above was attempted as previous studies

have found the problem where participants are unable to switch percept being stuck in one percept (Rock et al., 1992). Other experiments in the literature seem to have had similar problems to this with a number of participants; some had success by explicitly pointing out the alternative percept to their participants which caused them to start switching (Leeper, 1935; Attneave, 1971). However explicitly pointing out the alternative percept was not an option in this experiment as the participants were to be kept naive to the stimulus thus it was attempted using the directional disparity events near threshold, which are not detectable as different by the participants (Nawrot et al., 1993a), with no success.

It has been shown that individuals with autism have much greater visual acuity than typical individuals (Baron-Cohen et al., 2009). Baron-Cohen et al., suggest that the increased performance seen in embedded figures in individuals with autism (Shah et al., 1983; Jolliffe 1997) could be due to this increase in visual acuity, in conjuncture with weak central coherence, not allowing individuals to see the Gestalt. Thus the same line of thought might apply to the result of this study. If individuals with autism have enhanced low level local processing it could explain why they might show shorter perceptual durations as their top-down processes might be less involved in visual processing. Thus a less stable perception may form when viewing bistable figures as bottom-up control take over the perceptual switching without interplay from top-down control. This in turn would lead to a less stable percept formed of the stimulus and a shortening of perceptual durations.

Pellicano et al. (2005) showed that participants with autism are not able to pick up global motion on a stimulus as well as typical individuals. Using a stimulus made up of randomly moving dots to which a percentage of which were made to move in the same direction, participants were asked to indicate which direction dots were moving. They found children with autism needed a significantly greater percentage (22.4%; 95% CI: 16.0-28.9%) than typical children (11.1%; 95% CI: 9.4-12.9%). They also found similar results to Baron-Cohen et al. (2009) where no early impairment of contrast sensitivity was found in participants with autism. However they did find an inverse correlation ($p<0.005$) between time taken to locate embedded figures and global motion threshold. Therefore participants with autism that had better scores on the embedded figures task (less time to find embedded figures) needed a greater percentage of dots to be moving in the same direction to identify global motion.

Considering the differences in perceptual durations, it would be interesting to test individuals with autism in the MEG scanner in a study similar to that described in chapter 3 of this thesis. It might be discovered that participants with autism lack the top down control over the stimulus and switching occurs predominantly through bottom up mechanisms. Therefore it is hypothesised that individuals with autism might lack the left frontal activation seen at around 1 second before the behavioural response in typically developed individuals.

CONCLUSION

In conclusion this study found that participants with autism have borderline statistically significant shorter perceptual durations of a bistable SFM stimulus than those of age, IQ and gender matched control participants ($p<0.10$). It is suggested that this could be due to participants with autism having greater influence of lower level processing, such as local instability, on the perceptual switch subsequently forming a less stable percept of the SFM cylinder. No such statistical significant difference was found on the global influences of perception on an SFM cylinder between individuals with autism and typical individuals ($p<0.10$). However it is noted that only a small number of participants was used and as such this study would recommend further work performed in this interesting area of visual neuroscience

Chapter 5

CONCLUSIONS

This thesis set out to further the understanding of visual perception. The first half of the thesis discussed a relatively new neuroimaging technique, MEG. MEG was then used as a tool for probing into the activity differences between perceptual switches and stimulus induced switched on a SFM rotating cylinder. Results showed a statistically significant increase in activity during perceptual switches at 1180ms before the behavioural response in the left frontal cortex. It was hypothesised that this increase in activity was due to a higher order neural process involved in causing the bistable SFM cylinder to switch. This could be the neuronal signature for the top-down control over perceptual switching of bistable SFM rotating figures. A good next step would be to analyse this data splitting it up into the spectral bands typically associated with EEG research. This way frequency analysis of the beta band activity could be analysed for oscillations that might explain the result found in this thesis as being due to the oscillations being in phase at 1180ms before the behavioural response.

Further research could use source localisation – a method of taking MEG data and increasing the spatial detail by combining the traces with those of structural MRI data. This would allow identification of the exact region in the left frontal cortex responsible for the increase in signal strength seen in perceptual switches 1180ms before the behavioural response. Additionally the use of a greater

number of participants would lead to stronger statistical results and more confidence in the conclusions drawn. The result presented in this thesis does not show causality, it only shows that a signal exists which precedes the behavioural response consistently. Investigation of causality could be achieved using human transmagnetic stimulation or electrical stimulation in monkeys after further work identifies more accurately the location of the signal.

The second half of this thesis looked at how participants with autism spectrum disorder, who, importantly, have shown reduced frontal lobe volume (Schmitz et al., 2007; Courchesne et al., 2007 for review), may differ in their perception of such a SFM rotating cylinder. Two paradigms were used; one of a continuous SFM rotating cylinder and one of two smaller SFM rotating cylinders placed side by side. The first was looking at the stability of participants' perception, paying particular attention to the perceptual duration of each bistable percept. The second paradigm was looking at how global processing of vision might be affected. Both experiments were designed to probe behaviourally the underlying neuronal defects expected in autism, namely frontal lobe failure and reduced interconnectivity of the cortex respectively. Results showed that participants with autism held shorter perceptual durations of the SFM rotating cylinder than age, IQ and sex matched controls however due to small participant numbers this result was only shown with borderline statistical significance ($p>0.10$). It was suggested that participants with autism might lack influences of top-down control over the perceptual switch leaving less stable bottom-up mechanisms at play such as local instability. No statistically significant difference was seen in

global processing of SFM rotating cylinders between participants with autism and age, IQ and sex matched controls ($p<0.10$). However, this result shouldn't discourage further research in this area as it was noted that only a small number of participants were used in this study and as such more subtle effects might have been missed.

Research would benefit from further study into the effect of autism on perception of SFM figures. This would allow greater understanding of how higher cognitive functions interact with lower cortical function and could further the understanding of this subtle neurodevelopmental disorder. It is suggested by this thesis that a study could be conducted using a similar protocol as that used in chapter 3 of this thesis comparing the functional neuroimaging of individuals with autism to those of typically developed individual – however it would be necessary to confirm the result in this thesis with a greater number of participants first. It is suggested that the activation seen at 1180ms prior to the behavioural response in typically developed individuals, such as those used in this thesis, would be dampened or even absent in autistic individuals. Participants with autism have decreased stability of perceptual durations when viewing a constant bistable SFM. When viewing such stimuli it is thought now that both bottom-up and top-down control interact to create the bistable perception. I suggest that due to the 'frontal lobe failure' seen in autism (see chapter 1, or Courchesne et al., 2007 for review), bottom-up control would play a more prominent role in viewing such bistable SFM stimuli.

Bibliography

BIBLIOGRAPHY

Amano K, Nishida S & Takeda T. (2006). MEG responses correlated with the visual perception of velocity change. *Vision Res* **46,** 336-345.

Andersen GJ, Braunstein ML & Saidpour A. (1998). The perception of depth and slant from texture in three-dimensional scenes. *Perception* **27,** 1087-1106.

Andersen RA. (1997). Neural mechanisms of visual motion perception in primates. *Neuron* **18,** 865-872.

Asperger H. (1944) Die Autistischen Psychopathen im Kindesalter, Archiv fur Psychiatrie und Nervenkrankheiten, **117**, 76-136. Translated by U. Frith in U. Frith (ed.), Autism and Asperger Syndrome (Cambridge, UK: Cambridge University ress, 1991, pp.37-92).

Attneave F. (1971). Multistability in perception. *Sci Am* **225**:63-71

Bailey AJ, Braeutigam S, Jousmaki V & Swithenby SJ. (2005). Abnormal activation of face processing systems at early and intermediate latency in individuals with autism spectrum disorder: a magnetoencephalographic study. *Eur J Neurosci* **21,** 2575-2585.

Baron-Cohen S, Leslie AM & Frith U. (1985). Does the autistic child have a "theory of mind"? *Cognition* **21,** 37-46.

Blake R & Logothetis NK. (2002). Visual competition. *Nat Rev Neurosci* **3,** 13-21.

Blake R, Sobel KV & Gilroy LA. (2003). Visual motion retards alternations between conflicting perceptual interpretations. *Neuron* **39,** 869-878.

Blake R, Sobel KV & James TW. (2004). Neural synergy between kinetic vision and touch. *Psychol Sci* **15,** 397-402.

Bleuler E. (1916) Lehrbuch der Psychiatrie. Translated by A. A. Brill as Textbook of Psychiatry (New York: Dover, 1951).

Bradley DC, Chang GC & Andersen RA. (1998). Encoding of three-dimensional structure-from-motion by primate area MT neurons. *Nature* **392,** 714-717.

Braeutigam S, Bailey AJ & Swithenby SJ. (2001a). Phase-locked gamma band responses to semantic violation stimuli. *Brain Res Cogn Brain Res* **10,** 365-377.

Braeutigam S, Bailey AJ & Swithenby SJ. (2001b). Task-dependent early latency (30-60 ms) visual processing of human faces and other objects. *Neuroreport* **12,** 1531-1536.

Braeutigam S, Rose SP, Swithenby SJ & Ambler T. (2004). The distributed neuronal systems supporting choice-making in real-life situations: differences between men and women when choosing groceries detected using magnetoencephalography. *Eur J Neurosci* **20,** 293-302.

Braeutigam S, Stins JF, Rose SP, Swithenby SJ & Ambler T. (2001c). Magnetoencephalographic signals identify stages in real-life decision processes. *Neural Plast* **8,** 241-254.

Braeutigam S & Swithenby SJ. (2003). Endogenous context for visual processing of human faces and other objects. *Neuroreport* **14,** 1385-1389.

Braunstein ML, Anderson GJ & Riefer DM. (1982). The use of occlusion to resolve ambiguity in parallel projections. *Percept Psychophys* **31,** 261-267.

Britz J, Landis T & Michel CM. (2009). Right parietal brain activity precedes perceptual alternation of bistable stimuli. *Cereb Cortex* **19,** 55-65.

Brouwer GJ & van Ee R. (2006). Endogenous influences on perceptual bistability depend on exogenous stimulus characteristics. *Vision Res* **46,** 3393-3402.

Brouwer GJ & van Ee R. (2007). Visual cortex allows prediction of perceptual states during ambiguous structure-from-motion. *J Neurosci* **27,** 1015-1023.

Carew O. (2008). Stabilising an ambiguous figure using binocular depth. *Oxford University*, Dissertation.

Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, Hof PR, Trippe J, Stone J & Schmitz C. (2006). Minicolumnar abnormalities in autism. *Acta Neuropathol* **112,** 287-303.

Cohen D. (1968). Magnetoencephalography: evidence of magnetic fields produced by alpha-rhythm currents. *Science* **161,** 784-786.

Cohen D. (1972). Magnetoencephalography: detection of the brain's electrical activity with a superconducting magnetometer. *Science* **175,** 664-666.

Courchesne E. (2002). Abnormal early brain development in autism. *Mol Psychiatry* **7** (Suppl 2)**,** S21-23.

Courchesne E. (2004). Brain development in autism: early overgrowth followed by premature arrest of growth. *Ment Retard Dev Disabil Res Rev* **10,** 106-111.

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP & Morgan J. (2007). Mapping early brain development in autism. *Neuron* **56,** 399-413.

Dalferth M. (1989). How and what do autistic children see? Emotional, perceptive and social peculiarities reflected in more recent examinations of the visual perception and the process of observation in autistic children. *Acta Paedopsychiatr* **52,** 121-133.

Dodd JV, Krug K, Cumming BG & Parker AJ. (2001). Perceptually bistable three-dimensional figures evoke high choice probabilities in cortical area MT. *J Neurosci* **21,** 4809-4821.

Eby DW, Loomis JM & Solomon EM. (1989). Perceptual linkage of multiple objects rotating in depth. *Perception* **18,** 427-444.

Fang F & He S. (2004). Stabilized structure from motion without disparity induces disparity adaptation. *Curr Biol* **14,** 247-251.

Ffytchc DH, Catani M. (2005). Beyond localization: from hodology to function. *Philos Trans R Soc London* B **360**:767-79

Fisher RA, Frank Y. (1963). Statistical tables for biological, agricultural and medical research. *Oliver and Boyd***,** Edinburgh.

Frith U. (1989). Autism: explaining the Enigma. *Blackwell*

Frith U & Happe F. (1994). Autism: beyond "theory of mind". *Cognition* **50,** 115-132.

Gilroy LA & Blake R. (2004). Physics embedded in visual perception of three-dimensional shape from motion. *Nat Neurosci* **7,** 921-922.

Grossmann JK & Dobbins AC. (2003). Differential ambiguity reduces grouping of metastable objects. *Vision Res* **43,** 359-369.

Hamalainen MS. Introduction to MEG as a tool for functional imaging: Sources, measurements, and analysis.

Hamalainen MS, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV. (1993). Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Physics* **65**, 413-497.

Happé FG. (1996). Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. *J Child Psychol Psychiatry* **37**(7):873-7.

Happé F, Ehlers S, Fletcher P, Frith U, Johansson M, Fillberg C, Dolan R, Frakowiak R, Frith C. (1996). 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. *Neuroreport* **8**(1):197-201.

Haynes JD & Rees G. (2005). Predicting the stream of consciousness from activity in human visual cortex. *Curr Biol* **15,** 1301-1307.

Heekeren HR, Marrett S, Bandettini PA & Ungerleider LG. (2004). A general mechanism for perceptual decision-making in the human brain. *Nature* **431,** 859-862.

Henson RN, Mouchlianitis, Friston KJ. 2009. MEG and EEG data fusion: Simultaneous localisation of face-evoked responses. *NeuroImage* ***47***(2), 558-9.

Hildreth EC, Ando H, Andersen RA & Treue S. (1995). Recovering three-dimensional structure from motion with surface reconstruction. *Vision Res* **35,** 117-137.

Hill EL. (2004). Executive dysfunction in autism. *Trends Cogn Sci* **8,** 26-32.

Hol K, Koene A & van Ee R. (2003). Attention-biased multi-stable surface perception in three-dimensional structure-from-motion. *J Vis* **3,** 486-498.

Jolliffe T & Baron-Cohen S. (1997). Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? *J Child Psychol Psychiatry* **38,** 527-534.

Julesz B & Oswald HP. (1978). Binocular utilization of monocular cues that are undetectable monocularly. *Perception* **7,** 315-322.

Kallen RJ. (2001). A long letter and an even longer reply about autism magnetoencephalography and electroencephalography. *Pediatrics* **107,** 1232-1235.

Kanner L. (1995). [Follow-up study of eleven autistic children originally reported in 1943. 1971]. *Psychiatr Enfant* **38,** 421-461.

Kornhuber HH, Deecke L. (1964). Hirnpotentialanderungen beim Menschen vor und nach Willkurbewegungen, dargestellt mit Magnetband-Speicherund und Ruckwartsanalyse. *Pflugers Arch* **218**, 52.

Kornhuber HH, Deecke L. (1965). Hirnpotentialanderungen bei Willkurbewegungen und passiven Bewgungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflugers Achiv* **284**, 1-17.

Kreiman G, Fried I & Koch C. (2002). Single-neuron correlates of subjective vision in the human medial temporal lobe. *Proc Natl Acad Sci U S A* **99,** 8378-8383.

Krug K. (2004). A common neuronal code for perceptual processes in visual cortex? Comparing choice and attentional correlates in V5/MT. *Philos Trans R Soc Lond B Biol Sci* **359,** 929-941.

Krug K, Akerman CJ & Thompson ID. (2001). Responses of neurons in neonatal cortex and thalamus to patterned visual stimulation through the naturally closed lids. *J Neurophysiol* **85,** 1436-1443.

Krug K, Brunskill E, Scarna A, Goodwin GM & Parker AJ. (2008). Perceptual switch rates with ambiguous structure-from-motion figures in bipolar disorder. *Proc Biol Sci*.

Krug K, Cumming BG & Parker AJ. (2004). Comparing perceptual signals of single V5/MT neurons in two binocular depth tasks. *J Neurophysiol* **92,** 1586-1596.

Kubota T, Kaneoke Y, Maruyama K, Watanabe K & Kakigi R. (2004). Temporal structure of the apparent motion perception: a magnetoencephalographic study. *Neurosci Res* **48,** 111-118.

Kylliainen A, Braeutigam S, Hietanen JK, Swithenby SJ & Bailey AJ. (2006). Face and gaze processing in normally developing children: a magnetoencephalographic study. *Eur J Neurosci* **23,** 801-810.

Leeper R. (1935). The role of motivation in learning: a study of the phenomenon of differential motivation control of the utilization of habits. *J genet Psychol*

Leopold DA & Logothetis NK. (1999). Multistable phenomena: changing views in perception. *Trends Cogn Sci* **3,** 254-264.

Leopold DA, Wilke M, Maier A & Logothetis NK. (2002). Stable perception of visually ambiguous patterns. *Nat Neurosci* **5,** 605-609.

Leslei AM. (1987). Pretense and representation: The origins of “theory of mind” *Psychological Review* **94**:412-26.

Levy F. (2007). Theories of autism. *Aust N Z J Psychiatry* **41,** 859-868.

Liu J, Harris A & Kanwisher N. (2002). Stages of processing in face perception: an MEG study. *Nat Neurosci* **5,** 910-916.

Livingstone MS & Conway BR. (2004). Was Rembrandt stereoblind? *N Engl J Med* **351,** 1264-1265.

Livingstone M, Hubel D. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science* **240**:740-9

Logothetis NK, Leopold DA, Sheinberg DL. (1996). What is rivalling during binocular rivalry? *Nature* **380**, 621-4.

Long GM, Stewart JA & Glancey DE. (2002). Configural biases and reversible figures: evidence of multilevel grouping effects. *Am J Psychol* **115,** 581-607.

Long GM & Toppino TC. (2004). Enduring interest in perceptual ambiguity: alternating views of reversible figures. *Psychol Bull* **130,** 748-768.

Maestu F, Ortiz T, Fernandez A, Amo C, Martin P, Fernandez S & Sola RG. (2002). Spanish language mapping using MEG: a validation study. *Neuroimage* **17,** 1579-1586.

Maier A, Wilke M, Logothetis NK & Leopold DA. (2003). Perception of temporally interleaved ambiguous patterns. *Curr Biol* **13,** 1076-1085.

Masic I. (2008). Ibn al-Haitham--father of optics and describer of vision theory. *Med Arh* **62,** 183-188.

Masoud MT MF. (2006). How Islam changed medicine: Ibn al-Haytham and optics. *BMJ* **332,** 120.

Miller SM, Liu GB, Ngo TT, Hooper G, Riek S, CArson RG, Pettigrew JD. (2000). Interhemispheric switching mediates perceptual rivalry. *Curr Biol* **10**(7), 383-92

Milne E, Swettenham J, Hansen P, Campbell R, Jeffries H & Plaisted K. (2002). High motion coherence thresholds in children with autism. *J Child Psychol Psychiatry* **43,** 255-263.

Muckli L, Kriegeskorte N, Lanfermann H, Zanella FE, Singer W & Goebel R. (2002). Apparent motion: event-related functional magnetic resonance imaging of perceptual switches and States. *J Neurosci* **22,** RC219.

N'Diaye K, Ragot R, Garnero L & Pouthas V. (2004). What is common to brain activity evoked by the perception of visual and auditory filled durations? A study with MEG and EEG co-recordings. *Brain Res Cogn Brain Res* **21,** 250-268.

Nawrot M & Blake R. (1989). Neural integration of information specifying structure from stereopsis and motion. *Science* **244,** 716-718.

Nawrot M & Blake R. (1991a). The interplay between stereopsis and structure from motion. *Percept Psychophys* **49,** 230-244.

Nawrot M & Blake R. (1991b). A neural network model of kinetic depth. *Vis Neurosci* **6,** 219-227.

Nawrot M & Blake R. (1993a). On the perceptual identity of dynamic stereopsis and kinetic depth. *Vision Res* **33,** 1561-1571.

Nawrot M & Blake R. (1993b). Visual alchemy: stereoscopic adaptation produces kinetic depth from random noise. *Perception* **22,** 635-642.

Ngo TT, Liu GB, Tilley AJ, Pettigrew JD & Miller SM. (2008). The changing face of perceptual rivalry. *Brain Res Bull* **75,** 610-618.

Noguchi Y, Kaneoke Y, Kakigi R, Tanabe HC & Sadato N. (2005). Role of the superior temporal region in human visual motion perception. *Cereb Cortex* **15,** 1592-1601.

Papanicolaou AC, Simos PG, Breier JI, Zouridakis G, Willmore LJ, Wheless JW, Constantinou JE, Maggio WW & Gormley WB. (1999). Magnetoencephalographic mapping of the language-specific cortex. *J Neurosurg* **90,** 85-93.

Paradis AL, Cornilleau-Peres V, Droulez J, Van De Moortele PF, Lobel E, Berthoz A, Le Bihan D & Poline JB. (2000). Visual perception of motion and 3-D structure from motion: an fMRI study. *Cereb Cortex* **10,** 772-783.

Parker AJ. (2007). Binocular depth perception and the cerebral cortex. *Nat Rev Neurosci* **8,** 379-391.

Parker AJ & Krug K. (2003). Neuronal mechanisms for the perception of ambiguous stimuli. *Curr Opin Neurobiol* **13,** 433-439.

Parker AJ, Krug K & Cumming BG. (2002). Neuronal activity and its links with the perception of multi-stable figures. *Philos Trans R Soc Lond B Biol Sci* **357,** 1053-1062.

Pellicano E, Gibson L, Maybery M, Durkin K & Badcock DR. (2005). Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence? *Neuropsychologia* **43,** 1044-1053.

Petrides M, Alivisatos B, Evans AC & Meyer E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proc Natl Acad Sci U S A* **90,** 873-877.

Pettigrew JD & Miller SM. (1998). A 'sticky' interhemispheric switch in bipolar disorder? *Proc Biol Sci* **265,** 2141-2148.

Polonsky A, Blake R, Braun J & Heeger DJ. (2000). Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. *Nat Neurosci* **3,** 1153-1159.

Roberts TPL, Disbrow EA, Roberts HC, Rowley HA. (2000). Quantification and Reproducibility of Tracking Cortical Extent of Activation by Use of Functional MR Imaging and Magnetoencephalography. *AJNR Am J Neuroradiol* **21**:1377–1387

Rock I, Mitchener K. (1992). Further evidence of failure of reversal of ambiguous figures by uninformed subjects. *Perception* **21**:39-45

Rockel AJ, Hiorns RW & Powell TP. (1980). The basic uniformity in structure of the neocortex. *Brain* **103,** 221-244.

Russell J. (1997). Autism as an Executive Disorder (Oxford: Oxford University Press).

Rutter M, Bolton P, Harrington R, Le Couteur A, Macdonald H & Simonoff E. (1990a). Genetic factors in child psychiatric disorders--I. A review of research strategies. *J Child Psychol Psychiatry* **31,** 3-37.

Rutter M, Macdonald H, Le Couteur A, Harrington R, Bolton P & Bailey A. (1990b). Genetic factors in child psychiatric disorders--II. Empirical findings. *J Child Psychol Psychiatry* **31,** 39-83.

Saenz M, Buracas GT & Boynton GM. (2002). Global effects of feature-based attention in human visual cortex. *Nat Neurosci* **5,** 631-632.

Salzman CD, Britten KH, Newsome WT. (1990). Cortical microstimulation influences perceptual judgements of motion direction. *Nature* **346**:174-7.

Salzman CD, Murasugi CM, Britten KH, Newsome WT. (1992) Microstimulation in visual area MT: effects on direction discrimination performance. *J Neurosci* **12**:2331-55.

Schmitz N, Daly E & Murphy D. (2007). Frontal anatomy and reaction time in Autism. *Neurosci Lett* **412,** 12-17.

Sengpiel F, Blakemore C & Harrad R. (1995). Interocular suppression in the primary visual cortex: a possible neural basis of binocular rivalry. *Vision Res* **35,** 179-195.

Shadlen MN, Britten KH, Newsome WT & Movshon JA. (1996). A computational analysis of the relationship between neuronal and behavioral responses to visual motion. *J Neurosci* **16,** 1486-1510.

Shah A & Frith U. (1983). An islet of ability in autistic children: a research note. *J Child Psychol Psychiatry* **24,** 613-620.

Shibasaki H, Barrett G, Halliday E, Halliday AM. 1980. Components of the movement-related cortical potential and their scalp topography. *Electroenceph Clin Neurophysiol* **49**, 213-26.

Shibasaki H, Hallett M. (2006). What is the Bereitschaftspotential? *Clinical Neurophysiology* **117**, 2341-2356.

Shinozaki T & Takeda T. (2004). Investigation of color motion using MEG and binocular rivalry stimuli. *Neurol Clin Neurophysiol* **2004,** 108.

Spencer J, O'Brien J, Riggs K, Braddick O, Atkinson J & Wattam-Bell J. (2000). Motion processing in autism: evidence for a dorsal stream deficiency. *Neuroreport* **11,** 2765-2767.

Srinivasan R & Petrovic S. (2006). MEG phase follows conscious perception during binocular rivalry induced by visual stream segregation. *Cereb Cortex* **16,** 597-608.

Sterzer P & Kleinschmidt A. (2007). A neural basis for inference in perceptual ambiguity. *Proc Natl Acad Sci U S A* **104,** 323-328.

Sterzer P, Kleinschmidt A & Rees G. (2009). The neural bases of multistable perception. *Trends Cogn Sci* **13,** 310-318.

Sterzer P, Russ MO, Preibisch C & Kleinschmidt A. (2002). Neural correlates of spontaneous direction reversals in ambiguous apparent visual motion. *Neuroimage* **15,** 908-916.

Talulu S, Simola J, Kajola M. 2005. Applications of the signal space separation method. *IEEE Trans Signal Process* **53**, 3359-3372.

Treue S, Husain M & Andersen RA. (1991). Human perception of structure from motion. *Vision Res* **31,** 59-75.

Treue S & Martinez Trujillo JC. (1999). Feature-based attention influences motion processing gain in macaque visual cortex. *Nature* **399,** 575-579.

Treue S & Maunsell JH. (1999). Effects of attention on the processing of motion in macaque middle temporal and medial superior temporal visual cortical areas. *J Neurosci* **19,** 7591-7602.

Uka T & DeAngelis GC. (2006). Linking neural representation to function in stereoscopic depth perception: roles of the middle temporal area in coarse versus fine disparity discrimination. *J Neurosci* **26,** 6791-6802.

Ullman S. (1979). The interpretation of visual motion. *Cambridge*, MA: MIT Press

Wallach H & O'Connell DN. (1953). The kinetic depth effect. *J Exp Psychol* **45,** 205-217.

Wimmer H & Perner J. (1983). Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception. *Cognition **13:**103-128.*

Windmann S, Wehrmann M, Calabrese P & Gunturkun O. (2006). Role of the prefrontal cortex in attentional control over bistable vision. *J Cogn Neurosci* **18,** 456-471.

Yang CY, Hsieh JC & Chang Y. (2006). An MEG study into the visual perception of apparent motion in depth. *Neurosci Lett* **403,** 40-45.

Zimmerman, J. E., Thiene, P., and Hardings, J. (1970). Design and operation of stable r-f biased superconducting point-contact quantum devices. *J. Appl. Phys.*, **41**:1572–1580.