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# MONITORING AND PREDICTING ACTIONS AND THEIR CONSEQUENCES IN THE HUMAN BRAIN

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## ABSTRACT

There is substantial evidence that our ability to monitor our actions is based on the use of an internal forward model that uses an efference copy of the motor command to predict the sensory consequences of an action. This prediction is used to attenuate the sensory consequences of our actions. There is accumulating evidence that our ability to understand and predict the actions of others and their consequences is based on the same systems that are involved in monitoring our own actions. This thesis describes a series of experiments investigating the neural mechanisms underlying our ability to monitor our actions and predict their sensory consequences, and our ability to understand and predict the actions of others.

I describe two fMRI experiments investigating the neural mechanism underlying sensorimotor attenuation during eye-blinks. I find that the neural response to visual stimulation is actively suppressed during eye-blinks. Another two studies provide evidence that our ability to monitor the actions of others and their consequences is based on the same neural mechanisms that are involved in monitoring our own actions and predicting their sensory consequences. They also suggestthat the mirror system acts in a predictive manner, anticipating the actions of others, rather than merely responding to sensory input. I also examine the possibility that, in addition to using our motor systems to understand the actions of others, we understand the sensations experienced by others by representing these sensations in our own sensory cortices. I find evidence of a touch mirror system, which responds to both the observation and experience of touch. Finally, I describe two electroencephalography experiments that shed light on the development of our ability to understand other people's actions, providing evidence for the early development and involvement of the mirror system in action observation and in predicting the sensory consequences of actions.

## DECLARATION

I, Davina Bristow, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The study described in Chapter 8 of this thesis was carried out in collaboration with Jamie Ward, Sarah-Jayne Blakemore, and Geoffrey Bird. I designed and constructed the stimuli, ran the experiment and performed a preliminary analysis of the data. The data analysis was completed by Geoffrey Bird.

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# CHAPTER 1: GENERAL INTRODUCTION

To successfully interact with the world we must be able to monitor our actions and their consequences. One possible mechanism that might underpin this ability is the use of an internal forward model that predicts the consequences of an action on the basis of an efference copy of the motor command eliciting that action. This prediction can be used for motor control by comparing it to the desired outcome of an action and thus allowing us to rapidly adjust the motor command if the prediction does not match the desired outcome. The predicted sensory feedback can also be compared to the actual sensory feedback following an action, thus allowing self-produced stimuli to be distinguished from externally generated stimuli. Self-produced stimuli can then be attenuated and processing capacity directed towards externally-produced stimuli, which are more likely to correspond to important environmental changes that could impact on survival.

Amongst all externally generated stimuli the actions of other living creatures are most significant. An animal's survival depends on its ability to monitor the actions of prey, predators and conspecifics, and to predict their future actions, the consequences of which will have significant implications for the animal. Anticipating a predator's actions may allow one to escape, whereas anticipating the behaviour of prey could make the difference between lunch and starvation. The ability to monitor and predict the actions of conspecifics can be equally important as they are potential mates, rivals and allies. For highly social animals, such as primates, including humans, the actions of conspecifics are of particular importance. Human survival therefore also depends on our ability to successfully navigate our social world, thus as well as being able to predict the consequences of our own actions, we need to be able to monitor and predict the actions of others and the consequences of these actions, so that we can adjust our behaviour accordingly.

There is substantial evidence that our own motor system in intrinsically involved in our ability to understand the actions of others, and predict their future actions. Action observation activates a network of regions, known as the 'mirror system' that is also activated by execution of the same action. This mirror system is believed to be the basis of action understanding through simulation of the observed movement. It has

been proposed that the mirror system acts in a predictive manner, simulating the actions of others, predicted on the basis of the current situation and prior knowledge, and using the internal forward model, normally used to predict the consequences of our own actions, to verify its prediction. Minimising the prediction error allows us to recognise what actions others are performing and to infer the intentions behind these actions.

In this thesis I will investigate some of the neural mechanisms underlying our ability to monitor our own actions and predict their sensory consequences, and our ability to understand and predict the actions of others.

### 1.1 An internal forward model for predicting the consequences of our actions

It has been proposed that animals use an efference copy (von Holst, 1954) of their motor commands sent from the motor areas controlling the actions, in parallel with the motor signals, to predict the sensory consequences of their actions. On the basis of this efference copy, a prediction of the sensory consequences of the action is generated by an internal forward model (Wolpert and Miall, 1996). This sensory prediction is known as a corollary discharge (Sperry, 1950). This idea of an internal forward model that predicts the consequences of our actions was first proposed by Helmholtz in 1867 in the context of eye movements (Helmholtz, 1867). Helmholtz observed that when making eye movements we do not perceive the world as moving despite visual input moving across the retina, whereas if you moved your eye, without using the eye muscles, by pushing it with your finger, the world does appear to move. This led him to suggest that the motor command contained information that enabled the visual system to predict and compensate for the sensory consequences of the eye movement. This idea was elaborated by Von Holst and Sperry in the 1950s, and is now a well established concept.

As initially proposed in the context of eye movements, the sensory prediction, or corollary discharge, generated by the forward model can be used to cancel self-produced sensory stimulation. It can also be compared to actual sensory feedback, and thus be used to distinguish self-produced from externally produced sensory stimuli. It has also been proposed that the sensory prediction can be compared to the

desired outcome of an action and thus plays a role in motor control (Wolpert and Miall, 1996).

### *1.1.1 Prediction in motor control*

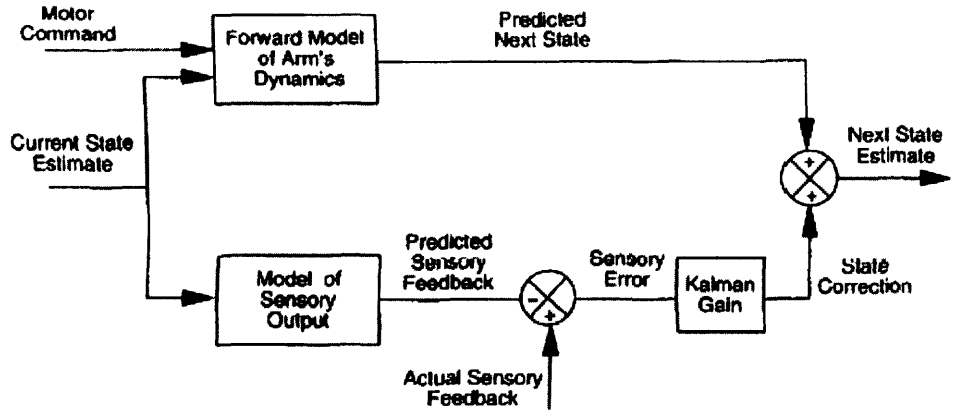
For accurate motor control the current state of the moving body part must be monitored during the action and compared to the desired state, so that if necessary the motor commands can be adjusted to correct for any discrepancy. The current state of the limb could be assessed on the basis of sensory feedback in the form of proprioceptive and visual signals, but this is not ideal due to delays in sensory transduction, central processing and in motor output. These delays can combine to give a total delay of up to 300ms for feedback during a visually guided response (Wolpert and Miall, 1996). Since fast arm movements can last as little as 200ms a motor control system based purely on sensory feedback is clearly inadequate.

Instead it has been proposed that a forward model predicts the outcome of a motor command, and this prediction can then be used to provide an internal feedback signal by comparing the prediction to the desired state of the limb, which is much more rapid than actual sensory feedback (Wolpert and Miall, 1996). The forward model uses an efference copy of the motor command and information about the current state of the system, to predict the next state of the system, i.e. the position in space, joint angles, velocity etc. of the moving limb, and associated proprioceptive and visual feedback. The error between the predicted state and the desired state can then be used to correct the movement. The predicted sensory feedback is subsequently compared to the actual sensory feedback so that any errors in the forward model can be detected and corrected, thus ensuring the accuracy of the forward model. Such a system is known as an observer model and combines the advantages of predictive control, namely speed, with those of sensory feedback control.

Wolpert and colleagues demonstrated that a Kalman Filter version of such an observer model accurately predicts the empirical data from a task in which participants had to estimate the location of their arm at the end of movements made in the dark, with and without externally applied forces (Wolpert et al., 1995) (see Figure 1.1). This model uses Kalman gain to weight the effects of sensory feedback

correction and internal simulation on the next state estimate. Models based solely on sensory feedback or internal simulation, were unable to accurately predict the empirical data. This provided direct evidence supporting the existence of an internal forward model that uses motor commands to estimate the current state of the arm, and sensory feedback to update the model, by comparing it to sensory feedback predicted by the forward model.

***Figure 1.1- A Kalman filter observer model*** *(from Wolpert et al. 1995)*




Further evidence for the use of an internal forward model in motor control comes from studies of grip force modulation. When an object is held between the thumb and index finger, the grip force counteracts the load force. When the object is moved acceleration causes changes in the load force and therefore the grip force must change to prevent the object from slipping. A series of experiments have demonstrated that when objects are moved by the subject, the grip force changes in parallel with the load force and is always slightly greater than the load force (Johansson et al., 1992b;Johansson et al., 1992a;Johansson and Westling, 1984;Westling and Johansson, 1984). This close association between grip force and load force implies predictive control, as if subjects were relying on sensory feedback there would be a delay between the change in load force and the necessary adjustment in grip force. In contrast when the movement of the object is externally generated, the change in grip force lags behind the load force by 60-100ms, suggesting that in this case the subject is relying on sensory feedback rather than prediction to adjust their grip (Johansson et al., 1992b;Johansson et al., 1992a). Examination of grip force modulation under different external load conditions

demonstrates that the motor system is able to predict both the trajectory of the movement, and the load properties of the object (Flanagan and Wing, 1997). Subjects moved an object under 3 different load conditions: inertial, viscous and elastic loads. The load force during the movement depends on the external load conditions and on the trajectory of the hand movement. In all three conditions the grip force fluctuated in parallel with the load force, thus showing that the modulation of grip force anticipates the changes in load force. In fact the grip force led the load force by 14ms on average. This suggests that the central nervous system has an internal model of both the load properties and of the movement trajectory, and that it integrates these two to predict the load force, and thus the necessary grip force.

### *1.1.2 Attenuation of the sensory consequences of our own actions*

In addition to enabling rapid and accurate motor control, an internal forward model can in principle be used to recognise and attenuate or cancel the sensory consequences of our own actions. All organisms, including humans, are constantly bombarded with signals arising from their environment. Some of these are the sensory consequences of their own actions, but others are sensory consequences of the environment or of the actions of others. Somehow, from this undifferentiated mass of signals, humans (and other organisms) must extract the few stimuli that correspond to important changes in their environment. It is therefore a basic requirement for an organism that it should be should be able to distinguish the sensory consequences of its own actions from those of the environment or other agents.

It has been proposed that animals use the sensory prediction, known as corollary discharge, generated by an internal forward model on the basis of an efference copy of their motor commands to distinguish the sensory consequences of their own actions from externally produced sensory stimuli (Sperry, 1950;von Holst, 1954;Wolpert and Miall, 1996). This sensory prediction, or corollary discharge, is compared with the actual sensory feedback, thus allowing self and externally produced sensory stimuli to be distinguished. The self-produced sensory stimuli can then be attenuated, cancelled, or compensated for. In contrast, externally produced stimuli cannot be predicted and so their perception is not attenuated.

As already mentioned, this idea was first introduced in the context of eye movements in the 1870s (Helmholtz, 1867) and elaborated in the 1950s (Sperry, 1950;von Holst, 1954). It was proposed that motor areas involved in the control of eye movements, as well as sending motor commands to the eyes, simultaneously sent an efference copy of those commands to visual cortex, predicting the sensory consequences of the movement. This would allow the visual system to compensate for the retinal displacement that occurs during eye movements. However it seems that such a compensation mechanism is not restricted to eye movements. Support for the existence of such a mechanism comes from a number of experiments demonstrating attenuation of the response to self-produced sensory stimulation in several modalities.

Evidence for attenuation of self-produced somatosensory stimulation comes from a series of experiments involving tickling (Blakemore et al., 1998b;Blakemore et al., 1999a;Blakemore et al., 1999b;Blakemore et al., 2001). Starting from the common observation that one can not tickle oneself, Weiskrantz demonstrated experimentally that self-produced stimulation to the sole of the foot was indeed perceived as less tickly than externally administered tactile stimulation (Weiskrantz et al., 1971). On the basis of this finding Blakemore and colleagues investigated why self-produced tactile stimulation was perceived as less ticklish than an identical externally produced tactile stimulus. In the self-produced condition, subjects moved a robot arm in a controlled manner with their left hand. This caused a second robot to reproduce the same movement with a piece of foam on their right hand. In the externally produced situation the second robot simply applied the same pattern and force of tactile stimulation to the right hand as in the self-produced condition. Subjects consistently rated the externally produced stimulus as more ticklish than the self-produced stimulus (Blakemore et al., 1999a). The robotic interface allowed a delay, which was varied parametrically, to be introduced between the movement of the left hand and the movement of the tactile stimulus on the right hand. Parametrically varying degrees of trajectory perturbation, (0°, 30°, 60° and 90°), between the movement of the left hand and the movement of the tactile stimulus, were also introduced. The tickliness rating of the tactile stimulus increased significantly with increasing delay and trajectory perturbation (Blakemore et al., 1999a). These results suggest that self-

produced movements attenuate the response to tactile stimuli, which arise as a consequence of that movement. The degree to which self-produced tactile stimuli are attenuated depends on the degree of error between the sensory stimulation predicted by an internal forward model of the motor system and the actual sensory feedback produced. Thus when the delay or trajectory perturbations are high there is a greater discrepancy between the sensory stimulation predicted by the movement of the left hand and the tactile stimulation actually received by the right hand so attenuation of the stimulation is reduced.

An fMRI study comparing the same self-produced (the left hand stimulates the right hand via a robot) and externally produced (the robot alone stimulates the right hand) tactile stimulation conditions as described above, plus an extra condition in which the left hand was moved without resulting in stimulation of the right hand, revealed that the somatosensory cortex was activated more by externally produced tactile stimulation than by self-produced stimuli (Blakemore et al., 1998b). This reduction in somatosensory cortex activation is likely to be the neural correlate of the reduced perception of tickliness associated with the self-produced stimulation. In the cerebellum, activity was reduced when movement of the left hand generated a tactile stimulus compared to when movement of the left hand did not result in tactile stimulation of the right hand. The cerebellum was also significantly activated by externally produced tactile stimulation alone. In other words, when the actual sensory feedback following movement matched the predicted sensory feedback (self-produced tactile stimulation) activity in the cerebellum decreased, as did that of the somatosensory cortex. This suggests that the cerebellum differentiates between movements on the basis of their sensory consequences. Thus it may be involved in the modulation of the somatosensory cortex, by predicting the sensory consequences of a movement, and providing a signal which leads to the attenuation of the sensory response to the self-generated stimuli.

Positron Emission Tomography was subsequently used to investigate the effect of the parametrically varied distortion in the timing of the self-produced tactile stimulation described earlier (Blakemore et al., 2001). As the delay between the tactile stimulus and the motor commands for the movement causing it increases, the sensory predictions of the postulated forward model in the brain will become less and less

accurate and the discrepancy between the predicted and actual sensory consequences of the movement will increase. The study showed that activity in the right lateral cerebellar cortex was positively correlated with the delay between movement of the right hand and stimulation of the left hand. This supports the earlier proposal that the cerebellum is involved in signalling the discrepancy between the actual sensory consequences of a movement and those predicted by the forward model on the basis of motor commands (Blakemore et al., 1998b).

Further evidence for attenuation of self-produced somatosensory stimuli comes from studies of force perception. Shergill and colleagues demonstrated that self-generated forces are perceived as weaker than externally generated forces (Shergill et al., 2003). A torque motor applied a force to the subject's left index finger. Subjects were then instructed to apply the same force to their left finger with their right index finger by pushing on a force transducer placed above the left index finger. The force transducer measured the applied force. Subjects consistently applied a force greater than that previously applied by the motor, suggesting that in the case of the self-produced force the somatosensory consequences of the finger press are predicted and that this prediction is use to attenuate the perception of the sensory stimulation.

A similar study replicated these findings and demonstrated that the sensory attenuation decreases if there is a discrepancy between the predicted and actual sensory consequences of the movement (Bays et al., 2005). Subjects tapped one of their fingers with the other via a force sensor placed between the two fingers. Their right index finger tapped on a force sensor above their left index finger, while a similar force was applied to the left index finger below by a torque motor. The force on the left finger was perceived as weaker when it occurred while the right index finger pressed on the force sensor, compared to when the right finger made no movement. The attenuation of the perceived force of the tap on the left index finger decreased as a delay was introduced between the tap of the right index finger and the tap applied to the left hand). After a delay of 300ms there was no longer any significant attenuation.

In a second study, in some trials the force sensor was moved at the start of the trial unbeknown to the subject so that when they made the tapping movement with their

right index finger it did not make contact with the sensor (Bays et al., 2006). Meanwhile the tap was still applied to the left index finger by the motor at the time when the right finger would usually have made contact with the force sensor. In this condition the tactile stimulation on the left index finger was still attenuated, demonstrating that attenuation does not rely on a postdictive mechanism requiring sensory feedback from the active finger. Instead it is consistent with a predictive mechanism of attenuation based on the motor commands. However the mere presence of a motor command is not sufficient for attenuation as demonstrated in a second experiment. This time the subjects' right index finger never made contact with the force sensor but the tap on the left index finger was still associated with the movement of the right index finger, except in delay trials when the tap occurred 500ms after the movement of the right index finger. The tap felt on the left index finger was not perceived as stronger in the delay conditions, showing that a simple association between a movement and a tactile stimulus is not enough for attenuation of that tactile stimulus to occur. Instead the attenuation of tactile sensations depends specifically on the prediction of contact between the two fingers.

Further evidence that attenuation of self-produced sensory stimulation is caused by a predictive mechanism based on motor commands rather than on sensory feedback from the moving body part, comes from a recent study demonstrating sensorimotor attenuation by central motor command signals in the absence of movement (Voss et al., 2006). Subjects moved their right finger in response to a tone, and had to judge the intensity of cutaneous stimulation to the moving finger (relative to a simultaneously applied stimulus to their stationary left finger). In control conditions the right finger was also kept still. As expected, cutaneous stimulation was perceived as weaker when applied during finger movement, compared to rest. TMS was applied over the primary motor cortex at the time when the subject normally initiated a finger movement (synchronous with the tone), thus delaying the actual movement of the finger by an average of 145ms. The TMS delays the corticospinal output of the motor commands, without otherwise affecting the motor pattern. Cutaneous stimulation was applied to the finger between the TMS pulse and the delayed finger movement. Sensation of this cutaneous stimulus was attenuated even though the finger movement had not yet occurred, and this attenuation did not differ significantly from that observed during actual finger movement. This demonstrates

that the prior motor command to move is sufficient for sensory attenuation to occur, and that movement itself is not necessary, and thus that attenuation of sensation during voluntary movements arise from an efferent signal rather than sensory feedback from the moving body part. The attenuation was not merely due to the TMS alone, as it was greater than attenuation seen after TMS without movement, nor was it due to presence of a movement shortly after the stimulation, as the sensation of stimuli applied prior to a movement (without TMS) was not attenuated in control trials.

There is also evidence for attenuation of self-produced stimuli in the auditory modality in humans and monkeys. Shafer and Marcus first demonstrated that the EEG potentials evoked by self-triggered auditory stimuli had a significantly smaller amplitude and faster latency than the potentials evoked by externally triggered auditory stimuli (Schafer and Marcus, 1973). The degree of attenuation decreased linearly with the length of delays introduced between the auditory stimulus (a tone) and the action generating the stimulus (a button press). A reduced response to self-produced compared to externally generated tones has also been demonstrated using MEG (Martikainen et al., 2005). Similarly the MEG response to self-generated speech is reduced compared to the MEG response to playback of the same speech sounds (Curio et al., 2000;Numminen et al., 1999). Furthermore in squirrel monkeys, over half of neurons in the STS that respond to vocalisations of other monkeys, do not respond when the monkey itself vocalises, but they do respond to the play back of recorded self produced vocalisations (Muller-Preuss, 1978;Muller-Preuss and Ploog, 1981).

In the visual modality, in which context sensorimotor attenuation was first proposed, there is also some evidence supporting this idea. Firstly as observed by Helmholtz, when we move our eyes the world does not appear to move even though visual objects move across the retina, whereas if our eyes are moved by an external force (such as a finger pushing the eyeball to one side) the world does appear to move (Helmholtz, 1867). This suggests that the motor command is necessary for the visual system to anticipate and compensate for the sensory consequences of the eye movement. Conversely if we try to move our eyes but our eye muscles are paralysed so that the eye does not actually move, the world appears to move in the direction of

the attempted eye movement (Kornmuller, 1932). This suggests that the visual system is trying to compensate for the intending eye movement even though it never happened.

Prediction and cancellation of the sensory consequences of our actions also appears to operate during blinks. Humans blink every few seconds, yet remarkably the pronounced interruptions to visual input they cause are rarely noticed. In contrast external darkenings of the visual field that have a similar duration and magnitude as the interruption to visual input caused by a blink are immediately apparent (Volkmann et al., 1980). During blinks neither the eyelid sweeping across the pupil nor the transient changes in brightness that occur at the beginning or end of the blink are usually perceived. Moreover, visual experience remains constant across the significant gap in visual input that results from eyelid closure.

Several psychophysical studies have demonstrated that visual sensitivity is reduced during eyeblinks, an effect known as blink suppression (Manning et al., 1983;Riggs et al., 1982;Volkmann et al., 1978;Volkmann et al., 1980;Volkmann et al., 1982;Volkmann, 1986). Blink suppression mainly affects sensitivity to low spatial frequency visual stimuli (Ridder and Tomlinson, 1993) and reaches a maximum 30–40 ms before the eyelid begins to cover the pupil (Manning et al., 1983;Volkmann, 1986). It has been proposed that blink suppression may represent a neural mechanism associated with the blink motor command that has evolved to minimise the percept of the eyelid occluding the pupil (a low spatial frequency stimulus) and the transient changes in illumination that occur during the blink (Volkmann, 1986). The existence of blink suppression therefore implies an underlying neural mechanism by which blinking influences the processing of visual stimulation.

A recent fMRI study has shown that the response to visual stimulation is attenuated by voluntary saccades, which may account for the observed reduction in visual sensitivity during saccades, a phenomenon known as saccadic suppression (Sylvester et al., 2005). However the neural mechanism underlying the phenomenon of blink suppression and the maintenance of visual continuity across blinks remains unknown. In Chapters 4 and 5, I investigate the neural basis of these phenomena using fMRI. In Chapter 4, I compare the neural responses to self-produced

darkenings (blinks) and externally generated darkenings, and in Chapter 5, I investigate whether the neural response to visual stimulation is suppressed during blinks, a possible explanation of the psychophysical phenomenon of blink suppression.

## 1.2 Monitoring other people's actions

The actions of others, whether they are predators, prey, or conspecifics will have a significant impact on the survival of an animal and thus it must be able to modulate its own behaviour accordingly. Therefore, as well as being able to monitor their own actions and predict the sensory consequences of their own actions, animals should also be able to monitor and predict the actions of others and the consequences of these actions. There is accumulating evidence that we use the same neural systems for controlling and monitoring our own actions and their consequences, and for understanding and predicting the actions of others.

### *1.2.1 The mirror system for the observation of action*

There is increasing evidence that our own motor system is activated during the observation of action, and that it is this involvement of our motor system that allows us to understand the actions of others. Activation of parts of the motor system during action observation was first discovered in monkeys in 1992 (Di Pellegrino et al., 1992).

Area F5 is a region of the monkey premotor cortex characterised by the presence of neurons that code for goal related motor actions such as hand and mouth grasping. In 1996, Rizzolatti and colleagues discovered a set of neurons, termed "mirror neurons", in area F5, which fire both when the monkey performs a specific action and when it observes another individual, in this case the experimenter, performing the same, or a similar, action (Gallese et al., 1996;Rizzolatti et al., 1996a). Observation of either the agent performing an action, such as grasping, or of an object, e.g. food, alone was not sufficient to elicit firing of the mirror neurons. An interaction between the agent, either a person or another monkey, and the object of the action is required to visually trigger mirror neurons. The actions most commonly

represented by mirror neurons were grasping, manipulating and placing, and the most effective observed actions for triggering premotor neuron activity were performed by the hands or mouth. Most mirror neurons showed a congruent relationship between the actions they fired to during observation and execution. In around 30% of mirror neurons this congruence is extremely strict; the observed and executed actions correspond both in terms of type of action, such as grasping as opposed to reaching, and in terms of the specific manner in which the action is executed, for example a precision grip as opposed to a power grip. It has been proposed that these mirror neurons represent an action observation/execution matching system, which may play a role in the recognition and understanding of actions performed by others (Gallese et al., 1996;Rizzolatti et al., 1996a;Rizzolatti et al., 2001)..

Mirror neurons still fire when the action is hidden behind a screen as long as the monkey knows that there is an object behind the screen and thus can infer that a certain action, namely a hand grasping an object, is being performed (Umilta et al., 2001). The response of the mirror neurons were recorded in two conditions: in one the monkey observed an entire action, e.g. a hand grasping an object, but in the second condition the monkey could only see the hand reaching behind a screen, while the hand actually grasping the object (the crucial part of the action) was hidden behind the screen. In this condition the monkeys knew that the object was behind the screen but they could not actually see the action. Nevertheless over half the recorded neurons still fired.

More recently neurons have been found in the monkey premotor cortex that fire when the monkey performs a specific action, e.g. breaking open a peanut, and when it hears the sound related to that action, e.g. the sound of the peanut cracking open (Kohler et al., 2002). Most of these neurons (22 out of 29 studied) also fired when the monkey observed another person carrying out the same action. About 15% of F5 neurons that fired to action execution and observation also responded to the sounds of the same actions. Thus, they appear to constitute a subclass of mirror neurons, termed audiovisual mirror neurons by the authors, which code actions irrespective of whether they are performed, observed or heard. These results suggest that mirror neuron activity correlates with action understanding, and a motor representation of the action, not simply the visual, or other specific sensory features of an action.

There is growing evidence that a similar mirror system may also exist in humans that is activated by action execution, action observation and also by hearing action related sounds. MEG and EEG have shown that when a human observes hand actions being made by another person there is a desynchronisation of the motor cortex similar to, but weaker than, that occurring when the subject makes active hand movements, (Cochin et al., 1999;Hari et al., 1998). EEG and MEG have also shown that hearing piano tunes activates the motor cortex in piano experts (Bangert and Altenmuller, 2003;Haueisen and Knosche, 2001) and also in novices undergoing piano training after just 20 minutes of practice, though the effect was enhanced after 5 weeks of training (Bangert and Altenmuller, 2003). When expert pianists listen to a familiar melody the location of the activation in their motor cortex was specific to the finger that would normally be used to play a particular note (Haueisen and Knosche, 2001).

Transcranial magnetic stimulation (TMS) experiments also support the existence of a mirror system in humans. Fadiga et al (1995) stimulated the motor cortex of subjects using TMS, and recorded the induced motor evoked potentials (MEPs) from various arm and hand muscles. Simultaneously, subjects watched various types of hand movements and control visual stimuli. The authors found that the threshold for MEPs recorded from the hand muscles involved in making a particular movement decreases during observation of the same hand movement, but not during observation of other non-action stimuli (Fadiga et al., 1995). This shows that action observation affects the peripheral motor system.

Similarly when subjects listen to or watch speech, muscle potentiation increases in the subjects' own mouth muscles (Fadiga et al., 2002;Watkins et al., 2003). MEPs were recorded in subjects' tongue muscles in response to TMS of left motor cortex, while they listened to speech sounds requiring different amounts of tongue movement (double 'f', which requires slight tongue tip movement, compared to double 'r' which requires strong tongue tip movement). MEPs were greatest when listening to sounds that required greater tongue movements. This demonstrates that hearing phonemes, which require strong tongue muscle activation when produced, activates the listeners' motor centres that control the tongue muscles (Fadiga et al., 2002). In a similar study MEPs in the lip muscles, produced by TMS of the face area of the left motor cortex, were recorded while subjects heard speech sounds versus

non speech sounds and watched speech related lip movements versus eye and brow movements (Watkins et al., 2003). These MEPs were greater while subjects listened to speech sounds compared to non-speech sounds, and when subjects saw lip movements compared to eye and brow movements. This demonstrates that speech perception, whether visual or auditory, enhances the excitability of the motor areas underlying speech production in the left hemisphere (Watkins et al., 2003).

Thus it appears that several neurophysiological experiments, using different techniques, demonstrate that observation of actions is correlated with activation of cortical areas normally associated with motor control in humans, suggesting that there is a mirror system in humans, analogous to that found in monkeys.

Brain imaging studies also provide evidence in favour of this idea. A number of brain imaging studies have found activation of the premotor cortex, the parietal lobe and the superior temporal sulcus, when subjects observe arm and hand actions (Grafton et al., 1996;Grezes et al., 2003;Rizzolatti et al., 1996b). A recent fMRI experiment showed that observing hand, mouth and foot actions led to activation of the premotor cortex in a somatotopic manner (Buccino et al., 2001). The premotor activation varied somatotopically in a pattern similar to that of the classical motor cortex homunculus, with the mouth represented ventrally and the foot dorsally, and the hand in between. This experiment provides strong evidence that action observation involves activation of the same functionally specific neural structures that are normally involved in the execution of action.

In addition speech perception has been shown to activate the premotor regions involved in speech production. Viewing silent articulatory mouth movements activates Broca's area (Calvert and Campbell, 2003). Listening to speech sounds also activates premotor areas involved in speech production; 73% of voxels activated by listening to speech were also activated during speech production (Wilson et al., 2004). More recently Skipper et al have replicated these findings and shown that observation of silently articulating faces, and listening to speech sounds activates a network of brain regions involved in speech production including the premotor cortex, inferior frontal gyrus, primary motor cortex and superior temporal sulcus (Skipper et al., 2005).

Most recently Gazzola and colleagues have demonstrated activation of a temporo-parieto-premotor network during execution of hand and mouth actions and while subject's listened to the sounds of the same actions (Gazzola et al., 2006). Activation in the premotor cortex was somatotopically organised in both the listening and execution conditions, with hand actions activating a dorsal cluster, while mouth actions activated a ventral cluster. A second study with the same subjects showed that most of this auditory mirror system was also activated by the sight of similar grasping hand actions, apart from the premotor region that responded selectively to mouth action execution and listening.

Thus it appears that, as in monkeys, the human motor system is intrinsically involved in action observation. The consistent activation of the motor system during the perception of actions, whether in the auditory or visual modality, suggests that we represent the actions of others by activating a motor representation of that action, rather than by representing the action in terms of its specific visual or other sensory features.

It has been proposed that the simulation of others' actions by our mirror system underlies our ability to understand the actions of others, and allows us to infer the intentions of others on the basis of what our own intentions would be for that action (Blakemore and Decety, 2001;Rizzolatti et al., 2001). There is evidence that inferring intentions of others involves the mirror system. When actions are observed in a context that indicates the intention behind the actions (e.g. a hand grasping a mug in a context implying an intention to drink, or to clean up) activity in the mirror system is increased compared to when the action is observed outside of any context (i.e. on a blank background) and parts of the mirror system (inferior frontal region) show differential activation depending on the context (Iacoboni et al., 2005). This indicates that the mirror system is not simply an action recognition mechanism (i.e. that is a hand grasp) but is also involved in understanding the intentions/goals behind the actions of others.

### *1.2.2 Predicting the actions of others*

It has been proposed that the mirror system acts in a predictive manner, predicting and simulating the actions of others, on the basis of the current situation and prior knowledge, and using the internal forward model, normally used to predict the consequences of our own actions, to verify its prediction (Kilner et al. in submission). According to this hypothesis the observer anticipates the actions of the other, and simulates the predicted actions with their own motor system. The same internal forward model, that is used to predict the sensory consequences of our own actions, is used to predict the sensory consequences of the simulated actions. This prediction is transformed to give a prediction of the sensory consequences of the other's action from the observer's view point and then compared to the actual sensory feedback from the observed action. For example, if the observer anticipates that the subject will move their hand, their motor system simulates the movement of the observer's own arm and the internal forward model predicts the visual consequences of this arm movement. This visual prediction can then be transformed to generate a prediction of the visual consequences of the same movement made by another person. The sensory prediction can then be compared to the actual sensory input received from the observed action and a prediction error is calculated. This prediction error is then used to modify the original prediction of what action the other person is performing, and new sensory prediction can be generated. By minimising the prediction error the most likely cause of the observed visual input can be inferred, allowing us to recognise what the other person is doing.

Kilner and colleagues propose that a predictive account of the mirror system can also account for our ability to infer the intention behind an observed action. They proposed that the observed movement is represented on a number of different levels arranged in a hierarchy: the visual representation of the movement, the motor representation of the action, the goal of the action, and the context in which it occurs. The observer predicts the goal of the actor on the basis of the context, and then predicts and simulates the appropriate action to achieve this goal within the context. As described above, an internal forward model then predicts the sensory consequences of the action and compares it to the actual consequences to generate a prediction error. The simulated action that minimises this prediction error can be

compared to the action predicted on the basis of the predicted goal, and another prediction error is generated. By adjusting their representation of the goal of the other person so as to minimise this prediction error, the observer can infer the goal of the observed action. Thus, minimising the prediction error at all levels in this hierarchy allows us to recognise what actions others are performing and to infer the intentions of behind these actions.

There is increasing evidence that the mirror system actively predicts the actions of others, rather than simply responding to sensory input. A recent study has shown that 75.6% of parietal mirror neurons that respond to the sight of a hand grasping an object respond differentially depending on the final goal of the action (Fogassi et al., 2005). Of these, some responded preferentially when the hand grasped the object and put it in the experimenter's mouth, and some responded when the hand grasped the object and placed it in a container next to the mouth. This differential activation was observed, not during the final part of the action when the object is placed in the mouth or in the container, but instead during the initial part of the action when the monkey sees the hand grasp the object, an action which is common to both conditions. Thus it appears that the parietal mirror neurons are able to predict the second part of the action. This prediction could be based on the type of object being grasped, a food object indicating grasping to eat, and also on the presence or absence of the container, which was only present in the grasping to place trials. Thus, in line with the predictive account of the mirror system, this study demonstrates that at least some parietal mirror neurons predict a subsequent action on the basis of the context in which the action is performed.

Further support for this idea comes from a previous study showing that mirror neurons in monkey F5 that respond to grasping hand actions still fire when a hand reaches to grasp an object hidden behind a screen, even though the monkey cannot actually see the hand grasp the object (Umilta et al., 2001). This suggests that the monkey's mirror neurons are predicting that the hand will grasp the object from the knowledge that an object is behind the screen and the sight of the arm reaching for it.

In humans also, there is evidence of prediction by the mirror system during action observation. Using EEG, Kilner and colleagues have demonstrated activation of the

motor system prior to the observation of a predicted movement (Kilner et al., 2004). Subjects were shown short video clips of a hand (the right hand). In half the trials the hand moved and grasped an object, and in half the trials it remained still. The colour of the object indicated whether the hand would move or not. A significant negative potential was observed contralateral to the observed action, starting around 500ms prior to the onset of the predictable hand movement. This negativity was comparable in timing and location to the movement readiness potential that was observed when subjects actually executed a movement with their own hand, and is typically observed prior to making any movement. According to the authors these results suggest that the mirror system sets up a predictive model of another person's actions. This allows the brain to anticipate rather than merely react to another person's actions.

Similarly, activation of the motor system has been demonstrated prior to hearing the sound of a predicted action with MEG (Haueisen and Knosche, 2001). When expert pianists listened to a familiar melody their finger related motor cortex was activated, and the location of the activation for each note was specific to the finger that would normally be used to play a particular note. Activity in response to notes usually played by the thumb was localized to an area inferior to activation in response to notes usually played by the little finger, consistent with the motor homunculus in M1. The note specific activation in the motor cortex occurred 300ms prior to the onset of each note, thus demonstrating that the mirror system anticipates the unfolding melody and the associated action sequence.

There is also behavioural evidence of prediction during action observation. When watching predictable actions, a subject's eye gaze lead the observed movement, demonstrating that gaze predicts rather than reacts to the observed action (Flanagan and Johansson, 2003). In our own visually guided actions eye movements lead hand movements and are crucial for planning and control. In Flanagan and Johansson's study, subjects either executed a block moving task or observed another person doing the same task. The pattern of eye movements was the same in both conditions and preceded the hand movement. In comparison when the blocks alone moved without a hand visibly picking them up the subject's eye movements followed the blocks, rather than anticipating the movement of the blocks.

When observing actions whose target was unknown in advance subjects' gaze nevertheless fixated ahead of the actor's hand, i.e. gaze was still proactive not just reactive, however the gaze shifts occurred later when the observer did not know the goal in advance compared to when they were following their own actions (Rotman et al., 2006). In a separate task subjects were asked to guess the target of the action. The time at which subjects were able to correctly guess the target was very similar to the time at which they made the predictive gaze shift in the observation task. This suggest that subjects use the kinematics of the actor's movements and knowledge about the rules of the task to predict the goal of the movement and as soon as they can tell where the hand is going to move to, they make a gaze shift to the target.

There is also evidence from fMRI studies that the mirror system is involved in predicting the actions of others (Ramnani and Miall, 2004). Subjects together with a training partner learned to make specific finger movements in response to simple visual cues. During scanning subjects did not actually observe their training partner executing a finger movement but viewed the learned visual cues and believed that their training partner was making the appropriate movement in the adjacent room. In one condition the visual cue indicated precisely which finger movement the partner would make and then a second cue indicated when to make the movement. In another condition the initial visual cue merely indicated that an action would occur, but the precise finger movement was not cued in advance and subjects only knew which movement their partner would make when the second cue triggering the action appeared. Only in the first condition when the precise movement was cued in advance could the subjects predict which movement their training partner would have to make. In the control conditions the subject was instructed that a computer would be executing an action in response to the cues. Brain activity was examined in response to the first visual cue. Parts of the motor system, including the dorsal prefrontal cortex, the primary motor cortex, and Broca's areas were activated when subjects anticipated the actions of other, as was the posterior superior temporal sulcus (STS). The posterior STS is not activated by action execution, however it is generally considered to be part of the human mirror system, as it responds to biological motion (Allison et al., 2000). This study supports the notion that the mirror system is involved in predicting others actions and is not merely activated in

response to sensory stimuli (whether auditory or visual) that arise as a consequence of the actions of others.

The STS shows greater activity to unpredicted compared to predicted movements (Pelphrey et al., 2003;Pelphrey et al., 2004a). Subjects observed an avatar making gaze shifts in the presence of a visual target. A smaller haemodynamic response was evoked in the observer's STS and IPS in response to gaze shifts directed towards the target, compared to gaze shifts to another location in the avatar's visual field (Pelphrey et al., 2003). Similarly, reaching-to-grasp arm movements directed towards a target elicited less activation in the observer's STS compared to arm movements directed away from the target (Pelphrey et al., 2004a). The authors propose that the STS is involved in predicting the actions of others, and that the prolonged activity seen when the actor does not look at or grasp the target, is due to violation of the observer's expectations and the reformulation of the observer's prediction. Alternatively the activation of the STS could reflect the prediction error. These findings fit well with Kilner's predictive model of the mirror system, which includes the STS (Kilner et al. in submission).

In Chapter 6, I will further investigate the effect of the observer's expectation on the brain activity evoked by observation of another person making a gaze shift. I will compare the response to gaze shifts towards a visible target, with the response to gaze shifts away from a visible target. I will also modify the observer's expectation by modifying the intention attributed to the person making the gaze shift.

### *1.2.3 Mirroring the sensory consequences of actions*

In addition to there being evidence that we use our own motor system to monitor and predict the actions of others, there is evidence that action observation affects our sensory cortices, supporting the idea that we predict the sensory consequences of observed actions.

Several studies have demonstrated modulation of somatosensory activity during action observation. Avikainen and colleagues recorded somatosensory evoked field potentials in response to medial nerve stimulation using MEG, during rest, while

subjects manipulated a small object or while subjects observed the experimenter manipulating a small object (Avikainen et al., 2002). SI signals were enhanced during both execution and observation of hand actions compared to rest, whereas SII signals were suppressed during action observation and execution, (except for when the right hand was moved while right medial nerve stimulation was applied, in which case the opposite effect was found, i.e. decreased SI and increased SII). In a similar study Rossi and colleagues recorded somatosensory evoked potentials in response to stimulation of the right median nerve using EEG and MEG, while subjects executed, and observed hand actions, performed mental calculations and were at rest (Rossi et al., 2002). The amplitude of the N30 component of the somatosensory evoked potentials increased during action observation but decreased during action execution relative to rest. Likewise, the strength of somatosensory evoked fields (recorded by MEG) at 30ms in SI increased during action observation and decreased during action execution. The strength of the MEG signal in SII at 100ms decreased during both action observation and execution versus rest, but the effect was not quite significant p=0.058).

Similarly, activity in the mouth and hand areas of SI was recorded with MEG in response to tactile lip and electrical medial nerve stimulation respectively, during rest, while subjects listened to speech, while subjects viewed silent articulations, and while subjects executed lip protrusions. Mouth movements decreased the strength of mouth SI sources bilaterally. Viewing speech increased activation of mouth SI in the left hemisphere, but there was no clear effect in the right hemisphere. Listening to speech did not have any systematic effects on activity in SI in either hemisphere (Mottonen et al., 2005).

Modulation of somatosensory cortices has also been observed using fMRI. Observation of someone silently articulating speech has been shown to activate the auditory cortex (Calvert et al., 1997;Pekkola et al., 2005). It has also been demonstrated that observation of grasping hand actions activates the secondary somatosensory cortex (SII) in the parietal operculum (Grezes et al., 2003). The authors propose that this activation in SII consists of a representation of the sensory consequences of the action being observed that is associated with the motor representation of that action.

Together these studies demonstrate that action observation modulates activation of sensory cortices. This may represent a prediction of the sensory consequences of the observed action on the basis of activation of the motor representation of the observed action. This would be in line with the proposal that the mirror system uses the same forward model used to predict the sensory consequences of our own action to predict the sensory consequences of the actions of others.

In Chapter 7, I will investigate the neural systems involved in monitoring the sensory consequences (a tone) of our own actions (a button press) and those involved in monitoring the sensory consequences of the actions of another person, and whether the neural response to sensory stimuli caused by the actions of others is modified in the same way as the response to self-produced sensory stimuli.

In Chapter 8, I will investigate whether in addition to representing actions of others in our own motor system, and representing the sensory consequences of these actions in our sensory cortices, we also represent the sensations experienced by others in a similar manner. Recently, a number of brain systems with 'mirror' properties have been described. Common regions are activated by the experience and mere observation of disgust (Wicker et al., 2003), emotional facial expression (Carr et al., 2003), pain (Singer et al., 2004), and touch (Keysers et al., 2004). In the latter study, observing touch to someone else's legs activated similar regions in the secondary somatosensory cortex (SII) in the observer's brain as when the observer's own legs were touched. However, this SII activation was also found during the observation of touch to an object, and no primary somatosensory cortex activity was found in either condition (Keysers et al., 2004). In Chapter 8, I will investigate the potential existence of a touch mirror system by comparing the neural response to the observation of touch to a human face, and touch to an object.

## 1.3 Development of action monitoring

### *1.3.1 Our own actions*

There is evidence that infants as young as 3-5 months can distinguish between the perceptual consequences of self-induced versus externally-induced actions, on the

basis of contingencies between their actions and sensory input. Five month old infants can distinguish between a live contingent video of their own legs moving and a non-contingent video of moving legs, either another infant's or a previous recording of their own legs (Bahrick and Watson, 1985). Infants preferentially looked at the non-contingent feet, presumably making use of the contingency between the movements seen on the screen and proprioceptive feed back from their own legs (which were hidden from view). In contrast three-month old infants do not show any preference across the group, but when the data are examined more closely, looking times have a bimodal distribution, with approximately half preferring to look at their own feet and half preferring the non-contingent feet. Three month old infants viewing faces also show a significant preference for a contingent self-image (i.e. mirror image) over a non-contingent image of another child (Field, 1979).

Thus it appears that between 3 and 5 months of age there is a change in attentional preference from contingent to non-contingent, and that some of the 3 month olds in Bahrick and Watson's study have undergone this transition while others are yet to do so. Bahrick and Watson suggest that up to 3 months infants seek out perfect contingency, while they learn about "self", that at around 3 months a bias matures to the effect that perfect contingency is categorized as self and thereafter becomes less interesting than imperfect contingencies, which imply an external cause.

Bahrick and Watson's findings have been replicated with 5 month old infants but with the infant's hand exploring a hidden toy rather than their feet (Schmuckler, 1996). Again, infants preferentially looked at the non-contingent video. There is even evidence suggesting that infants aged 4 weeks and under can distinguish between external and self-stimulation (Rochat and Hespos, 1997). Newborns display significantly more rooting responses when touched on the cheek by the experimenter compared to when they touched their own cheek. Four week old infants show the opposite pattern.

Taken together these studies, and several others, suggest that infants from around 3 months of age, or even younger, can detect contingencies between their actions and a stimulus and that by 5 months they can definitely distinguish between self-produced stimuli and externally generated stimuli as demonstrated by the differential responses

they show to the two types of stimuli, i.e. by 3-5 months of age infants can recognise the consequences of their own actions.

### *1.3.2 The actions of others*

Adults' ability to understand the actions of others appears to be based on the involvement of their own motor systems during action observation, which provides a motor representation of the perceived actions. Evidence for the involvement of the motor system in action observation in young infants comes mainly from studies of imitation.

Imitation was first observed in very young infants by Meltzoff & Moore in 1977. Newborn infants between 12 and 21 days old observed adults making the following movements: lip protrusion, mouth opening, tongue protrusion, and opening and closing the hand. The infants' hand and face movements were video taped and independent coders rated which movement they thought the infant was making (the coders did not know which action the infant was observing at the time). The judged behaviour of the infants matched the observed action (Meltzoff and Moore, 1977). For example the infants made significantly more tongue protrusions after they had seen the adult perform tongue protrusions. Meltzoff and Moore replicated this finding in new born infants ranging from 42 minutes to 71 hours old. When infants observed the adult making tongue protrusions, the frequency and duration of the neonates' tongue protrusions was greater than when they observed the adult making mouth openings and vice versa (Meltzoff and Moore, 1983). Another study demonstrated imitation of head movement as well as tongue protrusion in neonates (Meltzoff and Moore, 1989).

There is also evidence that infants imitate vocalisations. Infants, aged 12-20 weeks, listening to an adult speaker produce a particular vowel, /a/, /i/, or /u/, produced more vocalisations resembling that particular vowel (Kuhl and Meltzoff, 1996). More recently, it has been shown that new born infants, aged from 1 to 7 days, make the appropriate mouth movement (mouth opening for /a/ and mouth clutching for /m/) in response to the speech sounds /a/ and /m/, both when they can see the speaker articulating and when their eyes are closed (Chen et al., 2004). This suggests that

there is an innate connection between heard speech and the corresponding motor representation.

This ability of young infants to imitate actions, demonstrated by the above studies, provides strong evidence of early development of system for coupling the perception and production of actions. However, there is some controversy surrounding imitation by infants and alternative interpretations have been proposed to explain the findings described above, one such alternative being that the behaviours studied are relatively fixed action patterns that are similar in form to the visual stimuli releasing them (Anisfeld, 1979;Anisfeld, 1991;Anisfeld et al., 2001).

There is recent evidence that 12 month old infants can predict or anticipate the actions of others. When observing goal-directed hand actions, the eye movements of both adults and 12 month old infants anticipated the observed movement (Falck-Ytter et al., 2006). Such proactive eye movements have previously been demonstrated only in adults (Flanagan and Johansson, 2003). Both adults and 12 month old infants shifted their gaze towards the goal of the action before the hand reached the goal. In contrast, the gaze of 6 month old infants shifted to the goal after the hand reached the goal. However when observing the object moving in a self-propelled fashion without an arm movement, gaze did not shift to the goal of the movement significantly ahead of the moving object, demonstrating that predictive eye-movements depend on the presence of a human action, rather than mere predictability of the movement. This study shows that by 12 months of age infants are able to predict the actions of others, and the authors suggest that this ability is mediated by the mirror system.

It also appears that as well as being able to recognise the consequences of their own actions, infants can recognise the consequences of actions made by others from 2 months of age, at least in the context of speech. There is strong behavioural evidence that infants as young as 2 months of age can match observed articulatory mouth movements to the appropriate sound. When presented with two videos of faces articulating vowels, 4.5 month old infants spent significantly longer fixating the video that matched the auditory vowels they were played (Kuhl and Meltzoff, 1982;Patterson and Werker, 1999). This finding has been replicated with 2 month old

infants (Patterson and Werker, 2003). In an operant sucking paradigm, 4 month old infants will suck more to receive a face that matches the heard speech sound (Walton and Bower, 1993). So it seems that they can predict the precise sensory consequences of articulations. However the neural basis of this ability remains unknown. One possibility is that infants represent both seen and heard speech amodally in their motor system. Supporting this possibility is the fact that in adults both seeing and hearing speech has been shown to activate regions involved in speech production (Skipper et al., 2005;Wilson et al., 2004), and evidence that young infants imitate heard speech implying an early correspondence between speech perception and production (Chen et al., 2004;Kuhl and Meltzoff, 1996). In Chapters 9 and 10, I will investigate the neural mechanism underlying infants' ability to recognise the auditory consequences of observed articulatory movements.

### 1.4 Summary

In this thesis I will investigate the neural mechanisms underlying our ability to monitor our own actions and predict their sensory consequences, and our ability to understand and predict the actions of others. There is substantial evidence that our ability to monitor our actions and their consequences is based on the use of an internal forward model that predicts the consequences of an action on the basis of an efference copy of the motor command eliciting that action. This prediction appears to be used both for motor control, and to attenuate, cancel or compensate for the sensory consequences of our actions. In Chapters 4 and 5, I will investigate the neural mechanism underlying sensorimotor cancellation during eye-blinks.

There is accumulating evidence that our ability to understand and predict the actions of others and their consequences is based on the same systems, including the internal forward model, that are involved in controlling and monitoring our own actions. In Chapters 6 and 7, I will investigate the neural mechanisms underlying our ability to monitor and predict the actions of others and the consequences of these actions.

In Chapter 8, I will investigate the possibility that, in addition to representing actions of other in our own motor system, and representing the sensory consequences of these actions in our sensory cortices, we also represent the sensations experienced by

others in a similar manner. I will investigate the potential existence of a touch mirror system, equivalent to the action mirror system, by comparing the neural response to the observation of touch to a human face, and touch to an object.

In this thesis I will also begin to investigate the development of our ability to monitor the actions of others. There is strong behavioural evidence, mainly from studies of imitation, of early development of a system for coupling the perception and production of actions. There is also behavioural evidence that infants can recognise the consequences of the actions of others from an early age. 2 month old infants are able to match observed articulations with the appropriate speech sound. In Chapters 9 and 10, I will investigate the neural mechanism underlying this ability, one possibility being that infants represent both seen and heard speech amodally in their motor system, as is the case in adults.

# CHAPTER 2: FUNCTIONAL MAGNETIC RESONANCE IMAGING METHODS

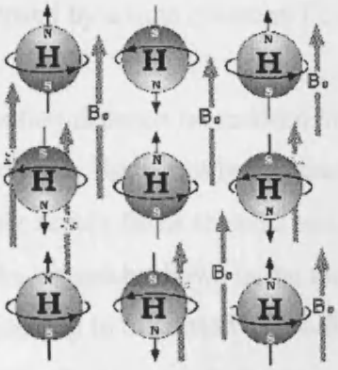
## 2.1 Basis of fMRI signal

### *2.1.1 Physics of Magnetic Resonance Imaging*

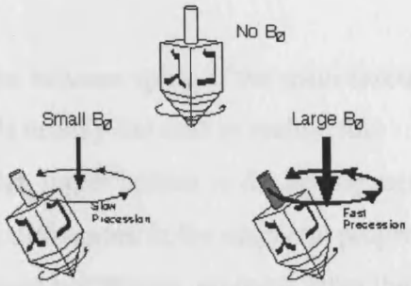
The physical basis of Magnetic Resonance Imaging lies in a property of protons called spin. Protons are positively charged and the spinning motion of the charge induces a local magnetic field. In the absence of a magnetic field these spins orient randomly and the material containing the protons has no net magnetisation. But in the presence of an external static magnetic field (Bø) the majority of spins will align with this field (See Figure 2.1). Some align against the field but the net magnetic field (Mø) of all the protons is in alignment with the external field. The spinning protons revolve, or precess, about the axis of the external magnetic field Bø (a bit like a spinning top) (see Figure 2.1). The frequency of this rotation is called the resonance frequency, and is proportional to the strength of the external magnetic field, Bø.

If a radio frequency (RF) pulse is then applied perpendicular to the main magnetic field, Bø at the resonance frequency the protons can absorb this energy. This changes the alignment of the magnetic moments of the protons, which causes the spins to move away from their equilibrium positions. The net magnetisation Mø now also aligns away from Bø, towards the new applied radio frequency magnetic field, $B_1$. This gives rise to a non-zero transverse magnetisation in the XY plane ($M_{xy}$), if we imagine that the original magnetic field, Bø, is aligned to the Z-axis. The duration of this new alignment and the angle from its original equilibrium direction inline with Bø, increases with the strength and duration of the RF pulse.

***Figure 2.1 Protons in an external magnetic field*** *(from www.simplyphysics.com)*




Protons align with external Magnetic field (Bø)




The protons precess around axis of Bø

Once the RF pulse is turned off the spins gradually return to their equilibrium positions over several seconds, and absorbed RF energy is retransmitted at the resonance frequency. This is the MRI signal. Once the net magnetisation vector, Mø, has been tipped away from the Z axis by the RF pulse, it continues to rotate around the main external magnetic field, Bø, at the resonance frequency. The rotating magnetic fields produces electromagnetic radiation at the resonance frequency and these waves induce a signal voltage in a receiver coil surrounding the object being scanned (typically the subject's brain).

The spins realign to their original positions in 2 ways simultaneously:
*Longitudinal relaxation (T1):* The excited protons transfer energy to neighbouring molecules, and return to their original orientation aligned to Bø along the Z-axis. This return to thermal equilibrium is called longitudinal or spin-lattice relaxation. It is an exponential process characterised by a time constant T1. T1 is affected by the composition of the environment and thus is different in different tissues, a fact which can used to provide contrast between tissues.
*Transverse relaxation (T2):* When the spins are tilted towards the RF pulse magnetic field, $B_1$, they are initially all in phase, but as the protons move together their magnetic fields begin to interact with one another in a random manner, quickly causing them to become desynchronised so that they are no longer in phase with one another. As the protons dephase the magnetisation in the XY plane, $M_{XY}$, decreases.

This process, called transverse or spin-spin relaxation, is exponential and is characterised by a time constant T2.

T2 relaxation depends on random interactions between spins. If the main external magnetic field, Bø, is not homogeneous, as is usually the case in reality, this dephasing occurs faster than T2 would predict. Imperfections in the homogeneity of Bø can be caused by flaws in the magnet, or differences in the magnetic properties of tissues leading to distortion of the field at tissue boundaries, amongst other things. These imperfections mean that spins in difference parts of the objects will rotate at slightly different frequencies and thus dephase more rapidly. T2* relaxation is the sum of the relaxation caused by these fixed effects and T2 relaxation, which is caused by random interactions. Functional MRI sequences usually measure T2*.

### *2.1.2 Image formation*

To create an image with MRI protons must be distinguishable according to their spatial location. The main external magnetic field Bø is homogeneous, and thus affects all protons in the sample in the same way, so the frequency of the emitted RF signals is not affected by location. Therefore a second magnetic field is applied, the frequency gradient field, that varies across the object, causing the resonant frequencies of the protons to vary according to their position. A particular resonant frequency (which depends on the strength and direction of the magnetic field) corresponds to a particular position in the sample, and the amplitude of the signal at that frequency depends on the number of protons in that particular location. Thus the gradient field allows the encoding of position in one dimension (along the x-axis) through frequencies, but a second type of variation in magnetic field is needed to encode position in a second dimension (along the y-axis) – this is achieved by phase encoding. Resolution in the third dimension (along the z-axis) is created by exciting the sample one slice at a time, by combining the frequency gradient with an RF pulse of a particular frequency and bandwidth. Discrete increases in the frequency encoding and phase encoding gradients divide each slice into small cubes, called voxels (volume elements). All the protons in a voxel experience the same frequency and phase encoding, and the signal from a voxel is the sum of the signal for all the

protons in that voxel. The protons within a voxel cannot be distinguished from one another.

Contrast in the image is created by the differences in signal intensity from different tissues. The largest contribution to the signal comes from protons in tissue water, and signal intensity depends in part on the density of these protons. But there is not much variation in proton density between different tissues so the contrast between them is not very large. Signal intensity is also determined by T1 and T2 relaxation times, the magnetic susceptibility of the tissue (determined by other protons and electron clouds in the tissue), and the characteristics of the RF pulse. Spins from solid tissues such as bone are not detectable by MRI because their relaxation times are so fast that they have returned to equilibrium before any signal is detected. Therefore MRI mainly detects protons present in biological fluids, such as blood. Differences between T1 and T2 relaxation times can be used to increase image contrast. By choosing appropriate sequence parameters the scan can be tuned to detect differences in T1, T2 or T2* between different parts of the imaged object. Thus an image can be T1, T2 or T2* weighted.

### *2.1.3 Echo-planar imaging*

Echo-planar imaging (EPI), invented by Mansfield in 1977 (Mansfield, 1977), allows extremely rapid acquisition of whole brain images. An image of a complete slice can be acquired in less than 100ms. The acquired data are Fourrier transformed from the time domain to the frequency domain. The transformed data are considered to lie in a two dimensional frequency space, called K-space. EPI sequences acquire data from all the lines of K-space after each RF pulse, whereas other MRI sequences can only acquire data from one line per RF pulse. This means that acquisition time is far lower for EPI, making it very suitable for recording dynamic information, like in fMRI. All the fMRI experiments in this thesis used EPI sequences.

### *2.1.4 BOLD signal*

Neuronal activity and the associated increase in local glucose metabolism in an area are tightly coupled to a local increase in blood flow. fMRI aims to measure neural

activity by detecting changes in blood flow as indicated by blood oxygenation levels. The MRI signal can be made sensitive to the oxygenation properties of blood (so called Blood Oxygenation Level Dependent contrast), because of the paramagnetic properties of haemoglobin. When haemoglobin has no oxygen bound to it, it has a net magnetic moment, but when oxygen binds this moment disappears. Thus the magnetic state of blood reflects its level of deoxygenation, with deoxyhaemoglobin being more paramagnetic than oxyhaemoglobin (Pauling and Coryell, 1936). It is this difference in paramagnetism that allows the oxygenation state of the blood to be detected by BOLD contrast fMRI. The more paramagnetic a substance the faster the transverse relaxation time of its protons, and the shorter its T2* time constant, resulting in the production of a reduced T2* weighted MRI signal. Thus deoxyhaemoglobin produces a smaller MRI signal than oxyhaemoglobin. This is what underlies the BOLD signal, as blood with more deoxyhaemoglobin will produce a reduced signal relative to highly oxygenated blood. This was first demonstrated in mice by Ogawa and colleagues in1990 (Ogawa et al., 1990) and in cats by Turner and colleagues in 1991 (Turner et al., 1991). It was subsequently demonstrated in 1992 in the human visual cortex by Kwong and colleagues (Kwong et al., 1992) and Ogawa and colleagues (Ogawa et al., 1992). They demonstrated an increase in the BOLD signal in the visual cortex following visual stimulation, indicating a decrease in the concentration of deoxyhaemoglobin during visual stimulation compared to rest.

BOLD contrast is determined by the balance between supply, determined by blood flow and blood volume, and demand, determined by the surrounding tissue's rate of glucose metabolism, and consumption of oxygen. Local increases in neural activity leads to an increase in glucose metabolism in the neurons and thus an increase in oxygen consumption (Hyder et al., 1997). This causes a relative deoxygenation of the blood in the surrounding blood vessels about 100ms after onset of neural activity (Vanzetta and Grinvald, 1999), coupled to vasodilation and an increase in blood flow to the area 500-1000ms after onset of neuronal activity (Villringer and Dirnagl, 1995). This increase swiftly reverses the deoxygenation, resulting in an overall increase in blood oxygenation level in the area that lasts for several seconds. This overcompensation is what causes the increased BOLD signal. There is a disproportionate increase in the amount of oxygenated blood flow to an activated

region, i.e. the rise in oxygen uptake is smaller than the rise in blood flow to activated brain regions (Fox and Raichle, 1986) thus the rise in BOLD signal during activation indicates, perhaps counter-intuitively, a decrease in the concentration of deoxyhaemoglobin in the area relative to rest.

The increase in BOLD contrast, caused by the decrease in deoxyhaemoglobin and measured in fMRI, is delayed in time with respect to the neural activity. Typically the BOLD signal peaks 4-6 seconds after the onset of neural activity. The rise and subsequent return to baseline of the BOLD signal is known as the Haemodynamic Response Function (HRF).

### *2.1.5 Neural basis of BOLD signal*

The specific cellular and molecular mechanisms underlying the BOLD signal detected by fMRI have not yet been definitively determined. Many researchers believe that the cerebral blood flow monitored by fMRI corresponds to activity in the pre-synaptic axon terminal of neurons (Jueptner and Weiller, 1995). 85% of cerebral glucose is used by neurons, primarily for the maintenance of membrane potentials and restoration of ion gradients (Kageyama and Wong-Riley, 1986). Several studies indicate that glucose consumption by neurons mainly reflects presynaptic activity at the axon terminal (Kadekaro et al., 1985;Kadekaro et al., 1987;Nudo and Masterton, 1986;Schwartz et al., 1979;Wree and Schleicher, 1988). However, the relationship between glucose consumption and neural activity may not be so straightforward. There is evidence for a central role for astrocytes in coupling presynaptic activity with energy consumption via the release of glutamate from the axon terminal and its reuptake by the surrounding astrocytes (Magistretti and Pellerin, 1999). The uptake of glutamate requires energy and thus glutamate stimulates glucose uptake by astrocytes, and its glycolysis resulting in the production of ATP, to power the glutamate uptake, and the release of lactate (Magistretti and Pellerin, 1997;Pellerin and Magistretti, 1997). This lactate may subsequently be oxidised by the adjacent neurons to meet their energy needs (Magistretti et al., 1999).

More recent research has shed doubt on the commonly held view that the BOLD signal is largely driven by energy use in the presynaptic terminals (Attwell and

Iadecola, 2002). Instead Attwell and colleagues concluded, on the basis of the measured properties of individual ion channels and synapses, that most of the energy used during neuronal activity is expended on reversing the ion movements that generate excitatory post synaptic potentials in the post-synaptic terminal, with a smaller proportion being used to reverse the ion movements that underlie action potentials (Attwell and Laughlin, 2001). In primates, postsynaptic responses were predicted to account for 74% of energy usage, while action potentials were predicted to account for 10% of energy usage.

Another recent and highly influential study has examined how the BOLD signal correlates with activity simultaneously recorded from microelectrodes placed in monkey primary visual cortex (Logothetis et al., 2001). Both multi-unit activity (MUA) and local field potential (LFPs) were recorded. MUA represents the action potentials, i.e. the spiking activity, of multiple neurons near (~100μm) the electrode tip, while LFPs, are thought to be a weighted sum of the membrane potentials of the neurons surrounding the electrode tip. Such changes in membrane potential mainly reflect synaptic activity in the dendrites and soma of neurons, so LFP is thought to mainly reflect subthreshold integrative processes in these areas.

Both MUAs and LFPs were found to correlate with the BOLD response. However, LFPs were the slightly better predictor, giving better estimates of BOLD response than MUAs. Therefore the authors concluded that the BOLD signal "reflects the input and intracortical processing of a given area rather than its spiking output". However, this may be an overstatement, because although the LFP mainly reflects dendritic and somatic membrane potentials arising from synaptic activity, action potentials can also contribute. LFPs thus do not simply reflect just inputs and cortical processing. Additionally, MUAs correlated well with BOLD activity, if not as well as LFPs. MUA does not necessarily reflect the only the output of an area, as around 80% of cortical axons terminate on other neurons in the local population. Therefore LFPs and MUAs, and thus the BOLD signal, are likely to both reflect varying types of neural activity.

Recent evidence suggests that the increase in regional cerebral blood flow (rCBF) associated with neuronal activity may not be directly related to the energy requirements of the brain but is instead mediated by neurotransmitters (Attwell and Iadecola, 2002). Though the usage of oxygen and glucose and the production of $CO_2$ and $H^+$ are correlated with an increase in rCBF, it appears that none of these directly bring about the changes in rCBF seen during neural activity (Astrup et al., 1978;Mintun et al., 2001;Pinard et al., 1984). Instead it appears that the haemodynamic response may be driven by glutamate mediated signalling, leading to an influx of $Ca^+$ in postsynaptic neurons. This leads to the production of NO, adenosine and arachionc acid metabolites, which in turn bring about vasodilation (Attwell and Iadecola, 2002). According to this theory the BOLD signal reflects neuronal signalling rather than energy usage (though the two will often be correlated). Therefore, in theory the BOLD signal could reflect a change in neural processing without a net change in energy usage, and conversely a change in spiking activity, which uses energy, but does not affect the signalling systems controlling rCBF could fail to generate a BOLD signal (Attwell and Iadecola, 2002).

### *2.1.6 Resolution*

The limitations on the spatial and temporal resolution of fMRI are physiological and are imposed by the spatio-temporal properties of the haemodynamic response function. Spatial resolution is limited to 2-5mm and temporal resolution is limited to seconds (Friston et al., 1998). The BOLD signal originates in red blood cells in capillaries and veins surrounding the activated neural tissue, and thus is an indirect measure of tissue oxygenation and neural activation, thus the maximum spatial resolution obtainable with the BOLD signal is dependent on the local structure and density of the vasculature in a particular brain region.

## 2.2 fMRI Analysis

All fMRI data acquired during the experiments in this thesis were analysed with Statistical Parametric Mapping software, SPM2, developed at the Wellcome Department of Imaging Neuroscience (http://www.fil.ion.ucl.ac.uk/spm/). Analysis of data with SPM starts with a series of spatial transformations, to align the data and

warp it into a standard anatomical space (e.g. a stereotactic space), so that data from several subjects can be combined and analysed together. A model of the expected BOLD signal changes during all conditions in the experiment is then created and the data are fitted to the model using the General Linear Model. Activation maps are created from the resulting parameter estimates, and tested for statistical significance.

### 2.2.1 Preprocessing

#### *2.2.1.1 Spatial Realignment*

Head motion during the scan causes changes in signal intensity of a voxel over time, due to movement of the head through the fixed field of view, a serious confound. Despite head restraints, most subjects will move their heads at least a few millimetres. Realignment involves applying an affine rigid-body transformation to align each scan with a reference scan (usually the first scan or the average of all scans) and resampling the data using tri-linear, sinc or spline interpolation. The 6 parameters of the rigid-body transformation, representing adjustments to pitch, yaw, roll, and in X, Y, Z position, are estimated iteratively to minimise the sum of squares difference between each successive scan and the reference scan (Friston et al., 1995). However, even after realignment some movement related signals persist. In extreme cases 90% of variance in the fMRI time-series can still be accounted for by movement affects after realignment (Friston et al., 1996). This is due to non-linear effects of movement which cannot be corrected using an affine linear transformation. These non-linear effects include movements between slice acquisitions, imterpolation artefacts, nonlinear distortion of magnetic field and spin excitation history effects. These effects make the movement related signal in a particular scan and non-linear function of the displacement in that and previous scans. These non-linear movement related effects can be estimated and subtracted from the original data by including the estimated movement parameters from the realignment procedure in the design matrix during the model estimation stage of the analysis (Friston et al., 1996).

### *2.2.1.2 Spatial Normalisation*

After realignment the mean functional image (created during realignment) is used to estimate the warping parameters that map this mean image onto a standard anatomical template image (Friston et al., 1995). The warping is modelled as a 12-parameter affine transformation, where the parameters constitute a spatial transformation matrix, or low frequency basis spatial functions (usually a cosine set or polynomials), where the parameters are the coefficients of the basis functions used. The parameters are estimated iteratively, within a Bayesian framework, to maximise the posterior probability of the parameters being correct, The posterior probability is the probability of getting the given data, assuming the current estimate of the transformation is true, times the probability of that estimate being true (Ashburner et al., 1997). Finding this solution involves jointly minimising the sum-of-squares differences between the template and the deformed mean functional image (the likelihood potential), and the prior potentials, which are used to incorporate prior information about the likelihood of a particular warp. The estimated warp is then applied to all the functional images. Anatomical T1 weighted images can also be normalised in this way to fit the same EPI template used for functional images, allowing the functional data to be overlaid onto the structural image of the subject.

The template used for normalisation is that of the Montreal Neurological Institute. The location of voxels is expressed using an XYZ coordinate system, where the origin (0,0,0) is located at the anterior commissure. The x-axis indicates distance to the left (negative) and right (positive) of the mid sagittal plane, the y-axis indicates distance posterior (negative) and anterior (positive) to the vertical plane through the anterior commissure, and the z-axis indicates distance below (negative) and above (positive) the inter-commissural line.

### *2.2.1.3 Spatial Smoothing*

Normalised images are spatially smoothed with a three-dimensional isotropic Gaussian kernel of 5-10 mm full width at half maximum. There are several reasons for doing this:

1) Smoothing the data makes the errors more normal ensuring the validity of parametric statistical test, which are based on the assumption that the errors are normally distributed.
2) Smoothing with a Gaussian kernel makes the data fit the assumptions of the Gaussian Random field model, which is used to make statistical inferences about regional effects, more closely (Adler R.J., 1981).
3) Smoothing ensures that the data from different subjects is assessed on a spatial scale at which homologies in functional anatomy are typically expressed among subjects. Smoothing compensates for any small variations in anatomy between subjects that still exist after normalisation, reducing the variation in the localisation of activations across subjects.

### 2.2.2 Statistical Parametric Mapping

#### *2.2.2.1 Basic approach*

The approach used by SPM for analysis of fMRI data is based on the conjoint use of the General Linear Model (GLM) and Gaussian random field (GRF) theory to test hypotheses and make inferences about spatially extended data through the use of statistical parametric maps. The GLM is used to estimate parameters for the variables that could explain the BOLD signal time series recorded in each and every voxel individually. The resulting statistical parameters are assembled into a three-dimensional image – the statistical parametric map (SPM), which can then be contrasted with one another. Gaussian random field theory is used to resolve the problem of multiple comparisons that occurs when conducting statistical tests across the whole brain. The voxel values of the SPM are considered to be distributed according to the probabilistic behaviour of Gaussian fields, and 'unlikely' excursions of the SPM are interpreted as regionally specific effects, caused by the experimentally manipulated variables.

#### *2.2.2.2 GLM*

The general linear model is used in SPM to partition the variance in the observed neurosphysiological response into components of interest, i.e. the experimentally

manipulated variables, confounds and error, and to make inferences about the effects of interest in relation to the error variance. For each voxel the GLM explains variations in the BOLD signal time series (Y), (where $j$ = timestamp) in terms of a linear combination of explanatory variables ($x$) plus an error term (e):

$$Y_j = x_{j1}\beta_1 + x_{j2}\beta_2 + \ldots\ldots + x_{jl}\beta_l + \ldots\ldots + x_{jL}\beta_L + e$$

The ß parameters reflect the independent contribution of each independent variable, $x$, to the value of the dependent variable, Y, .i.e. the amount of variance in Y that is accounted for by each $x$ variable after all the other $x$ variables have been accounted for. The errors, e, are assumed to be identically and normally distributed. The GLM can also be expressed in matrix formulation:

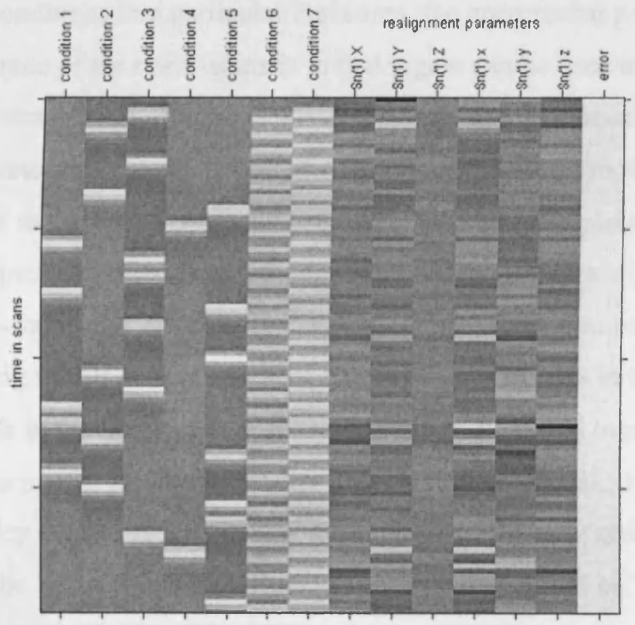
$$Y = X\beta + e$$

Where Y is a vector of J BOLD signal measurements (one per image volume) at a particular voxel (Y = [1...j...J]) and ß is the vector of the parameters to be estimated (ß=[ $\beta_1 \ldots \beta_j \ldots \beta_J$]. X is the design matrix containing the variables which explain the observed data. The matrix has J rows, one per observation, and L columns, one per explanatory variable ($x$) (also referred to as covariates or regressor).

The regressors, which form the columns of the design matrix (and have one value of $x$ for each time point $j$), are created for each explanatory variable manipulated in the experiment (the experimental conditions) by placing delta functions at the time points corresponding to the events of interest and convolving this vector with the haemodynamic response function. The HRF is modelled in SPM with a multivariate Taylor expansion of a mixture of Gamma functions (Friston et al., 1998). Additional columns can be created in the design matrix where the delta function is convolved with higher order basis functions. Those most commonly used are the time derivative of the HFR, which indicates variation in the latency of the haemodynamic response, and the dispersion derivative of the HRF, which indicates the dispersion of the HRF. To weight events in a single regressor differently from one another parametric modulators can be entered into the design matrix. These can model time dependent changes, or can be trial-specific values.

Movement parameters, calculated during realignment, can be including in the model as additional regressors to account for movement artefacts which are not corrected by realignment itself. Temporal confounds must also be eliminated from the data. Prior to fitting the model a high pass filter is applied to the data to eliminate drifts in the magnetic field and the effects of movement. A low pass filter is applied to eliminate the effects of biorhythms such as respiration or heart rate. The cut off of this filter is typically 128 seconds. Due to the serial acquisition of the fMRI data time-series successive time points will be correlated. To account for this temporal auto-correlation an autoregressive model of order 1 + white noise is fitted to the data.

***Figure 2.2 - A design matrix modelling the HRF for 7 conditions and realignment parameters***




The ß parameters (often referred to simply as 'betas') for each voxel are then estimated by multiple linear regression so that the sum of the squared differences between the observed data and the values predicted by the model is minimised.

### *2.2.2.3 t and F-statistics*

Inferences about the relative contribution of each explanatory variable ($x$), each represented by one column in the design matrix, can be made by conducting T or F-

tests on the parameter estimates. The null hypothesis that the parameter estimates are zero is tested by an F-statistic, resulting in an SPM(F). To compare the relative contribution of one explanatory variable compared to another one can contrast or subtract the parameter estimates from one another, and test whether the result is zero using a *t*-statistic, resulting in an SPM(*t*). The *t*-statistic is calculated by dividing the contrast of the parameter estimates by the standard error of that contrast. To make inferences about regionally specific effects the SPM(*t*) or SPM(F) is thresholded using height and spatial extent thresholds specified by the user.

#### *2.2.2.4 Correction for multiple comparisons*

When one has an anatomically constrained hypothesis about the effects of particular experimental conditions in a particular brain area, the uncorrected p-value associated with the magnitude of the t or F-statistic in that region can be used to test the hypothesis (Friston, 1997). However, if one does not have an a priori hypothesis, or if one has an anatomically open hypothesis (i.e. the null hypothesis that there is no effect anywhere in the brain) one must correct for multiple comparisons to avoid an excess of false positives. Gaussian Random Field theory provides a method of correcting the p-values for multiple comparisons while taking into account the fact that neighbouring voxels are not independent of one another, due to the anatomy of the brain (voxels in the same area are more likely to be activated together) and also due to the earlier spatial smoothing (Adler R.J., 1981;Friston et al., 1994b;Worsley et al., 1992;Worsley et al., 1996). Provided the data are sufficiently smooth the GRF correction will be less severe than a Bonferroni correction would be. Two assumptions underlie the use of the GRF correction. The error fields must be a reasonable lattice approximation to an underlying random field with a multivariate Gaussian distribution, which is ensured by smoothing, and these fields must be continuous, with a differentiable and invertible autocorrelation function. These assumptions are violated if the data is not smoothed or if the model is specified incorrectly such that the errors are not normally distributed.

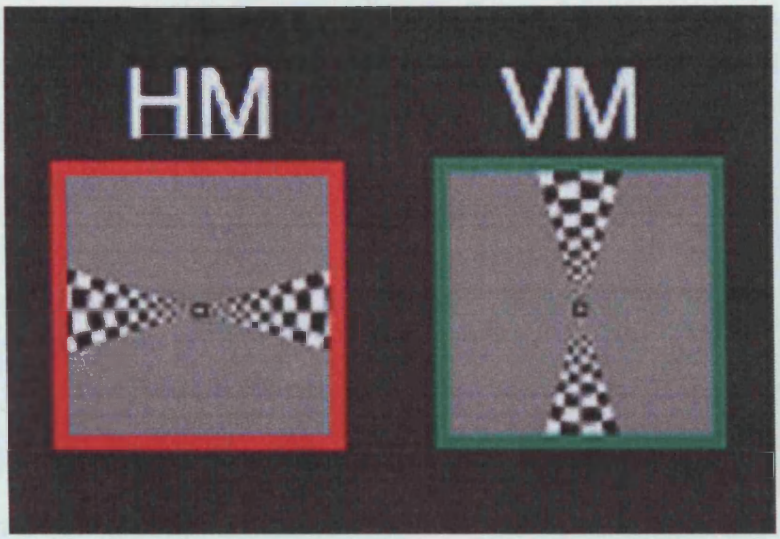
#### *2.2.2.5 Random Effect Analysis*

To draw inferences about fMRI data from a group of subjects that can be generalised to the population level one must conduct a Random Effects Analysis. A random effects analysis takes into account the variation in the activation effects from subject to subject. The term 'random-effect' indicates that the randomness of differential responses is taken into account by comparing the mean activation to the variability in activations from subject to subject. To conduct a random-effect analysis the contrasts of the parameter estimates from the 'first-level' analysis (described above) for each subject are entered into a 'second-level' analysis (the random-effect analysis). The second level design matrix can contain a single contrast (comparing the parameter estimates in different conditions) from each subject, and be used to conduct a simple t-test with the null hypothesis that the contrast is zero across subjects, i.e. there is no difference between conditions. Alternatively, more than one observation (one for each condition of interest) can be entered per subject into the second level design matrix and a repeated measures ANOVA can be conducted to compared conditions across subjects. In this way a single ANOVA can be used to test all contrasts of interest. In both cases the error variance is calculated using the subject to subject variability of the contrasts from the first level.

### 2.3 Retinotopic Mapping

To identify the boundaries of primary visual cortex (V1) and extrastriate retinotopic cortex (V2 and V3), I used standard retinotopic mapping procedures (Teo et al., 1997). Checkerboard patterns, flickering at 8 Hz, covering either the horizontal or vertical meridian were alternated with rest periods for 16 periods of 20.8 s over a scanning run lasting 165 volumes.

*Figure 2.3 - Stimuli: horizontal (HM) and vertical (VM) meridians*



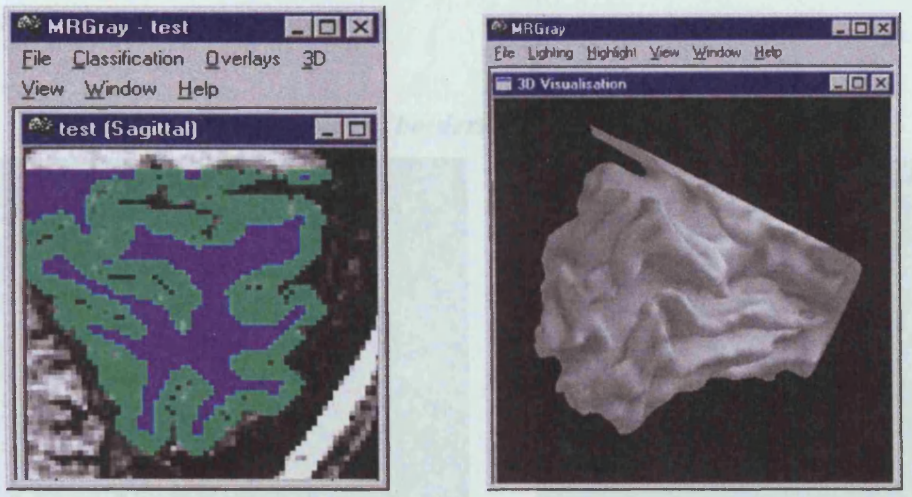

### *2.3.1 Imaging*

A 3T Siemens ALLEGRA system was used to acquire gradient-echo echo-planar T2*-weighted images with blood oxygenation level dependent (BOLD) contrast. Each volume consisted of 32 2mm axial slices with in-plane resolution of 3x3mm, with a 1mm gap between slices, positioned to cover the occipital lobe with a repetition time (TR) of 2.08s. Imaging was performed in three scanning runs of 165 volumes each. In each scanning run, five image volumes preceding presentation of the experimental conditions were discarded to allow for T1 equilibration effects. A T1-weighted anatomical scan was also obtained for each subject

### *2.3.2 Segmentaion and Flattening*

I used the segmentation software MrGray (Teo et al., 1997;Wandell et al., 2000) on each subject's structural scan to identify the grey matter in the visual cortex, and find a surface at the boundary between the grey and white matter.

***Figure 2.4 – Segmentation of occipital cortex in MrGray***




*Sagittal view of occipital cortex*
*Green = grey matte, Purple = white matter*

*3D visualisation of*
*grey matter in occipital cortex*

The cortical surface of the grey matter is then flattened using an unfolding tool, MrFlatMesh (by Alex Wade) (Wandell et al., 2000).

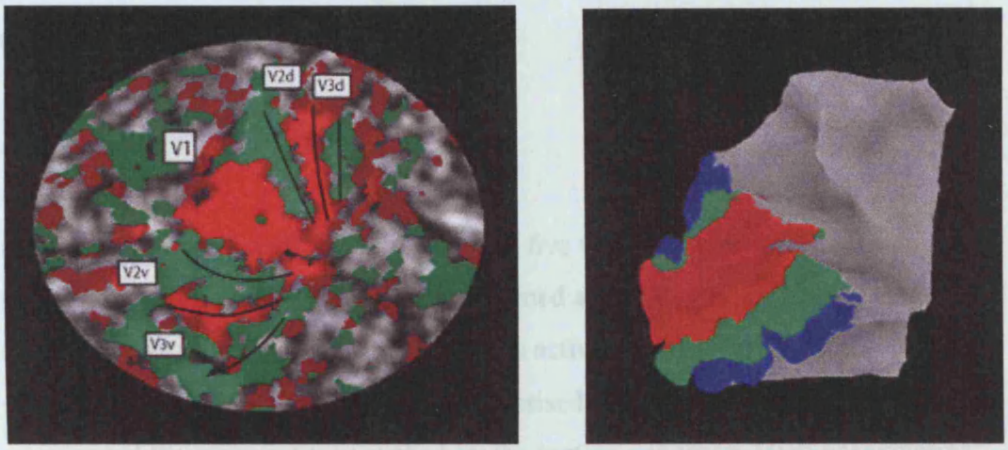
### *2.3.3 Statistical analysis*

Data were analyzed with Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm). The initial five volumes were discarded, and subsequent image volumes were then realigned and co-registered to each subject's structural scan (Friston et al., 1995). Voxels activated by the meridians were identified with a statistical model that comprised two delayed boxcar waveforms for each scanning run. These represented the mean activity evoked by the two meridian localizers: the vertical and horizontal meridians. High-pass filtering removed low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis, used to generate parameter estimates for each regressor at every voxel.

The functional data from each subject is then overlaid on the flat map of their visual cortex created by segmentation and cortical flattening (see above). Mask volumes for subregions (left and right, dorsal and ventral) of each region of interest (V1, V2, and

V3) were obtained by delineating the borders between visual areas with activation patterns from the meridian localizers.

***Figure 2.5 – Delineation of borders of visual areas V1, V2 and V3***




*Meridians overlaid on a flat map with visual areas delineated red = horizontal, green = vertical meridian*

*V1, V2 and V3 overlaid on 3D visualisation of grey matter red = V1, green = V2, blue = V3*

These mask volumes could then be used to extract the regression parameter estimates generated by the analysis of the main experimental fRMI data from retinotopic visual cortex for each sub-region (left and right, dorsal and ventral) of the regions of interest (V1, V2, and V3) in each subject. The parameter estimates can then be analysed using t-tests to compare neural responses in each visual region of interest between conditions, across subjects.

## 2.4 Localisation of V5/MT

To identify V5/MT, I used a standard motion localizer, consisting of randomly moving low-contrast dots (moving at 4°/s) alternating with static dots for 16 periods of 20.8 s over a scanning run lasting 165 volumes (Dumoulin et al., 2000).

### *2.4.1 Imaging*

A 3T Siemens ALLEGRA system was used to acquire gradient-echo echo-planar T2*- weighted images with BOLD contrast. Each volume consisted of 32 2 mm axial

slices with in-plane resolution of 3 _ 3 mm, with a 1 mm gap between slices, positioned to cover the temporo-occipital cortex with a TR of 2.08 s. Imaging was performed in a scanning run of 165 volumes. Five image volumes preceding presentation of the experimental conditions were discarded to allow for T1 equilibration effects.

### *2.4.2 Statistical analysis*

Data were analyzed with SPM2. The initial five volumes were discarded, and subsequent image volumes were then realigned and co-registered to each subject's structural scan (Friston et al., 1995). Voxels activated during the localiser were identified with a statistical model that comprised a delayed boxcar waveform. This represented the mean activity evoked by the motion condition. High-pass filtering removed low- frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis, used to generate parameter estimates for each regressor at every voxel.

The peak voxels activated by the motion localizer (revealed by the contrast moving dots – static dots) in each hemisphere were identified for each subject. The regression parameter estimates generated by the analysis of the main experimental fMRI data at these voxels could then be extracted for each subject. The parameter estimates can then be analysed using t-tests to compare neural responses in V5/MT between conditions, across subjects.

# CHAPTER 3: ELECTROENCEPHALOGRAPHY METHODS

In 1929 Hans Berger, a German physician, discovered that patterns of electrical activity could be recorded from the surface of the scalp (Berger, 1929). He recorded a rhythmic pattern of electrical oscillation using a primitive galvanometer with a surface electrode placed on his son's scalp. This electrical activity at the scalp surface, known as the electro-encephalogram (EEG) is produced by electrical activity in neural cell assemblies.

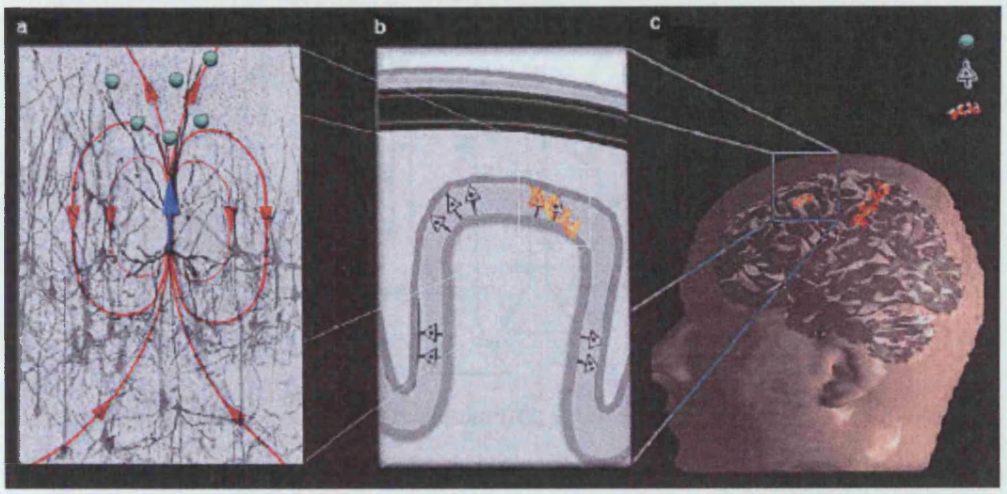
The main advantage of EEG over fMRI is its high temporal resolution, which is in the order of milliseconds. The main disadvantage of EEG compared with fMRI is its poor spatial resolution. It is not possible to specify the exact location of the neural generators that give rise to EEG without the use of other sources of information as constraints, because there is no unique solution to the 'inverse problem', (see Source Localisation below for details).

## 3.1 Electrophysiological basis of EEG

The electrical currents recorded at the scalp are thought to mainly reflect excitatory post-synaptic potentials (EPSPs) generated in the apical dendrites of pyramidal cells (Allison et al., 1986). Currents associated with EPSPs are thought to be the source of most of the signals detected by EEG, rather than action potentials, because they last much longer than action potentials (Nunez, 1981).

When pyramidal neurons receive synaptic input from another neuron, excitatory post-synaptic potentials (EPSPs) are generated in their apical dendrites. The post-synaptic membrane becomes transiently depolarised. This causes an intracellular current to flow from the non-excited parts of the neuron to the depolarised apical dendritic tree (Gloor, 1985). The current loop is closed by extracellular currents flowing in the opposite direction through the extracellular matrix. The intracellular currents are known as the primary currents, and the extracellular currents are known as secondary, return, or volume currents. Both primary and secondary currents contribute to electric scalp potentials.

***Figure 3.1 – Electrophysiological basis of EEG signal***




*a)Excitatory postsynaptic potentials (EPSPs) in the apical dendritic tree of a pyramidal cell causes an intracellular current to flow from the non-excited parts of the neuron to the apical dendritic tree within the dendritic trunk (primary current in blue. The current loop is closed by extracellular currents flowing through the extracellular matrix (secondary currents in red). b) Synchronous activation of large assemblies of cortical pyramidal nerve cells oriented parallel to one another and perpendicular to the local cortical surface are believed to be the main generators of recordable EEG signals. c) The EEG recorded at the scalp reflects activity from many such pyramidal cell assemblies in multiple brain regions.*

*(Illustration from (Baillet et al., 2001))*

The current from a single cell will be undetectable at the scalp surface, but a group of neurons can produce an externally observable electrical potential if 3 conditions are met (Kutas and Dale, 1997):

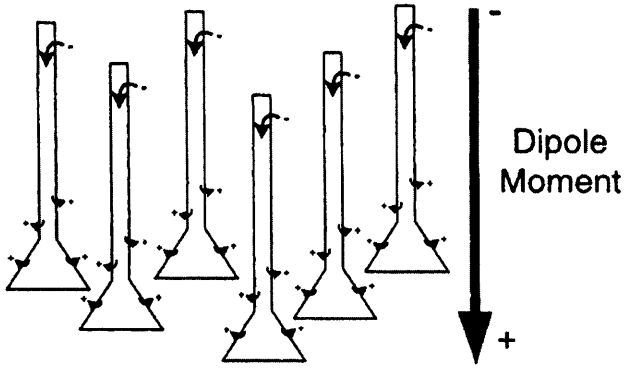
1) The average distribution of currents flowing in and out of the neurons within the neurons in the patch is not radially symmetrical

2) The neurons are aligned in some systematic fashion.

3) The neurons are activated in a synchronised fashion.

Meeting these three conditions ensures that the arrangement of the neurons is such that the currents from each neuron can be summed without cancelling each other out. Neural configurations that meet these 3 conditions give rise to 'open' electric fields which can be observed and recorded externally (Wood, 1987).

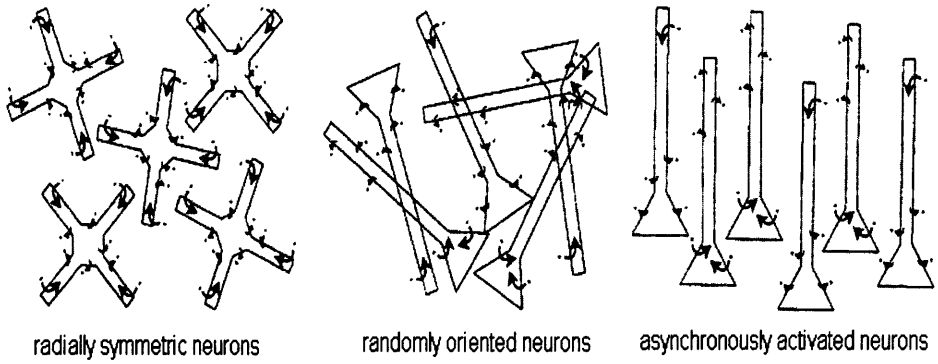
***Figure 3. 2 – Open field configuration***




*Neurons which are non-radially symmetric, spatially aligned and synchronously activated have dipoles that add up to produce externally observable electric potentials, e.g. neocortical pyramidal cells (adapted from (Kutas and Dale, 1997))*

When these three conditions are not met the configuration of the neurons is such that the electric potentials from the individual neurons cancel each other out. (See Figure 3.3 for example of such 'closed' field configurations). As electrical activity in closed fields sums to zero, such fields can not be measured at the surface and do not contribute to the scalp recorded EEG. Only open field configurations contribute to the EEG.

***Figure 3.3 – Closed-field configurations***




*Neurons which are radially symmetric, randomly oriented, or asynchronously activated do not produce externally observable electric potentials (adapted from (Kutas and Dale, 1997))*

Assemblies of pyramidal cells in the neocortex satisfy all the requirements for generating an 'open' field. The neocortical pyramidal cells are organised into large

assemblies of tens of thousands of neurons with their dendrites oriented parallel to one another and perpendicular to the local cortical surface. The potential produced by a single cortical pyramidal neuron is quite weak, but when these large assemblies of parallel pyramidal neurons are synchronously activated the net current flow can be detected even at a considerable distance. Such synchronous activation of these large pyramidal neuron assemblies is believed to be the main source of the EEG signals recorded at the scalp (Nunez and Silberstein, 2000). The scalp EEG reflects activity from many such pyramidal cell assemblies in multiple brain regions.

As well as depending on the properties and organisation of the neurons themselves, the amplitude of the electric field measured at the scalp is influenced by conductive properties of the intermediate tissues between the neurons and the scalp (e.g. neural tissue, blood, bone, skin). The tissues act as low-pass filters causing the field current to diminish with increasing distance from the neural source, and to be visible over broad areas of the scalp.

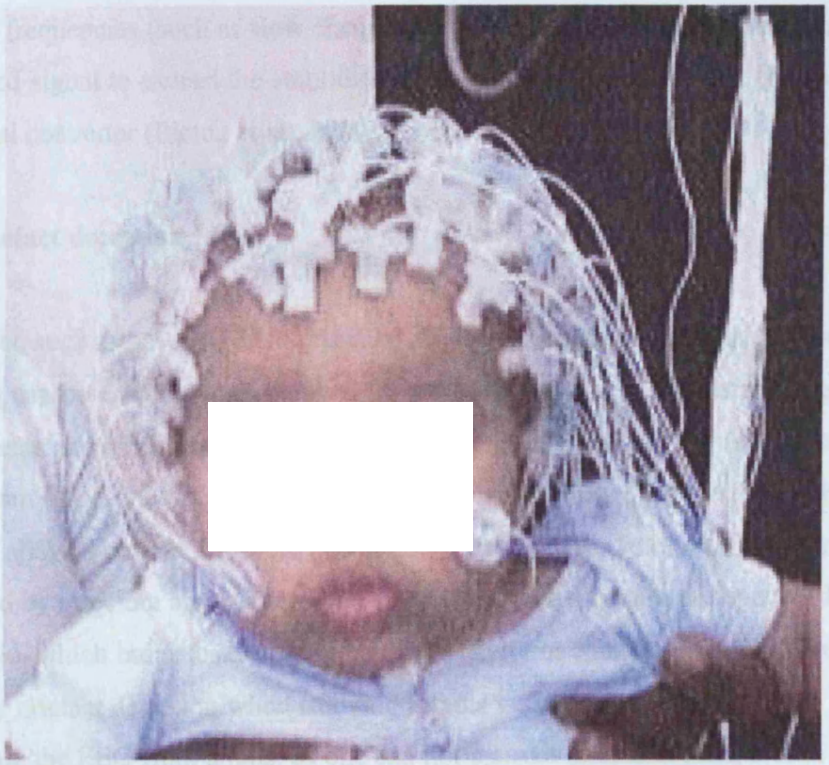
### 3.2 Measuring the EEG

The EEG consists of measurements of a set of electric potential differences between pairs of scalp electrodes. Electrodes are usually evenly distributed over the scalp and positioned in standard scalp locations to allow comparison across different EEG experiments. The sensors can either be directly glued to the skin at selected locations or fitted in an elasticated cap for rapid attachment with near uniform coverage of the scalp. For recording EEG from infants in the experiments described in this thesis (see Chapters 9 and 10) I used an elasticated Geodesic electrode cap, with 64 sponge electrodes, as rapid placement of the electrodes is necessary to minimise the risk of upsetting the infant (see Figure 3.4).

Typically the signal at each electrode is measured and recorded relative to a 'reference' electrode to which all other electrodes are connected. The resulting measurement is the difference in voltage between each individual electrode and the reference. The reference can be another electrode, placed so that it records background noise but not the electrical activity of experimental interest coming from the brain (Coles and Rugg, 1995). For example the reference electrode can be placed

on the mastoid bone. Alternatively, the reference can be a 'virtual reference'. The average of the signal from all the recording electrodes can be used as a reference (average reference derivations) or the weighted average of the electrodes around the site of interest can be used as the reference (source derivation). The recorded signals depend on the positions of the individual electrodes, and the nature and location of the reference site.

***Figure 3.4 –Infant wearing an elasticated electrode cap with 64 electrodes***



The EEG signal is initially recorded as a continuous analogue signal but is then amplified and converted to a digital signal, by sampling at discrete time intervals. The rate of conversion, i.e. the number of samples per second, determines the temporal resolution of the EEG.

### 3.3 Noise removal

As well as detecting field potentials from the brain, the electrodes also detect electrical activity from surrounding electrical equipment, such as the display monitor and the recording equipment. This background noise is generally greater than the

electrical activity at the scalp and thus must be removed from the EEG recording. This is achieved by using a ground and differential amplifiers which cancel out any activity common to all scalp electrodes.

In addition, the analogue signal is filtered during amplification in order to further remove background noise, which can derive from surrounding electrical activity. Frequencies that are unlikely to be related to brain activity are removed. High frequencies, attributable to muscle activity, that may cause aliasing are removed, as are low frequencies (such as slow changes in the baseline) that might cause the amplified signal to exceed the amplitude range of, and therefore block, the analogue-to-digital converter (Picton et al., 2000).

### 3.4 Artefact detection

Artefacts, such as baseline drift, muscular activity and eye movements, that survive filtering can be detected and removed from the EEG signal. Artefacts relating to eye-movements and blinks can be monitored and removed by recording the electro-oculogram (EOG), at the same time as the EEG, and rejecting any trials in which the EOG is above a certain threshold (Croft and Barry, 2000). Other artefacts can also be removed by rejecting any trials when the EEG exceeds a certain pre-specified threshold, which indicates excessive muscle activity or channel drift. The threshold used for artefact detection when studying infants is less stringent than when recording the EEG from adults, as one can not instruct infants to remain still, and it is hard to hold them completely still. Thus, if the threshold for detecting movement artefacts was as low as for adults, too many trials would be rejected. Thus data retained from infant EEG recordings is noisier than that retained from adult EEG data.

### 3.5 Event-Related Potentials

Event-related potentials (ERPs) are discrete epochs of the EEG wave form which are time-locked to a specific event. Since the evoked event-related potentials in response to a single stimulus at the scalp are quite small (5-10 microV) relative to the background activity (even after filtering and artefact detection), the ERPs epochs

must be extracted from background EEG and averaged together over trials to increase the signal to noise ratio (Kutas and Dale, 1997). Three assumptions underlie the use of averaging (Glaser and Ruchkin, 1976):

1) the signal and noise must linearly sum to produce the EEG
2) the background noise must be random and equal across all trials
3) the signal must remain constant over time and across repeated trials of the same type

If these conditions are met then averaging enhances the signal and reduces what is random noise to nearly zero, thus improving the signal to noise ratio by a factor proportional to the square root of the number of trials (Picton et al., 1995).

Not all noise can be removed by averaging. Any artefacts that are time-locked to the stimulus event will overlap and summate when averaged, rather than cancel out, and will contaminate the ERP. Artefacts that produce very large signals in a few trials are also a problem, as for averaging to successfully increase signal to noise ratio the background noise must be similar from trial to trial (Picton et al., 1995). This is why filtering and artefact detection are carried out prior to averaging. Prior to comparing conditions the ERPs are baseline corrected so that the waveform amplitude for each condition is quantified relative to a pre-stimulus baseline.

### 3.6 Interpretation of ERPs

ERPs provide information regarding the time course, frequency, strength, and scalp distribution of neural activity associated with that specific event. It is generally assumed that the activity represented by the ERP is associated with specific cognitive processing, and that differences in the ERP between conditions reflect differences in cognitive processing between conditions (Otten and Rugg, 2004). ERP waveforms can be analysed in terms of their magnitude or in terms of their topography. Thus differences in ERP between experimental conditions fall into two main categories: quantitative and qualitative differences. Qualitative differences between conditions are usually taken as evidence that different cognitive processes are engaged in the different conditions, whereas quantitative differences are taken as evidence of differential engagement of the same cognitive process between conditions.

Quantitative effects consist of differences in the magnitude of the ERP waveform (i.e. the amplitude measured with respect to the pre-stimulus baseline) between conditions (but not differences in the distribution of the ERP across the scalp). The amplitude of the ERP waveforms in different conditions are compared either at a specific time point and electrode site, or the mean amplitude of the waveform can be calculated across a number of time points and/or electrode sites and then compared across conditions using t-tests or ANOVAs. A difference in the amplitude of an ERP signal between two conditions is generally presumed to reflect a difference in the level of activity in the same underlying neural generators between the two conditions, due to differences in the number of activated cells or differences in the level of synchrony between neurons. But a difference in amplitude could also appear if the strength of the signal is the same across conditions but the proportion of trials in which the signal occurs differs between conditions. In this case the averaged ERP reflects the probability that a particular cognitive process is engaged in different conditions, rather than the degree of engagement. A third possibility is that in one condition there might be greater variability in the latency of the response from trial to trial, which would give rise to an average ERP with a lower amplitude and a longer duration.

Qualitative effects consist of differences in the distribution of ERP waveforms over the scalp. The distribution of ERPs can be represented by topographic maps, which plot the EEG amplitude at each recording site at each time point. Data between electrode sites is interpolated. These topographic maps can be used to highlight any differences in the scalp distribution of ERPs between conditions. Such differences are thought to reflect changes in the configuration of neural generators activated between conditions. In other words differences in scalp distribution imply that the patterns of neural activity generating the ERPs differ between conditions. The differences could simply reflect the involvement of a different combination of neural generators in the different conditions, or differences in the relative contributions of the same set of neural generators (Otten and Rugg, 2004).

The advantage of EEG over fMRI is its high temporal resolution. Information about the timing of a cognitive process can be inferred from the latency of the

corresponding ERP effect. The time at which ERP waveforms begin to differ between conditions can be used to infer the time by which the cognitive process that differentiates between the two conditions began. For example if the ERPs of two conditions start to differ 250ms after the stimulus onset, this means that the cognitive process distinguishing the two conditions began to differ by 250ms (Otten and Rugg, 2004). Differences in scalp distributions of ERPs over time imply that different underlying neural sources are engaged over time, or that the contributions of the same set of underlying neural generators changes over time, and therefore that different cognitive processes are engaged over time. Note that the onset of an effect does not necessarily indicate the actual time at which a cognitive process was engaged, as it is possible that neural activity differed before this time but that the EEG was not immediately sensitive to the effect (see below for possible reasons). The onset latency of an ERP effect merely represents an upper limit to the start of a cognitive process.

Significant differences in ERPs across conditions provide evidence of differences in cognitive processing between conditions, but strong conclusions cannot be drawn on the basis of a null result. A lack of difference in amplitude or scalp distribution between conditions does not mean there is no difference in cognitive processing between conditions for a number of reasons (Otten and Rugg, 2004). Firstly it is possible that the potential differences between conditions are too small to be detected at the scalp. The experiment may not have enough statistical power to bring out a small difference even when one exists. Secondly, the ERPs may not have been quantified or analysed in the best way. Lastly, only electrical activity from neurons with open field configurations can be measured at the scalp. Differences in cognitive processing that lead to changes in electrical activity in neurons with closed field configurations will never be detectable using EEG (Wood, 1987), but this does not mean that these differences do not exist.

### 3.7 Source localisation

The main disadvantage of EEG compared with fMRI is its poor spatial resolution. It is not possible to specify the exact location of the neural generators that give rise to EEG without the use of other constraining sources of information, because there is

no unique solution to the 'inverse problem' of determining the locations, orientations and time-courses of the neural sources underlying the EEG signals recorded at the scalp (Kutas and Dale, 1997). The problem is that there is an infinite number of possible neuronal source combinations within the brain that can give rise to any particular pattern of EEG signals (Nunez, 1981). For this problem to be solved additional constraints must be placed on the solution.

One approach for solving the inverse problem is to model the generators of the EEG signal as a number of "equivalent current dipoles", each representing activity in a particular brain area (Kutas and Dale, 1997). The precise anatomical locations, orientations, and strengths of the equivalent current dipoles can then be estimated iteratively using least-squares method to minimse the difference between the observed EEG recording and the predicted recording (Oostendorp and van Oosterom, 1989). The parameters of the equivalent current dipoles can be constrained on the basis of information from neurosphysiological studies, neuroimaging studies, and neurological studies. In practice this method cannot be used to localise more than a few dipoles (Kutas and Dale, 1997). An additional problem is that it is impossible to know exactly how many dipoles to include in the model *a priori.*

An alternative approach is to model the neural generators as a continuous dipole distribution (Kutas and Dale, 1997). On the basis that most of the recordable EEG signal is generated by cortical pyramidal cells, this approach limits the dipole distribution to the cortical grey matter and assumes that the dipoles are oriented perpendicularly to the cortical sheet. This reduces the inverse problem to estimating the dipole strength over the folded cortical surface. However, the number of dipole patches need to represent the cortical surface is far greater than the number of electrodes used, even at the highest levels of spatial sampling, so multiple solutions can still be generated for the same EEG data. This problem is often dealt with by choosing the 'weighted minimum-norm solution' (Dale and Sereno, 1993;Smith et al., 1990), but there is no guarantee that this approach will produce the correct solution. Therefore, additional constraints based on biological information must be incorporated into the model (Dale and Sereno, 1993). A potentially useful source of such constraints is functional magnetic resonance imaging, which provides information about brain activity with a high spatial resolution.

### 3.8 Habituation paradigms

In Chapters 9 and 10 of this thesis I have used a habituation paradigm to examine whether the same neural representations are accessed by phonetic stimuli presented in different modalities. Habituation paradigms are based on a phenomenon known as repetition suppression. Repetition of a stimulus leads to decreased activity within the neural networks representing that stimulus, in both auditory (Miller et al., 1991) and visual (Ulanovsky et al., 2003) cortices. Scalp potentials evoked by a stimulus and measured with EEG also show decreased amplitude with repetition (Woods and Elmasian, 1986). This response habituation with repetition is abolished by presentation of a new or deviant stimulus, due to activation of new set of neurons by the deviant stimulus. Thus trials where a stimulus is repeated elicit a smaller response compared to when the stimulus changes. By manipulating what stimulus changes elicit a difference in the brain response (the ERP), it is possible to infer what counts as a 'repetition' for a particular neural network and thus the nature of the representation computed by the network. For example, a network encoding a phonetic representation should habituate to repetition of a phoneme irrespective of the speaker, and should show renewed activity to a phonetic change only. In infants the neuronal response to auditory phonetic stimuli decreases with repetition, even when different speakers are used, and presentation of a new phoneme restores the amplitude of the ERP (Dehaene-Lambertz and Baillet, 1998;Dehaene-Lambertz and Dehaene, 1994;Dehaene-Lambertz and Pena, 2001;Woods and Elmasian, 1986). This demonstrates that infants have a neural network dedicated to phonetic processing, that normalises across acoustical differences in the stimuli. In Chapters 9 and 10, I use a similar habituation paradigm to examine whether infants have a neural network that represents phonetic information across modalities, i.e. a network that is activated by both visual articulations and auditory speech.

# CHAPTER 4: TWO DISTINCT NEURAL EFFECTS OF BLINKING ON HUMAN VISUAL PROCESSING

## 4.1 Introduction

It has been proposed that animals use an efference copy (von Holst, 1954) of their motor commands sent from the motor areas controlling the actions, in parallel with the motor signals, to predict the sensory consequences of their actions. On the basis of this efference copy, a prediction of the sensory consequences of the action is generated by an internal forward model (Wolpert and Miall, 1996). This sensory prediction is known as a corollary discharge (Sperry, 1950). As initially proposed in the context of eye movements (Helmholtz, 1867;Sperry, 1950;von Holst, 1954), the sensory prediction, or corollary discharge, generated by the forward model can be used to cancel self-produced sensory stimulation.

Such a mechanism appears to operate during blinking. Humans blink every few seconds, yet remarkably these pronounced interruptions to visual input are rarely noticed. In contrast external darkenings of the visual field that have a similar duration and magnitude as the interruption to visual input caused by a blink are immediately apparent (Volkmann et al., 1980). During blinks neither the eyelid sweeping across the pupil nor the transient changes in brightness that occur at the beginning or end of the blink are usually perceived. Moreover, visual experience remains constant across the significant gap in visual input that results from eyelid closure. In this chapter, I will investigate the neural basis of these phenomena.

Both voluntary and spontaneous blinks have highly stereotyped kinematics. Each blink lasts between 200-400ms with the pupil being fully occluded by the eyelid for 100-150ms (Riggs et al., 1981;Tsubota et al., 1996;VanderWerf et al., 2003;Volkmann et al., 1980), causing a reduction in retinal illumination of approximately 2 log units (Volkmann et al., 1980). In addition to this loss of visual input, visual sensitivity is actively reduced during voluntary and involuntary eye-blinks, an effect known as *blink suppression* (Manning et al., 1983;Riggs et al., 1981;Volkmann et al., 1980;Volkmann et al., 1982;Volkmann, 1986). Blink suppression mainly affects sensitivity to low spatial frequency visual stimuli (Ridder

and Tomlinson, 1993) and reaches a maximum 30–40 ms before the eyelid begins to cover the pupil (Manning et al., 1983;Volkmann, 1986). It has been proposed that blink suppression may represent a neural mechanism associated with the blink motor command that has evolved to minimise the percept of the eyelid occluding the pupil (a low spatial frequency stimulus) and the transient changes in illumination that occur during the blink (Volkmann, 1986). The existence of blink suppression therefore implies an underlying neural mechanism by which blinks influence processing of visual stimulation. The behavioural phenomenon of blink suppression may be mediated by suppression of the neural response to visual stimulation. Thus any brain area whose activity reflects blink suppression should show a reduced response to visual stimulation when the subject is blinking, compared with the normal response to visual stimulation in the absence of blinks. Moreover, such response suppression to visual stimulation during blinks should be greater than the reduction in activity caused by the loss of visual input that results from eyelid closure. However the existence and neural manifestations of any mechanism mediating blink suppression associated with human blinking remain largely uninvestigated. Previous studies of blinking in humans have primarily investigated oculomotor control of blinking (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Schmidt et al., 2003;Tsubota et al., 1999).

Though blink suppression may account for the ability of eyelid closure to pass unnoticed it cannot account for the continuity of visual perception across the prolonged interruption to visual input caused by eyelid closure. Such phenomenal continuity across blinks suggests the existence of a short-term mnemonic signal associated with the blink motor command that maintains the previous percept across the loss of visual input caused by the blink, thus ensuring an uninterrupted visual experience. In contrast to the predicted effects of blink suppression, any brain area whose activity reflects a mnemonic signal involved in the maintenance of *continuity* across blinks should show the opposite pattern of responses. Specifically, activity evoked in such regions by blinking, should be greater when visual stimulation is present, compared with blinking in the absence of visual stimulation, as a greater neural effort may be required to maintain continuity across the interruption caused by a blink when the background level of visual stimulation is high. Such a response profile has been observed in the posterior parietal cortex adjacent to the parieto-

occipital sulcus using MEG (Hari et al., 1994). Blinking evoked magnetic signals in this region in the presence of a visual stimulus, but not in darkness.

Here, I sought to investigate the neural underpinnings of these two complementary behavioural effects of blink suppression and visual continuity in humans. Using functional MRI (fMRI), I investigated how the presence (versus absence) of voluntary blinking affects the cortical responses to the presence (versus absence) of visual stimulation. By manipulating these two factors independently, and examining the interactions between them, I investigated whether any brain areas showed the response profiles predicted from the consideration of blink continuity and blink suppression outlined above. One problem in interpreting cortical responses to visual stimulation during blinking is that any changes in brain activity evoked by an extra-retinal signal associated with the blink motor command are potentially confounded by the reduction in retinal illumination resulting from pupillary occlusion. In order to circumvent this problem, I created a control condition in which I dynamically generated external darkenings of the visual scene. These precisely matched the timing and duration of the interruptions to visual stimulation caused by each subject's own voluntary blinks, which were recorded online. Each individual blink was matched by its own individual darkening. As changes in visual input were matched in the two conditions, any differences between the two conditions must reflect the presence of an extra-retinal signal associated with blinking and thus can be used to interpret the predicted interactions between blinking and visual stimulation outlined above. Specifically, areas mediating blink suppression should show a reduction in activity during blinks greater than any reduction in activity caused simply by the reduction in visual input as modelled by the darkening condition. In contrast areas mediating visual continuity should show greater activation during blinking than external darkenings, as during an external darkening there is no motor command, so an extra-retinal mnemonic signal associated with the blink motor command can not be produced.

## 4.2 Materials and Methods

### 4.2.1 Subjects

Fourteen normal volunteers (8 male and 6 female, aged 18 – 37, mean 25, SD 4.9) gave written informed consent to participate in the study, which was approved by the Institute of Neurology and National Hospital for Neurology and Neurosurgery Joint Ethics Committee.

### 4.2.2 Paradigm

Visual stimuli were presented on a small screen viewed by a mirror mounted on the head coil. During scanning, participants were asked to fixate on a small central grey cross that was presented on a black background. A blocked design was used with two factors manipulated independently: i) the presence (or absence) of *voluntary blinking*, and ii) the presence (or absence) of *visual stimulation*. The use of voluntary blinks allowed us to use a blocked design, which provides much greater power and sensitivity for this study than would an event-related design using spontaneous blinks. Moreover, blink suppression in humans has primarily been examined during voluntary blinks (Volkmann et al., 1980;Volkmann, 1986), and the psychophysical characteristics of blink suppression are virtually identical for all types of blink. Indeed, the same neural mechanism is believed to operate during both spontaneous and voluntary blinks (Manning et al., 1983;Volkmann, 1986). Prior to the start of each block, a visual cue indicated whether the impending block would require the subjects to blink, or merely maintain fixation. During 'blink' blocks, participants were required to blink binocularly at a fast regular rate. During 'steady fixation' blocks, subjects were simply required to maintain fixation, and were allowed to blink but asked to keep blinking to a minimum. Subjects were specifically instructed not to forcefully keep their eyes open, so that they did not inhibit spontaneous blinking. Independently of this factor, during some blocks a strong visual stimulus was presented. This consisted of a high-contrast black (1 cd/m$^2$) and grey (100 cd/m$^2$) checkerboard subtending 10 degrees of visual angle contrast-reversing at 7.5 Hz on a black background. Though the relative phase of the cycle at the onset of each blink or darkening may affect the response of individual neurons this will not affect my

results as the BOLD signal is a population response measure. The central 2.5 degrees of the checkerboard were blacked-out. All blocks lasted for 26 seconds. During the remaining blocks a small grey (100 cd/m$^2$) fixation cross on a black background was presented. Throughout the experiment, background illumination in the scanner bore was 0.14 cd/m$^2$.

During scanning, pupil diameter and eyelid position were monitored continually, using an ASL Eye-Tracking System (Applied Science Laboratories, Bedford) with remote optics (Model 504, sampling rate = 60 Hz, spatial error < 1° ) that was custom-adapted for use in the scanner. An on-line algorithm was used to identify the onset and offset of each blink during the 'voluntary blink' blocks. This information was used, on-line, dynamically to create a fifth 'external darkening' condition consisting of darkenings yoked to the subject's own blinks in the previous blinking block. In this condition, subjects were cued to maintain steady fixation and the same high-contrast reversing checkerboard as described above was presented. However, during a block, the checkerboard disappeared and reappeared, resulting in a darkening, with a time course that was determined by the blink onsets and offsets recorded from the immediately preceding 'voluntary blink during visual stimulation' block. Thus each individual blink was modelled by its own individual darkening. Eyelid closure causes a reduction in the luminance of visual stimulation reaching the retina of 1.8 - 2 log units (Volkmann et al., 1980) so the luminance levels of the checkerboard and the black screen were calibrated to mimic this reduction during the darkenings. This 'external darkening' condition thus attempted to match the pattern of retinal stimulation during the previous 'blinking with visual stimulation' block, but in the absence of voluntary blinks. The experiment thus consisted of five conditions constituting a 2 x 2 factorial design plus a 5$^{th}$ control condition. Note that it is not possible to create a fully factorial design with external darkenings as a flickering checkerboard stimulus must be present for external darkenings to have a physical correlate.

| | Visual stimulation | |
|---|---|---|
| | Present | Absent |
| Voluntary Blinking | **BV** | **BN** |
| No Voluntary Blinking | **FV** | **FN** |
| External Darkenings | **DV** | |

BV = Voluntary blinking during visual stimulation

FV = Fixation with no voluntary blinking during visual stimulation

BN = Voluntary blinking without visual stimulation

FN = Fixation with no voluntary blinking and no visual stimulation

DV = External darkenings during visual stimulation (control condition)

Conditions BV, FV, DV and BN were presented twice per scanning run; with condition FN presented four times, to allow subjects to rest their eyes. The order of conditions was randomly generated at the start of each session, with the restriction that each "darkening" block had to be preceded by a "blinking during checkerboard stimulation" block.

Retinotopic mapping was not conducted in this exploratory study because my intention was to carry out a random-effects analysis of the interaction between blinking and visual stimulation and of the differences between external darkenings and blinking over the whole cortex. Indeed, the planned statistical comparisons examining the interaction between blinking and visual stimulation (see Introduction and Results) did not reveal any significant activation in the medial occipital cortex, for example along the calcarine sulcus, where most retinotopic areas are located.

### 4.2.3 Functional imaging

A 3T Siemens ALLEGRA system (Siemens, Erlangen) was used to acquire gradient-echo echo-planar T2* weighted images with Blood Oxygenation Level Dependent (BOLD) contrast. (See Chapter 2: fRMI Methods for details of BOLD signal detection). Each volume consisted of forty 2 mm axial slices with in-plane resolution of 3x3 mm, with a 1mm gap between slices, positioned to cover the whole cortex

with a TR of 2.6 seconds. Imaging was performed in three scanning runs of 150 volumes each. In each scanning run, six image volumes preceding presentation of the experimental conditions were discarded to allow for magnetic saturation effects. Finally, a T1-weighted anatomical image was acquired from each subject.

### 4.2.4 Statistical Analysis

Data were analysed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm). The initial six volumes were discarded, and subsequent image volumes then realigned (Friston et al., 1995), spatially normalised (Ashburner and Friston, 1999) to the standard space defined by the Montreal Neurological Institute template (Mazziotta et al., 1995) and smoothed with a Gaussian kernel of 6 mm full-width half maximum. (see Chapter 2: fMRI Methods for details of realignment, normalisation and smoothing). Voxels activated during the experiment were identified using a statistical model that comprised five delayed boxcar waveforms for each scanning run. These represented the mean activity evoked in the five experimental conditions. High-pass filtering (cut-off 128 s) removed low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. (See Chapter 2: fMRI Methods for details of statistical analysis). The resulting parameter estimates for each regressor at each voxel were then entered into a second level analysis where subject served as a random effect in a within-subjects ANOVA. The main effects and interactions between conditions were then specified by appropriately weighted linear contrasts and determined using the t-statistic on a voxel-by-voxel basis. A statistical threshold of $p<0.05$, corrected for multiple comparisons across the entire cortex, was used except for regions that were hypothesized a priori, where a threshold of $p<0.001$, uncorrected for multiple comparisons was used. Regions where I had a prior hypothesis of finding blink-related signal modification included the occipital lobe up to the parieto-occipital sulcus, as the occipital lobe is involved in visual processing, and thus if blinking affects visual processing I would expect to see changes in activity in this region. I also expected to find activation in oculomotor regions, including the frontal eye-fields (FEF) and supplementary eye-fields (SEF), as these regions are known to be involved in blink motor control and have been activated by

blinking in previous fMRI studies (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a).

## 4.3 Results

### 4.3.1 Behavioural data

Subjects blinked at a significantly greater rate during voluntary-blinking blocks compared with blocks with no voluntary-blinking (137.0 / minute versus 8.0 / minute; $t(13) = 8.48$, $P<0.001$). Thus, subjects were able to comply with my behavioural instructions. There was no significant difference in blinking rate for the voluntary blinking or no voluntary blinking conditions between visual stimulation blocks compared with no visual stimulation blocks (comparing blinking with and without visual stimulation, $p = 0.10$; comparing no blinking with and without visual stimulation, $p = 0.81$).

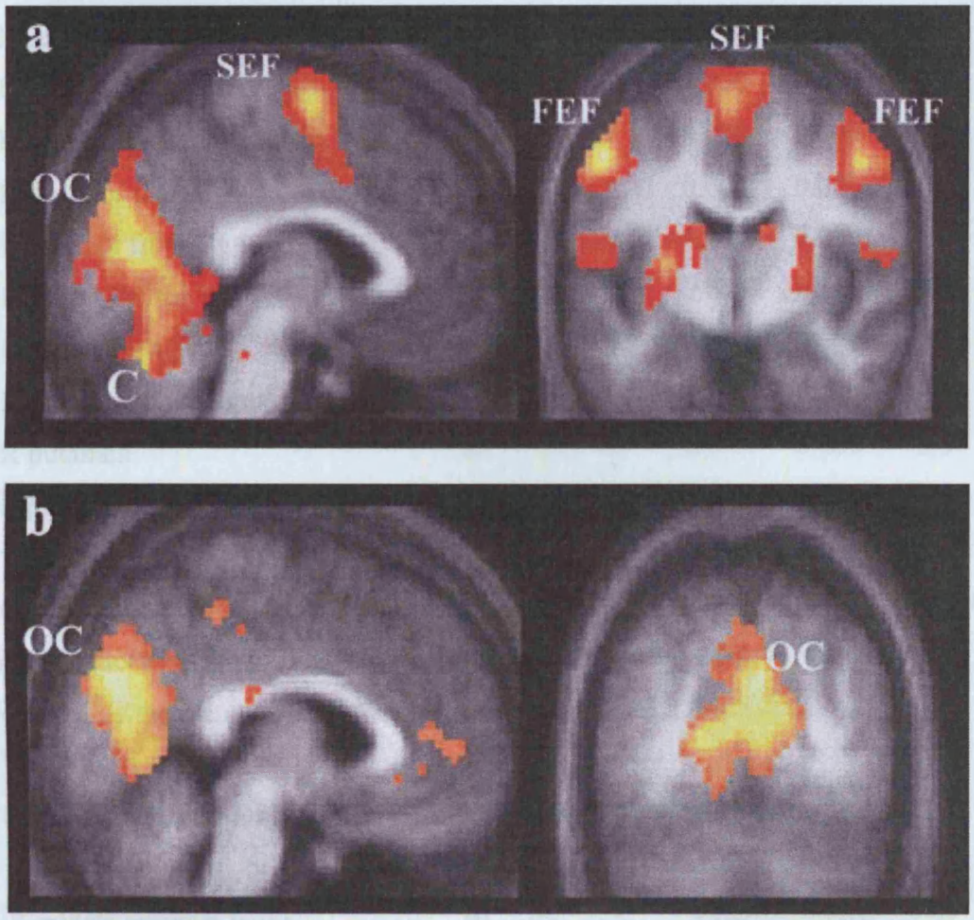
### 4.3.2 Main effect of voluntary blinking

Comparison of the two conditions during which subjects blinked voluntarily, versus the two conditions where subjects did not, identified those loci where activity was significantly greater during voluntary blinking compared with fixation, (i.e. the comparison {BV+BN}-{FV+FN}, see Methods-Paradigm above). By revealing which brain structures are activated by voluntary blinking per se, this comparison provides an important replication of previous studies that have investigated the oculomotor control of blinking, as well as providing new information about any responses in visual cortex to voluntary blinks.

This comparison revealed activation of the pre-central gyrus, superior pre-central sulcus (corresponding to the frontal eye fields, FEF), and the superior frontal gyrus (corresponding to the supplementary eye fields, SEF) and parts of the cerebellum (see Table 4.1 for full listing of loci). These activated loci are consistent with those previously described for the motor control of blinks (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Paus, 1996). In addition the cingulate gyrus adjacent to the SEF, the precentral sulcus, the lateral fissure, posterior lateral orbital gyrus, putamen, and inferior frontal gyrus were also activated. More posteriorly, widespread activation of occipital and parieto-occipital cortex was identified (displayed in Figure 4.1). This included superior occipital

gyrus, the precuneus and cuneus, the anterior calcarine sulcus (i.e. V1) and the parieto-occipital fissure. Thus, the presence of voluntary blinks leads to activation of an oculomotor network previously associated with the control of eye movements and blinks (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Paus, 1996), together with large areas of occipital cortex.

***Figure 4.1 - Effects of voluntary blinking and external darkening conditions***




***(a)*** *Activity revealed by the contrast between conditions where voluntary blinking occurred with those where it did not, irrespective of the presence of checkerboard stimulation (i.e. (BV+BN)-(FV+FN) see Methods) thresholded at $p < 0.001$ (uncorrected), overlaid on a sagittal and a coronal slice of the mean structural image obtained from all the subjects. The color scale reflects the t-value at each voxel. Blinking activates large parts of the occipital cortex (OC), the frontal eye-fields (FEF), the supplementary eye-fields (SEF), and the cerebellum (C).* ***(b)*** *Areas of activity revealed by the contrast external darkenings during checkerboard stimulation versus checkerboard stimulation with steady fixation (i.e. (DV-FV)). Darkenings activate large parts of the occipital cortex, as does voluntary blinking.*

**Table 4.1 - Voluntary Blinking > fixation {BV+BN} - {FV+FN}**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| R cerebellum | 9 | -66 | -21 | 0.000 | 0.000 | 7.7 |
| L cerebellum | -9 | -69 | -21 | 0.000 | 0.000 | 7.61 |
| L parieto-occipital fissure | 3 | -75 | 18 | 0.000 | 0.000 | inf |
| L parieto-occipital fissure | -6 | -75 | 9 | 0.000 | 0.000 | inf |
| R occipital cortex | 21 | -69 | 12 | 0.000 | 0.000 | 7.12 |
| L occipital cortex | -21 | -63 | 0 | 0.000 | 0.000 | 7.53 |
| R superior precentral sulcus (FEF) | 51 | -6 | 42 | 0.000 | 0.000 | 7.1 |
| L superior precentral sulcus (FEF) | -51 | -9 | 45 | 0.000 | 0.000 | inf |
| R superior frontal gyrus (SEF) | 6 | -9 | 72 | 0.000 | 0.000 | 5.18 |
| L superior frontal gyrus (SEF) | -3 | -6 | 63 | 0.000 | 0.000 | 7.32 |
| R precentral sulcus | 63 | 3 | 15 | 0.000 | 0.000 | 5.12 |
| L precentral sulcus | -60 | 0 | 18 | 0.000 | 0.000 | 6.62 |
| R inferior frontal gyrus | 66 | -30 | 9 | 0.000 | 0.000 | 4.94 |
| R putamen | 24 | 3 | 6 | 0.000 | 0.000 | 5.3 |
| L putamen | -27 | -9 | 6 | 0.000 | 0.000 | 6.23 |

In addition, the presence (versus absence) of voluntary blinks led to the deactivation of some areas in the more lateral and posterior parts of the occipital cortex, as revealed by the comparison {FV+FN} – {BV+BN} (see Table 4.2).

**Table 4.2 - Fixation > voluntary blinking {FV+FN} - {BV+BN}**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| R middle occipital gyrus | 30 | -93 | -3 | 1.000 | 0.001 | 3.07 |
| L middle occipital gyrus | -33 | -87 | -15 | 1.000 | 0.002 | 3.54 |
| L V5/middle temporal gyrus | -45 | -72 | -9 | 1.000 | 0.000 | 3.29 |
| R postcentral gyrus | 48 | -27 | 45 | 1.000 | 0.000 | 3.37 |
| L postcentral gyrus | -42 | -33 | 63 | 1.000 | 0.000 | 3.54 |

### 4.3.3 Interactions between voluntary blinking and visual stimulation

I hypothesised that any brain areas associated with the complementary behavioural effects of blink suppression and visual continuity across blinks would be associated with specific patterns of responses that reflected an *interaction* between blinking and visual stimulation with a checkerboard (see Introduction). In other words, I wished to examine how the neural correlates of visual stimulation are modulated by blinking, regardless of the effects of blinking and visual stimulation per se.

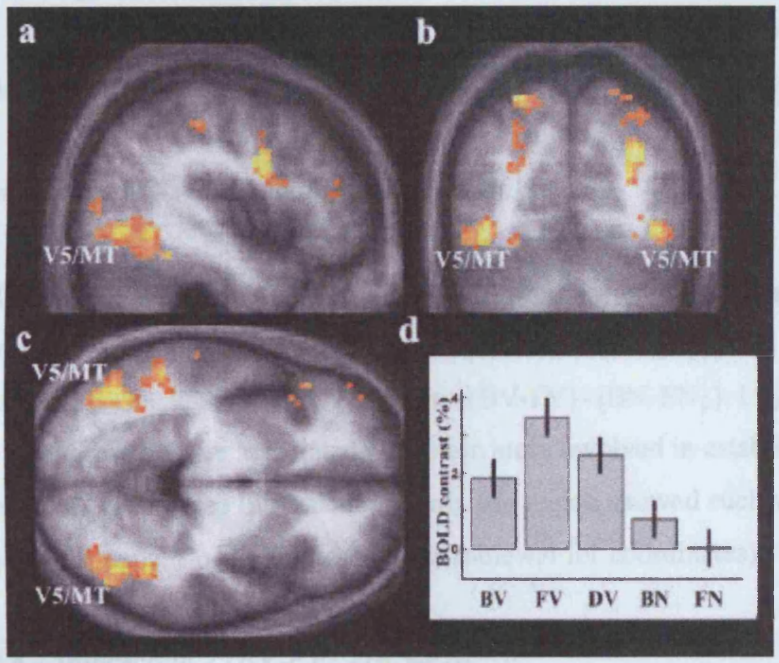
#### *4.3.3.1 Interaction 1 – blink suppression*

First, I identified brain areas that showed a smaller response to the presence, versus absence, of visual stimulation with a checkerboard during the presence, versus absence, of voluntary blinking (i.e. conditions {FV-FN}-{BV-BN}). I hypothesised that such a pattern would be associated with brain areas involved in blink suppression, as this represents a reduced response, i.e. a loss of sensitivity, to visual stimulation during blinking. Cortical areas that showed such an effect were located mainly in the lateral parts of temporo-occipital cortex, including the inferior, middle and superior occipital gyri, the fusiform gyrus, the inferior and middle temporal gyri (see Figure 4.2), the lateral and anterior occipital sulci, the transverse/intra occipital sulcus, and the collateral sulcus, (see Table 4.3 for full listing of loci). Specifically, the activated cortical loci included locations consistent with V5/MT bilaterally (e.g. x,y,z = 45, -69, -9 and x,y,z = -54, -48, -9) (Watson et al., 1993). In addition, a similar pattern of activation was also revealed in parietal cortex, including the superior parietal gyrus, postcentral gyrus, and intraparietal sulcus, and in the superior temporal sulcus.

Figure 4.2 displays a representative selection of these cortical activated foci, including V5/MT, overlaid on an anatomical image. Note the strongly lateralised position of the activated loci, and the failure to demonstrate any activation in more medial structures associated with retinotopic visual areas, V1,V2, and V3 (Hasnain et al., 1998). Activity from a representative cortical locus (right V5/MT, x,y,z = 45, -69, -9) is plotted for each of the five conditions (see Figure 4.2d) and clearly shows the interaction effect predicted. The difference between visual stimulation and no visual

stimulation in the absence of blinking (compare condition FV to FN), is larger than the difference between visual stimulation and no visual stimulation during blinking (compare condition BV to BN). In other words the effect of visual stimulation is reduced in the presence of blinking. Activity is also reduced during the control external darkening condition (DV) compared with uninterrupted visual stimulation (FV) but to a lesser extent that during the blinking condition (BV) (see Discussion).

***Figure 4.2 - Interaction 1: Regions showing reduced activation to the presence (v. absence) of visual stimulation during the presence (v. absence) of voluntary blinking***




***(a-c)*** *Areas of activity revealed by the contrast (FV-FN) – (BV-BN), thresholded at p<0.001 (uncorrected), overlaid on sagittal, coronal and axial slices of the mean structural image obtained from all subjects. The color scale represents the t-value at each voxel. These regions show a greater effect of the presence versus absence of visual stimulation, during steady fixation compared with voluntary blinking. The areas showing this interaction include more lateral parts of the occipital cortex, including V5/MT (Watson et al., 1993), and also parts of the parietal cortex.* ***(d)*** *Activity (percent BOLD contrast relative to fixation in the absence of visual stimulation. i.e. condition FN), at a representative voxel at the 3-dimensional location of V5/MT (Watson et al., 1993) (x,y,z = 45, -69, -9) under each condition. BV = blinking during visual stimulation. FV = fixation during visual stimulation. DV = external darkenings during visual stimulation. BN = blinking without visual stimulation. FN = fixation without visual stimulation.*

**Table 4.3 – Interaction 1 *{FV-FN} - {BV-BN}***

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| R middle/superior occipital gyrus(V3a) | 30 | -72 | 18 | 0.001 | 0.000 | 5.58 |
| L middle/superior occipital gyrus(V3a) | -30 | -87 | 12 | 0.001 | 0.000 | 4.87 |
| R middle temporal gyrus (V5) | 48 | -60 | -15 | 0.002 | 0.000 | 4.59 |
| L middle temporal gyrus (V5) | -54 | -48 | -9 | 0.005 | 0.000 | 4.23 |
| R post central gyrus/IPS | 42 | -27 | 42 | 0.006 | 0.000 | 4.16 |
| L post central gyrus/IPS | -42 | -39 | 36 | 0.014 | 0.000 | 3.73 |
| R IPS | 33 | -72 | 30 | 0.001 | 0.000 | 5.16 |
| L superior parietal gyrus/IPS | -27 | -69 | 57 | 0.001 | 0.000 | 4.85 |

#### *4.3.3.2 Interaction 2 – visual continuity across blinks*

Second, I identified areas where the response to the presence, versus absence, of voluntary blinks was greater during the presence, versus absence, of visual stimulation with a checkerboard (i.e. conditions {BV-FV}-{BN-FN}). I hypothesised that such a pattern would be associated with brain areas involved in establishing continuity across blinks (see Introduction). Only one region showed such an effect, located along the parieto-occipital fissure (see Table 4.4 for coordinates).

**Table 4.4 – Interaction 2 *{BV-FV} - {BN-FN}***

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| R parietal-occipital fissure | 6 | -75 | 24 | 0.064 | 0.000 | 4.58 |
| R parietal-occipital fissure | -6 | -75 | 9 | 0.098 | 0.000 | 3.86 |

Figure 4.3 illustrates the medial location of this activated area ('PO') and plots the response profile from a representative voxel within this region (x,y,z = 3, -75, 18). Note that this area is not activated by visual stimulation with a checkerboard per se (compare FV and FN i.e. presence versus absence of visual stimulation without any voluntary blinking in either condition), though it is activated when the visual stimulus is interrupted by blinking or darkenings. Similarly, comparison of all conditions where visual stimulation with a checkerboard occurred (BV + FV) with

all conditions where no such stimulation was present (BN + FN) failed to demonstrate significant activation of this region even at a greatly reduced threshold ($P<0.01$, uncorrected).

### 4.3.4 Control condition (external darkenings)

The external darkening condition (DV) consisted of dynamically generated external darkenings of the visual scene during visual stimulation with a checkerboard, in the absence of voluntary blinking (see Methods for details). Darkenings were modelled on each subject's own blinks in the preceding BV block, where voluntary blinking occurred in the presence of checkerboard stimulation. Thus retinal input is matched on a per-participant and per-blink basis between this condition (DV) and condition BV. Comparison of these two conditions will therefore reveal any changes in activity specifically associated with an extra-retinal signal associated with blinking, and can be used to interpret the results of the two interactions between visual stimulation and blinking described above.

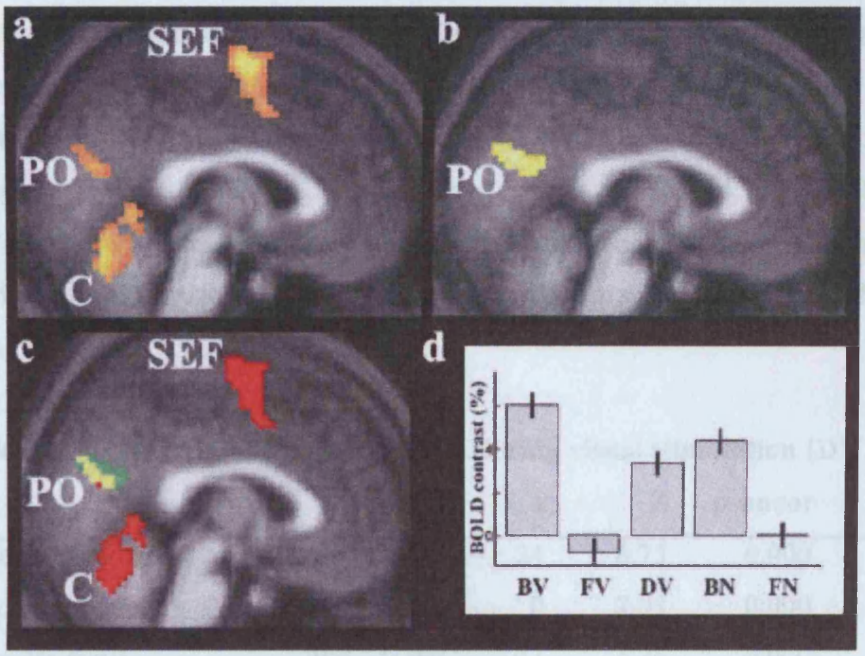
**Table 4.5 – Blinking during visual stimulation > external darkenings *{BV-DV}***

| | x | y | z | p-FDR | p-uncor | Z |
|---|---|---|---|---|---|---|
| R cerebellum | 9 | -66 | -21 | 0.000 | 0.000 | 6.47 |
| L cerebellum | -9 | -66 | -21 | 0.000 | 0.000 | 6.24 |
| R precentral sulcus | 63 | 3 | 12 | 0.001 | 0.000 | 4.39 |
| L precentral sulcus | -60 | 3 | 9 | 0.000 | 0.000 | 6.34 |
| R superior precentral sulcus(FEF) | 45 | -12 | 39 | 0.000 | 0.000 | 5.62 |
| L superior precentral sulcus(FEF) | -48 | -15 | 42 | 0.000 | 0.000 | 6.26 |
| cingulate gyrus/superior frontal gyrus(SEF) | 0 | -6 | 63 | 0.000 | 0.000 | 6.26 |
| L Superior frontal gyrus (SEF) | -6 | 0 | 45 | 0.000 | 0.000 | 5.25 |
| R parietal-occipital fissure | 3 | -75 | 18 | 0.001 | 0.000 | 4.29 |
| L parietal-occipital fissure | -3 | -75 | 12 | 0.001 | 0.000 | 4.48 |
| R lateral fissure | 45 | 6 | 0 | 0.001 | 0.000 | 4.18 |
| R putamen | 24 | 3 | 3 | 0.001 | 0.000 | 4.15 |
| L putamen | -27 | -9 | 6 | 0.001 | 0.000 | 4.95 |

Comparison of voluntary blinking during visual stimulation and matched external darkenings, (i.e. the comparison BV – DV), revealed activation in oculomotor areas, including the FEF, SEF and cerebellum. (See Table 4.5). This is consistent with the presence of oculomotor signals that are produced during voluntary blinking but not during external darkenings. More importantly, this comparison also revealed a restricted region of the occipital cortex along the parieto-occipital fissure that shows greater activity during blinking in the presence of visual stimulation than during the external darkening condition. This parieto-occipital area precisely overlapped with the parieto-occipital area described above that showed an interaction between visual stimulation and blinking consistent with visual continuity. (See Figure 4.3). This is readily apparent in Figure 4.3d, where the condition-specific plot of activity for this parieto-occipital area shows that activity for voluntary blinking during visual stimulation (BV) is significantly greater than that for the control external darkening condition (DV). Note that this region also shows greater activity for voluntary blinking in the absence of visual stimulation (BN) than during the external darkening condition where visual stimulation was present (DV).

Areas showing significantly less activity during voluntary blinking than during matched external darkenings were identified, (by the comparison DV – BV), in lateral and posterior occipital regions and parts of parietal cortex. These areas showed substantial overlap with areas described above that showed an interaction between visual stimulation and blinking consistent with blink suppression. This is apparent in Figure 4.2d, where the condition-specific plot of activity for area V5/MT shows that activity for voluntary blinking during checkerboard stimulation (BV) is significantly lower than that for the control external darkening condition (DV).

***Figure 4.3 - Interaction 2 - Parieto-occipital region hypothesized to be involved in maintaining visual continuity across voluntary blinks***




***(a)** Activity revealed by the contrast of voluntary blinking during visual stimulation versus external darkenings (i.e. (BV-DV)), thresholded at p<0.001 (uncorrected), overlaid on a sagittal section of the T1-weighted mean structural image of all subjects. The colour scale represents the t-value at each voxel. The SEF, FEF (not shown), the cerebellum (C), and a region along the parieto-occipital fissure (PO) all showed greater activity when blinking during visual stimulation than during the external darkenings condition (see Table 4.2). **(b)** Areas showing greater activation to the presence (versus absence) of voluntary blinking during the presence (versus absence) of visual stimulation, (i.e. the contrast {BV-FV} – {BN-FN}). Only one region along the parieto-occipital fissure (PO) showed a significant interaction effect **(c)** The previous two contrasts (shown in (a) and (b) overlaid on the same sagittal section of the mean T1-weighted structural. Red areas are those activated by the comparison of voluntary blinking versus darkenings (see (a)). Green areas are those whose activity showed an interaction between voluntary blinking and visual stimulation (see (b)). Yellow areas represent the region of overlap between areas revealed by these two contrasts. This shows that the same parieto-occipital region was revealed in each contrast. **(d)** Activity (percent BOLD contrast relative to fixation in the absence of checkerboard stimulation. i.e. condition FN) at a single representative voxel (x,y,z = 3, -75, 18) in the region along the parieto-occipital fissure under each condition.. BV = checkerboard stimulation, blinking. BV = blinking during visual stimulation. FV = fixation during visual stimulation. DV = external darkenings during visual stimulation. BN = blinking without visual stimulation. FN = fixation without visual stimulation.*

I also compared the external darkening condition to visual stimulation in the absence of voluntary blinks or darkenings, (i.e. comparison of conditions DV and FV). This contrast revealed brain areas that responded to the reduction in visual input and the transient changes in luminance that were associated with darkenings. This comparison revealed activation of medial occipital cortex, in a location that closely overlapped the region activated by the presence (versus absence) of voluntary blinks (see Figure 4.1 and Table 4.6), together with deactivation of areas in more lateral and posterior parts of the occipital cortex, during external darkenings. (See Table 4.7 for details).

**Table 4.6 - External darkenings > fixation during visual stimulation {DV – FV}**

| | x | y | z | Z | p-uncor | p-FDR |
|---|---|---|---|---|---|---|
| R occipital cortex | 6 | -75 | 24 | 6.75 | 0.000 | 0.000 |
| L occipital cortex | -21 | -63 | 0 | 7.03 | 0.000 | 0.000 |
| R angular gyrus | 48 | -48 | 33 | 4.36 | 0.000 | 0.000 |
| L angular gyrus | -51 | -60 | 33 | 3.44 | 0.000 | 0.010 |

**Table 4.7 – Fixation during visual stimulation > external darkenings *{FV - DV}***

| | x | y | z | Z | p-uncor | p-FDR |
|---|---|---|---|---|---|---|
| L middle temporal gyrus | -39 | -48 | -6 | 3.68 | 0.000 | 0.981 |
| L middle occipital gyrus | -45 | -81 | -9 | 3.11 | 0.001 | 0.981 |
| R inferior temporal gyrus | 48 | -57 | -15 | 3.29 | 0.001 | 0.981 |
| R intra parietal sulcus | 33 | -72 | 30 | 3.67 | 0.000 | 0.981 |
| L superior parietal gyrus | -18 | -69 | 51 | 3.67 | 0.000 | 0.981 |
| R post central gyrus | 45 | -27 | 42 | 4.12 | 0.000 | 0.981 |
| L post central sulcus | -63 | -27 | 30 | 3.46 | 0.000 | 0.981 |

## 4.4 Discussion

This study sought to characterise the effects of voluntary blinks on processing in the human visual system by manipulating visual stimulation and blinking independently. I hypothesised that the brain areas mediating the behavioural effects of blink suppression and visual continuity would show different response patterns. In order to distinguish the effects of extra-retinal neural signals associated with blinking from the effects of pupillary occlusion on visual input I compared the effects of blinking during visual stimulation to externally generated darkenings of the visual scene that closely mimicked the immediately preceding blinks produced by each subject.

Consistent with my hypothesis, I identified two distinct sets of regions showing opposite response patterns. I found an extensive set of lateral occipital areas that showed a smaller response to visual stimulation during the presence of voluntary blinks, consistent with a role in blink suppression. In addition, I identified a region of medial parieto-occipital cortex where activity evoked by blinking was greater when visual stimulation with a checkerboard was present, consistent with a role in the maintenance of visual continuity across blinks.

### 4.4.1 Effects of blinking and external darkenings in occipital cortex

Voluntary blinking, irrespective of the presence or absence of visual stimulation, was associated with strong and highly significant increases in activity throughout the occipital lobe (see Figure 4.1). These findings replicate earlier, and often unremarked, findings of activation of visual cortex in studies of human blinking (e.g. Fig 4 of Kato and Miyauchi, 2003a) that have focused primarily on frontal oculomotor control structures such as the FEF and SEF (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Schmidt et al., 2003;Tsubota et al., 1999). The increases in visual cortex activity that I observed during blinking do not merely reflect the presence of an extra-retinal signal associated with the oculomotor command, as external darkenings (DV), (which by definition have no oculomotor component), also increased activity in the visual cortex, compared with continuous visual stimulation in the absence of darkenings and blinking (FV) (see Figure 4.1). Rather, such enhancement of activity is

consistent with recent reports of a rectified positive response in human visual cortex to both increments and decrements in surface luminance (Haynes et al., 2004). Similarly, in monkey visual cortex a significant minority of neurons show strong transient increases in firing in response to the offset of visual stimulation caused by a blink or a darkening (Gawne and Martin, 2000;Gawne and Martin, 2002). The activation I observed during the presence of both voluntary blinks and external darkenings (compared with the absence of blinks and darkenings) may thus reflect transient responses to the frequent increases and decreases in luminance caused by both blinks and darkenings.

However I sought to examine the effects of blinking on visual processing beyond the simple effects of eyelid closure on visual input. By studying the interaction between blinking and visual stimulation and the differences between blinking and my control external darkening condition, I sought to uncover the neural correlates of blink suppression and of visual continuity across blinks.

### 4.4.2 Neural correlates of blink suppression – Interaction 1

I identified a set of bilateral lateral temporo-occipital and parietal cortical loci that showed reduced activation to the presence of visual stimulation with a checkerboard during the presence of voluntary blinking. Strikingly, medially located visual areas, such as the calcarine sulcus (V1), did not show this pattern of activation (see Figure 4.2), even at a reduced statistical threshold. Such an activation profile may indicate that voluntary blinking suppresses the normal response to visual stimulation in these lateral regions. Alternatively these regions may simply show a greater response to the presence of visual stimulation with a checkerboard, when the stimulus is visible for a greater uninterrupted period of time. Such a hypothesis predicts that both voluntary blinks and external darkenings should reduce activity in these regions equally, as both interrupt visual stimulation for the same period of time. Detailed examination of activity profiles in these regions, however, showed that external darkenings (DV) consistently reduced activity to a lesser extent than voluntary blinks (BV) (see Figure 4.2d). I therefore conclude that the lower activity associated with the voluntary blinking during visual stimulation, compared with visual stimulation without

voluntary blinking, reflects suppression of these lateral visual areas, mediated by an oculomotor signal associated with blinking.

I propose that this signal reflects a neural mechanism underlying blink suppression. The 3-dimensional location of these regions supports this hypothesis. Blink suppression primarily affects visual processing in the magnocellular pathway (Burr et al., 1994;Ridder and Tomlinson, 1993;Ridder and Tomlinson, 1995;Ridder and Tomlinson, 1997;Volkmann et al., 1978). Consistent with this, the regions I tentatively identify as mediating blink suppression included the magnocellular region V5/MT (see Figure 4.2 and Table 4.3) (Watson et al., 1993). In contrast the 3-dimensional location of V4 (Hasnain et al., 1998), a primarily parvocellular region, did not appear to show a suppressed response to visual stimulation with a checkerboard during blinking. The magnocellular pathway also provides the major input to parietal areas involved in visual attention (Ungerleider and Desimone, 1986a;Ungerleider and Desimone, 1986b), consistent with the reduction in activity that I observed in regions of parietal cortex associated with voluntary blinking (see Table 4.2).

### 4.4.3 Visual continuity across blinks – Interaction 2

Voluntary blinking (compared with no voluntary blinking) produced significantly greater activation in the presence of visual stimulation, than in the absence of visual stimulation, in only one locus in medial parieto-occipital cortex (Figure 4.3). I did not find activation to visual stimulation per se in this region (see Figure 4.3d, compare FV to FN) Rather, it was activated by blinking in a manner that was modulated by the level of visual stimulation. Such a response pattern has been observed before in this region with MEG (Hari et al., 1994). It was also activated during the external darkening control condition. Such a pattern of activation is consistent with the response properties of the human homologue of the macaque V6/V6A complex, area PO. This area is known to be preferentially sensitive to luminance stimuli rather than checkerboard stimuli (Dechent and Frahm, 2003;Portin et al., 1998). These properties of area PO are consistent with activation of my parieto-occipital region by blinks and external darkenings, presumably due to the changes in luminance that occur during both conditions, but not by my checkerboard

stimulus. But activity in this area was significantly greater during voluntary blinks with visual stimulation compared with the external darkening condition though these were matched for retinal stimulation (see Figure 4.3b). The increased activation in the parieto-occipital fissure during blinks compared to darkenings may therefore represent a neural signal specifically associated with voluntary blinks.

An alternative possibility is that activity in this region simply reflected the magnitude of the changes in luminance that occurred during blinks and darkenings. The changes in luminance that occurred during blinking blocks were greater in the presence than in the absence of visual stimulation, which could account for the increased activity I observed in this region when blinking during visual stimulation, compared with blinking without visual stimulation. The checkerboard stimulus is extinguished by both blinks and external darkenings. However, background luminance in the scanner is not entirely eliminated by the external darkenings. Thus greater activity evoked by blinking during visual stimulation compared with external darkenings could be due to the slightly greater reduction in luminance caused by blinks than darkenings, though this is unlikely as blinks do not entirely eliminate back ground luminance either. Direct inspection of the activity profile of this region (see Figure 4.3d) rules out this possibility, as blinking in the *absence* of visual stimulation also activated this region more than external darkenings. Such a difference in activity cannot be explained by changes in luminance being greater when blinking in the absence of visual stimulation (compared with external darkenings that occur in the presence of visual stimulation), as the luminance changes were greater in the darkening condition. Therefore I conclude that activity in this region is likely to reflect an extra-retinal neural signal associated with blinking and was not simply a response to the changes in luminance caused by eyelid closure.

A final possibility is that activity in this area simply reflects differences in the nature of the transients associated with voluntary blinking and darkenings. Though these two conditions were closely matched for visual input, it is theoretically possible that minor differences may exist in the nature of the retinal transients produced by external darkenings and blinks because the eyelid sweeps across the pupil while darkenings occurred uniformly across the visual scene. However, such differences are unlikely to affect my findings for three specific reasons. Firstly, although the

precise kinematics of darkenings and blinking differ, the overall effect on retinal illumination is very similar. This is because the eyelid is sufficiently close to the lens that it is not in focus, and so does not cause a sharp shadow to sweep across the retina as it closes (Gawne and Martin, 2000). Instead, eyelid closure causes a relatively uniform darkening. Secondly, the Stiles-Crawford effect (the peripheral pupil being less sensitive to light than the centre, (Stiles and Crawford, 1933)) means that only the time taken for the pupil to fully cover the central pupil (which can be < 4ms) is critical when considering the changes in retinal illumination during blinking. Finally, the visual system is not sensitive to very short differences (< 15ms) in the detailed dynamics of visual stimulus onset (Gawne and Martin, 2000;Gawne and Martin, 2002). Therefore I conclude that differences in the nature of the visual transient between blinks and darkenings are unlikely to affect my findings.

I propose that my parieto-occipital region may represent the human homologue of area V6A (the posterior portion) of the macaque V6 complex, which is located on the anterior bank of the parieto-occipital sulcus. In macaques, V6 and V6A respond preferentially to luminance stimuli rather than checkerboard stimuli, as does the region found in this study. However V6A responds more weakly than V6, and, unlike V6, contains visually unresponsive cells that respond to oculomotor activity, such as saccades (Galletti et al., 1991;Galletti et al., 1996). Human area PO can also be divided into two functionally distinct regions; an anterior portion, below the junction with the calcarine sulcus, equivalent to V6 that responds strongly to luminance stimuli, and a posterior portion, equivalent to V6A that responds more weakly to luminance stimuli (Dechent and Frahm, 2003). Like macaque V6A, the human posterior parieto-occipital sulcus is activated by self-generated saccades in the dark (Law et al., 1998), suggesting that it also contains neurons that respond to oculomotor signals. The region of the parieto-occipital sulcus found in my study is located immediately posterior to the junction with the calcarine sulcus, and is activated by changes in luminance during blinks and darkenings, reflecting the activity of neurons that respond to luminance stimuli. It is also activated by blinking in the dark, reflecting the activity of neurons that respond to oculomotor signals, suggesting that it is indeed equivalent to macaque area V6A. The greater activation of this region by blinking compared with darkenings during visual stimulation, may

reflect the activity of the non-visually responsive neurons in the part of human PO homologous to macaque V6A that respond to oculomotor signals.

V6A, and its human homologue are thought to be involved in the integration of visual and motor information, specifically oculomotor information, perhaps enabling guided hand-movements, and maintaining visual continuity during saccades (Galletti et al., 1995;Law et al., 1998). I propose that activity of non-visually responsive neurons in this region, putatively the human homologue of V6A, may reflect the active maintenance of visual continuity across blinks in response to a signal from the oculomotor system. Blink-related magnetic fields, localised to the posterior parieto-occipital sulcus have previously been implicated in the maintenance of visual continuity across blinks (Hari et al., 1994). One possibility is that activity in this region may reflect a mnemonic signal associated with the maintenance of perception of the preceding visual stimulus across the interruption caused by a blink, thus establishing visual continuity. Regions of the posterior parietal cortex are associated with visual short term memory (Todd and Marois, 2004;Vogel and Machizawa, 2004). I found that activity in this region reflected not just the presence of blink motor commands, but also depended on the level of background visual stimulation (i.e. presence versus absence of visual stimulation with a flickering checkerboard). Blinking caused greater activation of this region in the presence of visual stimulation. This is consistent with the notion that a short-term mnemonic signal is involved in maintaining perceptual continuity across blinks, as activity associated with visual short-term memory is strongly modulated by the amount of information being held in memory (Todd and Marois, 2004;Vogel and Machizawa, 2004). When blinks occur during visual stimulation with a checkerboard, the amount of information that needs to be retained across the blink is greater than during the absence of stimulation with a checkerboard. Greater activation to blinks is therefore expected during visual stimulation with a flickering checkerboard, as I observed. This visual short-term memory hypothesis suggests that future work should examine whether activity in this region scales with accuracy in a visual memory task carried out across a blink (for example, change detection before and after a blink).

## 4.5 Conclusion

My findings suggest that the two behavioural phenomena, of blink suppression and visual continuity across blinks, are mediated by two corresponding neural mechanisms reflected by activity in two distinct sets of cortical loci. First, suppression of normal responses to visual stimulation in lateral occipital visual areas during blinking may reflect a specific effect of blinking on magnocellular processing. The functional correlate of such suppression may be to reduce perception of the eyelid passing over the pupil. Second, I found activation of a region in the parieto-occipital fissure, putatively the human homologue of macaque area V6A, whose activity may reflect the active maintenance of visual continuity across blinks. I speculate that this may involve a mnemonic signal that bridges the interruption of visual activity caused by the reduction in visual input due to a blink, and by the suppression of lateral occipital areas.

# CHAPTER 5: BLINKING SUPPRESSES THE NEURAL RESPONSE TO UNCHANGING RETINAL STIMULATION

## 5.1 Introduction

My previous experiment (see Chapter 4) suggested that the two behavioural phenomena of blink suppression and visual continuity are mediated by two different neural mechanisms in distinct brain regions. First, I found that the normal response to visual stimulation was suppressed in lateral occipital areas during blinking, specifically in V5/MT and V3a. I suggest that this suppression may serve to reduce perception of the eyelid passing over the pupil. Second, I found activation of a parieto-occipital region, which I propose is the human homologue of macaque area V6A, and whose activity may reflect the active maintenance of visual continuity across blinking, perhaps via a mnemonic signal that bridges the interruption to visual stimulation that occurs during blinks.

These findings go a long way towards explaining why we do not notice our blinks despite the profound interruptions to visual stimulation they cause every few seconds. However, one problem in interpreting cortical responses to visual stimulation during blinking is that any changes in brain activity evoked by an extra-retinal signal associated with the blink motor command are potentially confounded by the reduction in retinal illumination resulting from pupillary occlusion. In the previous experiment, (Chapter 4), I created a control condition in which I dynamically generated external darkenings of the visual scene, in order to circumvent this problem. As changes in visual input were matched in the two conditions, any differences between the two conditions must reflect the presence of an extra-retinal signal associated with blinking. However, this experimental paradigm was not ideal as it was hard to precisely model the exact pattern of light falling on the retina as the eye is occluded by the eyelid during blinks.

In this second experiment I sought to directly distinguish the extra-retinal effect of blinking on neuronal activity, from the confounding effect of the loss of retinal stimulation caused by eyelid closure, without the need for an external darkening control condition. This was achieved by employing a specially designed apparatus to

stimulate the retina without light traversing the pupil (Volkmann et al., 1980) while brain activity was measured with fMRI. Retinal illumination therefore remained constant irrespective of whether the eyes were open or closed.

A fiber-optic light source was placed in the mouth of eight individual subjects while I measured their brain activity with fMRI. This apparatus could be used to trans-illuminate (through the palatine bone, which forms the posterior part of the roof of the mouth) both retinas with a flickering light source. Subjects additionally wore opaque light-proof goggles that prevented any light from entering the eye through the pupil. When the oral light source was switched on, retinal stimulation was produced by trans-cranial illumination that was completely unaffected by eyelid closure during blinks. I hypothesized that in such circumstances, any reduction in brain activity associated with blinking would represent a direct neural signature of blinking specifically associated with the blink motor command. Such a reduction would represent a decreased sensitivity to visual stimulation, thus potentially explaining the psychophysical phenomenon of blink suppression and why blinks go unnoticed.

Two factors were independently manipulated in a blocked design to test this hypothesis: the presence (or absence) of retinal illumination via my oral apparatus and the presence (or absence) of voluntary blinking. Functional MRI in combination with standard retinotopic mapping procedures (Teo et al., 1997) and cortical segmentation and flattening (Wandell et al., 2000) was used to functionally identify cortical areas V1–V3 in each individual subject, and the lateral geniculate nucleus (LGN) was localized with standard anatomical and functional criteria (Kastner et al., 2004) (see Methods for full details). Area V5/MT was localized with a separate motion localizer (see Methods).

I proceeded to characterize the effects of blinking on neural activity in these functionally defined retinotopic visual areas and the LGN. Next, to determine whether any brain regions outside functionally defined retinotopic visual cortex also showed any neural signature of blink suppression, I conducted an unrestricted whole-brain analysis.

## 5.2 Materials and Methods

### 5.2.1 Subjects

Eight normal volunteers (4 male and 4 female, mean age = 25, SD = 5) with normal or corrected to normal vision gave informed written consent to participate in the study, which was approved by the Institute of Neurology and National Hospital for Neurology and Neurosurgery Joint Ethics Committee.

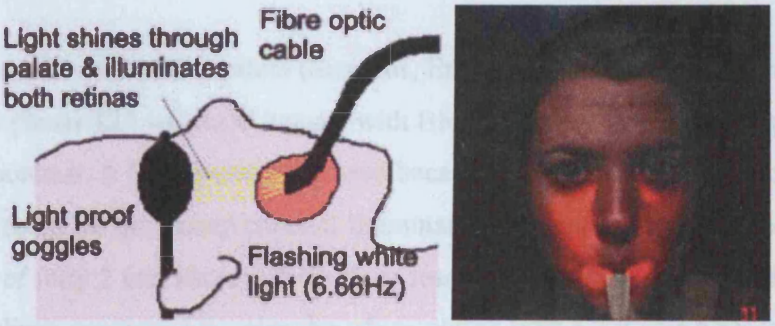
### 5.2.2 Experimental Procedure

Two factors were independently manipulated in a blocked design: the presence (or absence) of *retinal stimulation*, and the presence (or absence) of *voluntary blinking*.

Prior to the start of each block, an auditory cue indicated whether the impending block would require the subjects to blink, or merely maintain fixation. During 'blink' blocks, participants were required to blink binocularly at a fast regular rate. During 'no blink' blocks, subjects were required to maintain steady fixation, and were allowed to blink but asked to keep blinking to a minimum. Subjects were specifically instructed not to forcefully keep their eyes open, so that they did not inhibit spontaneous blinking.

Independently from the presence or absence of voluntary blinking, during half the blocks a visual stimulus was presented. Visual stimulation was delivered to the retina using an illumination technique that bypassed the normal optical path through the cornea and pupil (see Figure 5.1). A 6m long 8 mm diameter fibre optic cable (Pennine Radio Ltd), connected to a 250 W light source (Pennine Radio Ltd.) located in the scanner control room, was positioned against the roof of the mouth and used to deliver a bright flashing white light (6.66 Hz) to a region directly below the two eyes. A strong flashing light was used to maximise visual cortex activation and prevent adaptation.

*Figure 5.1 - Trans-palatine retinal stimulation apparatus*




This illumination was perceived as a diffuse cloud of flashing red light with two focal points in the left and right upper temporal visual fields, corresponding to the lower nasal retina of each eye. Subjects wore opaque light-proof goggles that prevented any other light from entering the eye through the pupil. This method of illumination resulted in retinal stimulation that remained constant whether the eyes were open or closed. Thus visual input was not affected by the presence or absence of blinks.

The experiment thus consisted of four conditions constituting a 2 x 2 factorial design:

| | Retinal stimulation | |
|---|---|---|
| | Present | Absent |
| Voluntary Blinking | **1** | **3** |
| No Voluntary Blinking | **2** | **4** |

1) *voluntary blinking during retinal stimulation*
2) *no voluntary blinking during retinal stimulation*
3) *voluntary blinking without retinal stimulation*
4) *no voluntary blinking without retinal stimulation*

Each condition was presented four times per scanning run. The order of conditions was pseudo-randomly generated at the start of each session, with the restrictions that "retinal stimulation" and "no retinal stimulation" blocks had to alternate, and no more than three "blinking" blocks could occur in succession, to prevent subjects from tiring.

### 5.2.3 Imaging

A 1.5T Siemens SONATA system (Siemens, Erlangen) was used to acquire gradient-echo echo-planar T2* weighted images with Blood Oxygenation Level Dependent (BOLD) contrast. A 1.5T system was used because the larger bore size allowed sufficient room for the unconventional illumination apparatus. Each volume consisted of forty 2 mm slices with in-plane resolution of 3x3 mm, with a 1 mm gap between slices, positioned to cover the whole cortex with a TR of 3.6 seconds. Imaging was performed in three scanning runs of 112 volumes each. In each scanning run, six image volumes preceding presentation of the experimental conditions were discarded to allow for T1 equilibration effects. Finally, a T1-weighted anatomical image was acquired from each subject.

### 5.2.4 Retinotopic mapping and V5/MT localisation

To identify the boundaries of primary visual cortex (V1) and extra-striate retinotopic cortex (V2 and V3), standard retinotopic mapping procedures were used (See Chapter 2: fMRI Methods – Retinotopic Mapping). Checkerboard patterns, flickering at 8 Hz, covering either the horizontal or vertical meridian were alternated with rest periods for 16 epochs of 20.8 seconds over a scanning run lasting 165 volumes. To identify V5/MT, a standard motion localiser was used, consisting of randomly moving low contrast dots (moving at 4°/s) alternating with static dots for 16 epochs of 20.8 seconds over a scanning run lasting 165 volumes (Dumoulin et al., 2000). A 3T Siemens ALLEGRA system (Siemens, Erlangen) was used to acquire gradient-echo echo-planar T2* weighted images with Blood Oxygenation Level Dependent (BOLD) contrast. Data were analysed using SPM2. Mask volumes for sub-regions (left and right, dorsal and ventral) of each region of interest (V1, V2, and V3) were obtained by delineating the borders between visual areas with activation patterns from the meridian localisers. I followed standard definitions of V1, V2 and V3 (Sereno et al., 1995) together with segmentation and cortical flattening in MrGray (Teo et al., 1997;Wandell et al., 2000). The peak voxels activated by the motion localizer (revealed by the contrast moving dots – static dots) in each hemisphere were identified for each subject. (See Chapter 2: fMRI Methods – Retinotopic Mapping and Localisation of V5/MT for full details of procedures).

### 5.2.5 Statistical Analysis

Data were analysed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm).

#### *5.2.5.1 Individual subject analyses*

Analyses of the effects of blinking and retinal stimulation that used the retinotopic mapping data (see above) to functionally localise activations in retinotopic visual cortex were carried out on each subject individually. The initial six volumes of each functional scanning run of the main experiment were discarded, and subsequent image volumes then realigned (Friston et al., 1995), co-registered to each subject's structural scan, and smoothed with a Gaussian kernel of 6 mm full-width half maximum. Voxels activated during the experiment were identified using a statistical model that comprised four delayed boxcar waveforms for each scanning run. These represented the mean activity evoked in the four experimental conditions. Motion parameters defined by the realignment procedure were added to the model as six separate regressors of no interest. High-pass filtering removed low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis, used to generate parameter estimates for each regressor at every voxel.

To extract activity from retinotopic visual cortex, I used the mask volumes for sub-regions (left and right, dorsal and ventral) of each region of interest (V1, V2, and V3) that were created by the retinotopic mapping analyses, described above. The regression parameter estimates generated by the analysis of the main experimental fMRI data, were extracted for the maximally activated voxel (comparing visual stimulation with darkness in the no-voluntary blinking conditions) in each sub-region (left and right, dorsal and ventral) of the regions of interest (V1, V2, and V3) in each subject.

Parameter estimates were also extracted for the LGN. The location of the LGN in each subject was first identified using an anatomical and radiological brain atlas to identify anatomical landmarks close to the LGN on each subject's high-resolution

structural scan. Next, the functional data co-registered to each structural scan was used to locate visually responsive voxels within the previously defined anatomical boundaries, using the statistical contrast of retinal stimulation without voluntary blinking versus no retinal stimulation without voluntary blinking.

For each visual region of interest, the parameter estimates were averaged across subjects, yielding a plot of BOLD signal for each experimental condition in V3, V2, V1 and the LGN across subjects. Averaging across all visually responsive voxels in V1, V2 and V3 produced qualitatively the same pattern of results, confirming that the pattern of responses was consistent over each region of interest.

#### *5.2.5.2 Whole cortex analysis*

In addition to the retinotopic analyses, I also conducted an unrestricted whole cortex random-effects analysis across subjects to examine the effects of blinking on visual processing outside retinotopic visual cortex. The realigned functional image volumes for each subject were spatially normalised (Ashburner and Friston, 1999) to the standard space defined by the Montreal Neurological Institute template (Mazziotta et al., 1995) and then smoothed with a Gaussian kernel of 6 mm full-width half maximum. Voxels activated during the experiment were again identified using the same statistical model as for the retinotopic analysis that comprised four delayed boxcar waveforms for each scanning run. These represented the mean activity evoked in the four experimental conditions. Motion parameters defined by the realignment procedure were added to the model as six separate regressors of no interest. High-pass filtering removed low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. The resulting parameter estimates for each regressor at each voxel were then entered into a second level analysis where subject served as a random effect in a within-subjects ANOVA. The main effects and interactions between conditions were then specified by appropriately weighted linear contrasts and determined using the t-statistic on a voxel-by-voxel basis. A statistical threshold of $P<0.05$, corrected for multiple comparisons across the entire cortex, and a spatial extent threshold of 5 voxels, was used.

## 5.3 Results

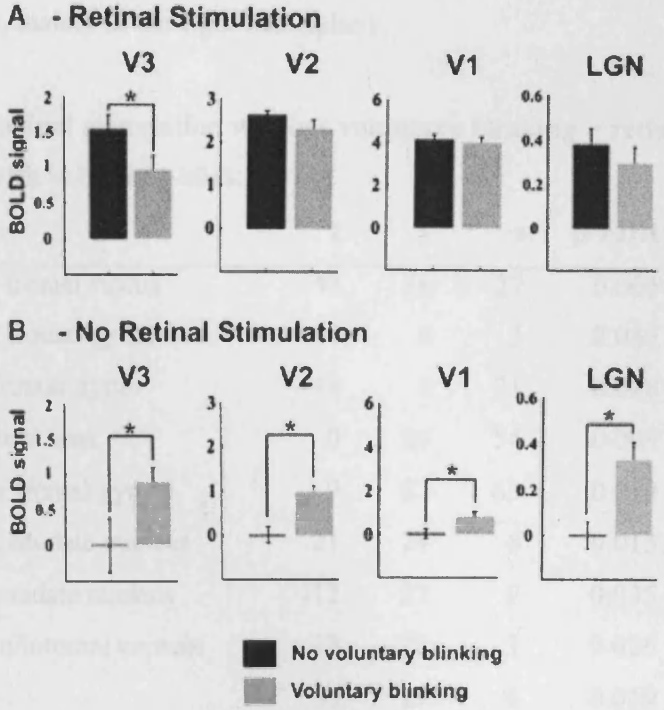
### 5.3.1 Retinotopic Analysis

Comparison of all conditions in which there was retinal stimulation with those without retinal stimulation confirmed activation of LGN and V1–V3 by the trans-cranial retinal illumination stimulus, but I found no reliable activation of V5/MT. Perhaps V5/MT was not strongly activated by my visual stimulus because it responds best to moving stimuli with high contrast, whereas my stimulus, although flashing, was static and phenomenally relatively diffuse and weak.

Having confirmed that my visual-stimulation device activated retinotopic visual cortex, I next proceeded to characterize the effects of blinking on neural activity in these regions. In the presence of retinal stimulation, activity was strongly and significantly reduced by blinking in retinotopic area V3 ($t_{[8]} = 2.974$, $p = 0.018$) (see Figure 5.2A). Thus, even when input to the visual system is held constant, blinks can modulate activity in retinotopic visual areas. Blinking also reduced activity during retinal stimulation in LGN and V2, but this difference did not reach statistical significance (LGN $t_{[8]} = 1.036$, $p = 0.335$; V2 $t_{[8]} = 1.462$, $p = 0.182$) (see Figure 5.1A). In V1, there was no significant difference between blinking and no blinking in the presence of visual stimulation ($t_{[8]} = 0.642$, $p = 0.539$).

In the absence of retinal stimulation, a different pattern of responses to blinks emerged. In contrast to the reductions in activity associated with blinking in the presence of retinal stimulation, blinking (compared to no blinking) in the absence of retinal stimulation significantly *increased* activation in both LGN ($t_{[8]} = -4.533$, $p = 0.003$) and retinotopic areas V1 ($t_{[8]} = -3.422$, $p = 0.009$), V2 ($t_{[8]} = -5.454$, $p = 0.001$), and V3 ($t_{[8]} = -5.501$, $p = 0.001$) (see Figure 5.1B). The effects of blinking therefore differed in the presence and absence of retinal stimulation. Whereas blinking strongly suppressed the response to retinal stimulation in retinotopic area V3, in the absence of any retinal stimulation blinking resulted in an enhanced signal in early cortical areas and the LGN.

*Figure 5.2 - Modulation of responses in human early visual cortex by blinking*




*(A and B) BOLD contrast responses in human V3, V2, V1, and LGN during no blinking (black) and blinking (gray) conditions in (A) the presence of retinal stimulation through the roof of the mouth and (B) the absence of retinal stimulation. Data are taken from individual retinotopic analyses, and BOLD signal is plotted as a function of condition and averaged across all eight subjects (error bars ± 1 SEM; see Methods for full details). The asterisk (*) denotes statistical significance ($p < 0.05$) in a two-tailed t test between conditions. (A) V3 shows significantly reduced BOLD signal when blinking in comparison to not blinking during retinal stimulation ($t_{[8]} = 2.974$, $p = 0.018$). Activity in V2 follows the same trend as V3 but does not reach significance ($t_{[8]} = 1.462$, $p = 0.182$). (B) All four retinotopic areas, V3–LGN, show a significant increase in activity during blinking in comparison to no blinking conditions in the dark (V3 $t_{[8]} = -5.501$, $p = 0.001$; V2 $t_{[8]} = -5.454$, $p = 0.001$; V1 $t_{[8]} = 3.422$, $p = 0.009$; and LGN $t_{[8]} = -4.533$, $p = 0.015$).*

### 5.3.2 Whole Cortex Analysis

To determine whether the neural responses to retinal stimulation in any brain regions outside the functionally defined retinotopic visual areas considered above were also affected by blinking, I conducted an unrestricted whole-brain analysis. When retinal stimulation was present, there were highly significant ($p < 0.05$ false discovery rate [FDR] corrected) reductions in activity during blinking (versus no blinking) in

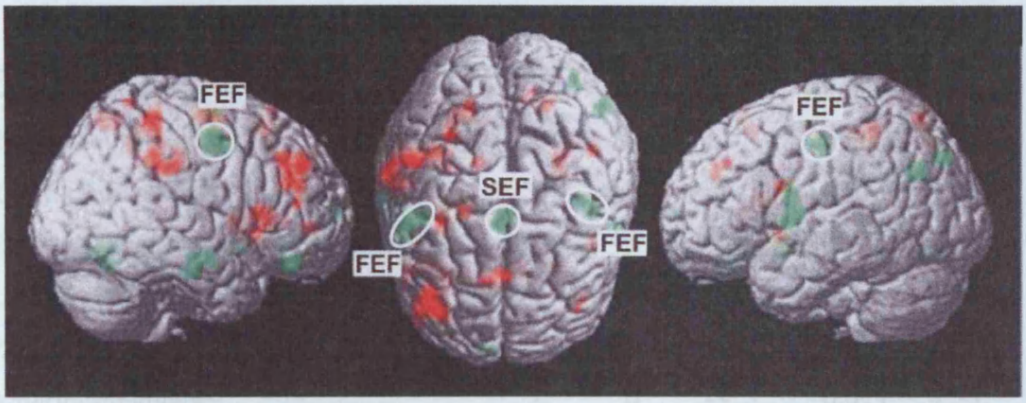
several regions of parietal and prefrontal cortices (see Figure 5.3; see Table 5.1 for full list of loci), mainly in the right hemisphere.

**Table 5.1 – Retinal stimulation without voluntary blinking > retinal stimulation with voluntary blinking**

| | x | y | z | p-FDR | Z |
|---|---|---|---|---|---|
| Right inferior frontal sulcus | 42 | 36 | 27 | 0.006 | 5.08 |
| Right inferior frontal gyrus | 48 | 6 | 3 | 0.045 | 3.81 |
| Left inferior frontal gyrus | -48 | 6 | 21 | 0.028 | 4.20 |
| Right cingulate sulcus | 0 | 24 | 54 | 0.009 | 4.90 |
| Right superior frontal gyrus | 9 | 27 | 63 | 0.010 | 4.82 |
| Right head of caudate nucleus | 21 | 24 | 6 | 0.013 | 4.72 |
| Left head of caudate nucleus | -12 | 27 | 9 | 0.035 | 3.97 |
| Right putamen/internal capsule | 18 | 12 | 3 | 0.026 | 4.25 |
| Right insula | 33 | 27 | 6 | 0.019 | 4.56 |
| Left short insular gyri | -39 | 6 | -6 | 0.024 | 4.31 |
| Left circular insular sulcus | -30 | 18 | 15 | 0.048 | 3.76 |
| Right pre-central gyrus | 15 | -36 | 63 | 0.019 | 4.52 |
| Right pre-central sulcus | 33 | -3 | 60 | 0.035 | 4.09 |
| Right superior pre-central sulcus | 21 | -12 | 60 | 0.019 | 4.46 |
| Right post-central gyrus | 30 | -36 | 45 | 0.035 | 4.03 |
| Left post-central gyrus | -30 | -42 | 54 | 0.035 | 3.94 |
| Right superior parietal gyrus/IPS | 21 | -69 | 57 | 0.020 | 4.43 |
| Left superior parietal gyrus/IPS | -21 | -66 | 60 | 0.050 | 3.70 |
| Right intra-parietal sulcus | 30 | -51 | 42 | 0.035 | 3.95 |
| Right angular gyrus/IPS | 57 | -39 | 39 | 0.023 | 4.33 |
| Right supramarginal gyrus | 63 | -30 | 33 | 0.035 | 4.11 |

*Cortical loci where voluntary blinking reduced activity associated with retinal stimulation. Shown in the table are the locations, stereotactic coordinates in the space defined by the Montreal Neurological Institute template, Z scores and corresponding P value (corrected for multiple comparisons across the volume examined). A statistical threshold of $P<0.05$, corrected for multiple comparisons across the entire brain volume, and a spatial extent threshold of 5 voxels, was used.*

***Figure 5.3 - Areas showing a reduced response to retinal stimulation when blinking***




*Left lateral, right lateral, and superior views of a standard T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template, with loci showing reduced responses to retinal stimulation when blinking in comparison to not blinking shown superimposed in red on the rendered images ($p < 0.001$ uncorrected and spatial extent threshold of 5 voxels for display purposes). Oculomotor regions showing greater activation when blinking in comparison to no blinking, across retinal-stimulation conditions, are shown superimposed in green on the rendered images ($p < 0.05$ FDR-corrected and spatial extent threshold of 5 voxels for display purposes). The main oculomotor regions controlling blinking, that is, the frontal eye-fields (FEF) and supplementary eye-field (SEF), are labelled (see Table 5.2) for full list of loci). Note the lack of overlap between these oculomotor structures (in green) and the regions suppressed by blinking (in red).*

The locations of these parietal and prefrontal regions, which were suppressed by blinking, are clearly spatially distinct from oculomotor structures such as the supplementary and frontal eye fields (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Paus, 1996), which were strongly activated by the reverse comparison of blinking versus no blinking conditions collapsed across retinal illumination conditions (see Figure 5.3; see Table 5.2 for full list of loci). Non-oculomotor regions of parietal and prefrontal cortex therefore show a reduction in activity during blinking in the presence of retinal stimulation.

**Table 5.2 – Voluntary blinking > no voluntary blinking (with and without reintal stimulation)**

| | x | y | z | p-FDR | Z |
|---|---|---|---|---|---|
| Cerebellar vermis | 9 | -66 | -12 | 0.001 | 5.5 |
| Right middle frontal gyrus | 33 | 39 | -21 | 0.009 | 4.8 |
| Right inferior temporal gyrus | 66 | -18 | -21 | 0.011 | 4.69 |
| Right superior precentral sulcus (FEF) | 54 | -3 | 45 | 0.011 | 4.64 |
| Left superior precentral sulcus (FEF) | -45 | -12 | 45 | 0.024 | 4.05 |
| Right superior frontal gyrus (SEF) | 3 | -6 | 63 | 0.011 | 4.61 |
| Anterior cingulate | 0 | 6 | -9 | 0.011 | 4.56 |
| Left lingual gyrus | -24 | -66 | 9 | 0.012 | 4.52 |
| Right inferior temporal gyrus | 60 | -9 | -15 | 0.014 | 4.45 |
| Right orbital gyrus | 6 | 36 | -21 | 0.018 | 4.23 |
| Left superior occipital gyrus | -36 | -81 | 39 | 0.018 | 4.22 |
| Left superior temporal gyrus | -57 | 0 | 6 | 0.020 | 4.22 |
| Right subcallosal gyrus | 15 | 6 | -12 | 0.022 | 4.15 |
| Right cerebellar hemisphere | 27 | -63 | -21 | 0.023 | 4.11 |
| Right cerebellar hemisphere | 30 | 51 | -39 | 0.025 | 4.02 |
| Left angular gyrus | -51 | -69 | 33 | 0.026 | 3.96 |
| Left cerebellar hemisphere | -6 | -75 | -15 | 0.026 | 3.95 |
| Medial frontal gyrus | 9 | 66 | 9 | 0.035 | 3.68 |

*The locations, stereotactic coordinates in the space defined by the Montreal Neurological Institute template, Z scores, and corresponding p value (corrected for multiple comparisons across the volume examined) for the regions activated by blinking versus no blinking. A statistical threshold of $p < 0.05$, corrected for multiple comparisons across the entire brain volume and a spatial extent threshold of 5 voxels, was used.*

## 5.4 Discussion

The neural mechanisms underlying blink suppression have always been challenging to study because of the confounding effects of the visual input loss caused by eyelid closure; these effects potentially mask any direct extra-retinal effects of blinking on brain activity. For example, activity of single neurons in monkey early visual areas V1, V2, V3V, and V4V decreases during blinks, demonstrating that visual continuity across blinks does not depend on the maintenance of continuous neural activity in early visual cortex (Gawne and Martin, 2000;Gawne and Martin, 2002). However, these reductions in activity may simply result from the dramatic loss of retinal illumination associated with eyelid closure during blinks, rather than reflecting an active top-down suppression of visual cortical activity. External darkenings of the entire scene also result in a decrease in neuronal activity in all these early visual areas (Gawne and Martin, 2002), although in V1 the rate of decay of average activity is slightly slower, and the overall reduction is smaller than during blinks, suggesting that some degree of top-down suppression may occur during blinks (Gawne and Martin, 2000).

Here, I successfully dissociated the extra-retinal effects of blinking on neural activity from its mechanical or optical effects, and I have demonstrated active suppression of neuronal activity during blinking, despite continuous visual input. I observed a strong and highly significant V3-activity reduction that was associated with blinking (versus no blinking) in the presence of retinal stimulation (see Figure 5.2a). This represents a reduction in sensitivity to visual stimulation in this region during blinks and, thus, could represent a neural mechanism underlying the psychophysical phenomenon of blink suppression. The suppression of the response to visual stimulation during blinking in this experiment is consistent with the results of my previous experiment which revealed a reduced response to visual stimulation in lateral occipital regions including V3a (see Chapter 4). However, unlike in my first experiment, this experiment did not reveal any suppression of the response to visual stimulation in V5/MT because my trans-cranial retinal stimulus failed to significantly activate V5/MT.

Blinking did not significantly suppress the responses to retinal stimulation in the LGN and cortical areas V1 and V2. This is consistent with the results of my first experiment, which likewise did not reveal a reduced response to the presence of visual stimulation during blinking in medial occipital regions (see Chapter 4). Therefore, it appears that, as in monkeys, activity in the LGN, V1, and V2 may reflect visual input during blinks (which here remained continuous) (Gawne and Martin, 2002), and any extraretinal modulation of visually evoked activity in these areas is modest (Gawne and Martin, 2000). However, note that a positive signal was consistently observed in association with blinking in darkness in these areas (see Figure 5.2b). This may represent a motor signal that, if also present during retinal stimulation, could lead to underestimation of any direct suppressive effect of blinks on sensory processing.

Whereas it might have been supposed that blink suppression is a purely low-level visual phenomenon, mediated solely by retinotopic visual areas, my whole-brain analysis surprisingly revealed that activity evoked by retinal stimulation in parietal and frontal cortices was also suppressed by blinking (see Figure 5.3). Similar parietal regions also showed a reduced response to visual stimulation during blinking in my first experiment (see Chapter 4, Table 4.3). In this study, these regions cannot merely be responding to a change in retinal illumination because retinal illumination was not affected by eyelid closure during blinks. My special stimulation apparatus and the use of opaque goggles ensured that retinal illumination remained constant whether the eyes were open or closed. The reduction in activity seen during blinks is therefore likely to be related to an extra-retinal neural signal associated with the blink motor command from the non-overlapping oculomotor regions (see Figure 5.3; see Table 5.2 for full list of loci).

Activation of parietal and prefrontal cortices has been consistently associated with fluctuations in the contents of consciousness, (Rees et al., 2002), for example as occurs during binocular rivalry (Lumer et al., 1998), when viewing ambiguous figures (Kleinschmidt et al., 1998), or during conscious detection of changes in the visual scene (Beck et al., 2001). Loci activated in those studies have similar spatial locations to those demonstrating suppressed activity when blinking in the present study. Thus, one possible interpretation of my findings is that the observed

*suppression* of these parietal and prefrontal regions during blinking represents a neural mechanism underlying the *lack* of awareness of the changes in visual input that normally occur during a blink. Specifically, it may account for the lack of awareness of the percept of the eyelid descending across the pupil and the resulting reduction in retinal illumination.

In contrast to the suppression of activity during retinal stimulation by blinks in both retinotopic V3 and parietal and prefrontal cortices, I also observed, in the LGN and early visual areas V1–V3, a positive signal associated with blinking in the absence of retinal stimulation (Figure 5.1B). Because retinal stimulation was entirely absent in these particular conditions, I propose that these activations represent a motor signal associated with blinking in visual cortex. This finding replicates earlier, and often unremarked, findings of visual cortex activation in darkness during blinking (e.g., Figure 4 of (Kato and Miyauchi, 2003a)) in studies that have focused primarily on frontal oculomotor control structures (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Tsubota et al., 1999). These observations, plus the contextual dependence of blink-associated signals on retinal illumination demonstrated here, run strikingly parallel to recent observations of a similar dependence of saccadic responses in these brain areas on the presence (or absence) of retinal stimulation (Sylvester et al., 2005). When saccades are made in the dark, a positive (motor) signal is seen in LGN and V1, whereas during retinal illumination, saccades result in a reduction in visually evoked activity in these areas. Taken together, these findings may represent some preliminary evidence that blink suppression and saccadic suppression share some common neural mechanisms, as previously predicted on purely theoretical grounds (Ridder and Tomlinson, 1997;Volkmann, 1986). Indeed, although any eye movements during a blink are very small (Bour et al., 2000;Evinger et al., 1984;Riggs et al., 1987), blinks themselves can change the kinematic properties of horizontal saccades (Rambold et al., 2002), suggesting that the motor signals associated with blinking and the saccadic premotor circuit can interact. Currently, there is good physiological evidence in monkeys for the existence of a corollary discharge pathway from the superior colliculus to the frontal eye-fields (FEF), during saccades, which may serve to coordinate sequential saccades and stabilize vision across saccades (Sommer and Wurtz, 2004a;Sommer and Wurtz, 2004b;Wurtz and Sommer, 2004). I speculate that a similar corollary

discharge pathway may operate during blinks to attenuate their sensory consequences.

In this experiment, I did not see any blink related activation in the region along on the parieto-occipital fissure (PO) found in the previous experiment (see Chapter 4). In Chapter 4, I hypothesized that this parieto-occitial region is the human homologue of macaque area V6A and that its activity reflected the maintenance of visual continuity across the interruption of visual input cause by a blink. In the previous experiment, activity in this region reflected not just the presence of blinking but also level of background visual stimulation, with greater activation occurring in the presence versus absence of visual stimulation. I proposed that this reflects the amount of visual information that needs to be maintained across the interruption caused by the blink (See Chapter 4, Discussion). Thus, it is not suprising that this region was not activated by blinking in this experiment, as my retinal illumination apparatus ensured that visual input was not interrupted by blinks.

## 5.5 Conclusion

In summary, my data demonstrate that responses to retinal illumination are suppressed by blinking in retinotopic visual area V3 and in parietal and prefrontal cortices, whereas in the absence of retinal stimulation, I identified a positive blink-related signal in early visual areas LGN–V3. I propose that these findings represent a neural signature of blinking associated with the blink motor command and may go some way toward explaining both the neural mechanisms underlying the visual-sensitivity loss, known as blink suppression that occurs during blinks, and why they go unnoticed. My findings parallel recent observations of saccade-related changes in activity in visual cortex during saccades, suggesting that blink suppression and saccadic suppression may indeed share common neural mechanisms. However, the precise neural mechanisms relating the blink motor command to the neural suppression that I observed here remain to be explored.

# CHAPTER 6: SOCIAL INTERACTION MODIFIES THE NEURAL RESPONSE TO GAZE SHIFTS

## 6.1 Introduction

As described in the General Introduction to this thesis, it has been proposed that the mirror system acts in a predictive manner, predicting and simulating the actions of others, and then using the internal forward model to predict the sensory consequences of these actions (Kilner et al. in submission). The sensory prediction can then be compared to the actual sensory feedback and the prediction error used to modify the original prediction of what the other person is doing. There is increasing evidence that the mirror system does indeed actively predict the actions of others rather than simply responding to sensory input (Flanagan and Johansson, 2003;Fogassi et al., 2005;Haueisen and Knosche, 2001;Kilner et al., 2004;Ramnani and Miall, 2004;Rotman et al., 2006;Umilta et al., 2001).

Two recent studies have found that the posterior STS, shows greater activity to unpredicted compared to predicted movements (Pelphrey et al., 2003;Pelphrey et al., 2004a). A smaller haemodynamic response was evoked in the observer's STS in response to gaze shifts directed towards the target, compared to gaze shifts to another location in the avatar's visual field (Pelphrey et al., 2003). Similarly, reaching-to-grasp arm movements directed towards a target elicited less activation in the observer's STS compared to arm movements directed away from the target (Pelphrey et al., 2004a). This suggests that the STS is sensitive to the goal directedness or intentionality of actions. The authors propose that the STS is involved in predicting the actions of others, and that the prolonged activity seen when the actor does not look at or grasp the target, is due to violation of the observer's expectations and the reformulation of the observer's prediction. Alternatively the activation of the STS could reflect the prediction error. These findings fit well with Kilner's predictive model of the mirror system, which includes the STS (Kilner et al. in submission).

In this chapter, I sought to investigate further the effect of the observer's expectation on the brain activity evoked by observation of another person making a gaze shift. In addition to modulating expectation via the presence of a visible target, I will also

modify the observer's expectation by changing the social context of the gaze shift and thus the intention attributed to the person making the gaze shift.

Gaze is an important social stimulus that indicates the direction of attention of an individual. This information is particularly important for social interactions as the direction of attention of other individuals can reveal their intentions and future actions. In everyday life, it is intuitively apparent that whether an individual is socially interacting with us (or not) will affect the significance of their gaze direction and thus the importance of determining their direction of gaze. Here I sought to examine whether the neural response to gaze shifts was modulated by the intention attributed to the person making the gaze shift. I therefore modified an established gaze perception paradigm (Pelphrey et al., 2003) to include a social context, and studied behavioural responses and brain activity in two linked behavioural and functional magnetic resonance imaging (fMRI) experiments.

On each experimental trial, two faces were always presented on screen either side of central fixation; but only one was socially relevant (see Figure 6.1). This was achieved by ensuring that at the start of each trial one face gazed directly at the subject (the 'social' face) while the other's gaze was averted (the 'unsocial' face). Direct gaze is a more salient and engaging stimulus than averted gaze (Gibson and Pick, 1963;Von Grunau and Anston, 1995) and can signal, amongst other types of social interaction, the intention to communicate (Kampe et al., 2003). A target then appeared on screen (c.f. Pelphrey et al 2003) between the two faces, and one of the faces made a gaze shift. This gaze shift could be either towards the target, which I termed a 'correct' gaze shift, or towards another location in space which I termed an 'incorrect' gaze shift. The gaze shift could be made by either the 'social' or the 'unsocial' face, so I could thus manipulate the social context in which a gaze shift occurred while controlling for the presence of direct and averted gaze per se. Two factors were thus modulated independently in a factorial design: the social context of the gaze shift, and the goal directedness of that gaze shift. To ensure that my results could not be due to differences in eye movements between conditions, subjects were instructed to fixate centrally throughout and their eye-movements were monitored with long-range eye tracking.

I hypothesised that the neural response to gaze shifts would be modulated by the feeling of involvement in a social interaction and the perceived communicative intention of the gaze shift. Such a feeling of personal involvement in a social interaction, mediated by direct versus averted gaze, has previously been shown to modulate activity in the medial prefrontal cortex (MPFC) (Schilbach et al., 2005). In addition to seeing increased activation in the STS to 'incorrect' compared to 'correct' gaze shifts (Pelphrey et al., 2003), I hypothesised that the communicative intent attributed to the 'social' face would give rise to the expectation that this face would make a gaze shift, leading to greater STS activation when this prediction is violated by the 'unsocial' face making the gaze shift, if, as has been proposed, the STS is indeed involved in predicting actions (Ramnani and Miall, 2004) and shows greater activation when these predictions are violated (Pelphrey et al., 2003).

Gaze perception activates a fronto-parietal network of regions, plus the occipito-temporal cortex, including the STS (Grosbras et al., 2005). This fronto-parietal network is also activated by execution of eye movements and by shifts of spatial attention (Corbetta et al., 1998;Grosbras et al., 2005;Kato et al., 2001;Nobre et al., 1997), suggesting that attentional and oculomotor processes are closely related at the neuronal level (Corbetta et al., 1998). Activation of common areas by eye movements and gaze perception therefore indicates the existence of an oculomotor "mirror system" (Grosbras et al., 2005), which could account for automatic reorienting of spatial attention in response to gaze (Driver et al., 1999;Langton and Bruce, 1999). If as proposed by Kilner and colleagues the mirror system acts in a predictive manner, then I would expect to see increased activation in this fronto-parietal network in response to the 'incorrect' and 'unsocial' conditions, compared to the 'correct' and 'social' conditions respectively. Such increased activation in this front-parietal network could reflect either a reformulation of the observer's prediction or the prediction error in these two conditions when the observer's expectation is violated in the 'incorrect' and 'unsocial' conditions, as would the predicted increased activation of the STS in these conditions. I also hypothesised that the salience of the social face might lead to enhancement of the effects of goal directedness (i.e. 'correct' versus 'incorrect' gaze shifts) on the response to gaze shifts, due to greater attention being paid to the gaze shifts made by the social face.

## 6.2 Materials and Methods

### 6.2.1 Behavioural experiment

Prior to scanning I conducted a behavioural experiment to verify that the face with direct gaze was indeed more engaging than the face with averted gaze, and to see whether the subject's spatial attention was attracted to the target prior to being shifted in the direction of gaze.

#### *6.2.1.1 Subjects*

Ten normal volunteers (5 male and 5 female, aged 18 to 41, mean=27.1, SD=8.2) gave written informed consent to participate in the study, which was approved by the Institute of Neurology and National Hospital for Neurology and Neurosurgery Joint Ethics Committee.

#### *6.2.1.2 Stimuli and paradigm*

Visual stimuli were presented on a computer screen, using Cogent (http://www.vislab.ucl.ac.uk/Cogent/). Stimuli consisted of video clips of two people, one male and one female, presented side by side, from the neck upwards. One of the faces, the 'social' face, looked directly towards the subject, and the other face, the 'unsocial' face had its gaze averted. The faces appeared on screen at the start of each trial, and after 1.5 seconds a target, consisting of a red and white flickering bull's eye, appeared at one of three possible locations between the two faces, within each character's field of view; at eye level, above eye level, and below eye level. 500ms after target appearance one of the faces shifted their gaze towards the target, a 'correct' gaze shift, or towards one of the two other locations at which the target could have but did not appear, an 'incorrect' gaze shift.

The experiment thus consisted of four conditions (See Figure 6.1):

1. SC 'Social' face makes a 'correct' gaze shift to target
2. SI 'Social' face makes an 'incorrect' gaze shift to empty location
3. UC 'Unsocial' face makes a 'correct' gaze shift to target
4. UI 'Unsocial' face makes an 'incorrect' gaze shift to empty location

***Figure 6.1 - Stimuli***


*In each trial two faces appeared on screen, one of which looked directly at the subject (the 'social' face), and the other with averted gaze (the 'unsocial' face). After 1.5 seconds a target appeared at eye level between the two faces at one of three possible positions. 500ms later one of the faces then made a gaze shift, which could either be towards the target ('correct' gaze shift) or towards an empty location ('incorrect' gaze shift). Thus there were four possible conditions: 'social' face makes a 'correct' gaze shift (SV); 'social' face makes an 'incorrect' gaze shift (SI); 'unsocial' face makes a 'correct' gaze shift (UV); 'unsocial' face makes an 'incorrect' gaze shift (UI). There was also a baseline condition in which neither face's eyes moved (NM).*

The gaze shifts lasted 100ms; the eyes then remained in their final positions, and the target remained on screen until the end of the trial. The size of the gaze shift made by the face was the same for each condition, and consisted of a 71° shift in the direction of gaze of the face, either from the centre to the side for the 'social' face, or between different locations around the face for the 'unsocial' face. A small white fixation cross was presented in the centre of the screen, (at eye level between the two faces), throughout the experiment and subjects were instructed to fixate this cross. Subjects were instructed to indicate whether the face which made the gaze shift looked at the target or not by pressing a button. They were told to respond as quickly as possible and reaction times were recorded. The next trial began 1 second after the subject pressed the button.

Each trial type was presented 48 times, with a total of 192 trials being presented to each subject, and trial order was randomised.

#### *6.2.1.3 Statistical analysis*

The mean of the reaction times was calculated for each condition for each subject, and a repeated measures ANOVA was used to examine the effects of sociability of the face making the gaze shift ('social' face versus 'unsocial' face), and direction of the gaze shift ('correct' versus 'incorrect' gaze shifts) on reaction times.

### 6.2.2 fMRI experiment

#### *6.2.2.1 Subjects*

Twelve normal volunteers (4 male and 8 female, aged 18 to 40, mean=24.73, SD=6.42) gave written informed consent to participate in the study, which was approved by the Institute of Neurology and National Hospital for Neurology and Neurosurgery Joint Ethics Committee.

### *6.2.2.2 Stimuli and paradigm*

Visual stimuli were presented on a screen viewed by a mirror mounted on the head coil, using Cogent (http://www.vislab.ucl.ac.uk/Cogent/). The same stimuli were used as in the behavioural experiment (see above), plus an additional baseline condition in which neither face made a gaze shift (NM) (see Figure 6.1).

As in the behavioural study the gaze shifts lasted 100ms. The eyes then remained in their final positions, and the target remained on screen until the end of the trial 2 seconds later. Trials were separated by a four second interval during which a blank screen was presented. A small white fixation cross was presented in the centre of the screen, (at eye level between the two faces), throughout the experiment and subjects were instructed to fixate this cross. Subjects were instructed to indicate whether the face which made the gaze shift looked at the target or not, or whether there had been no gaze shift, by pressing a button. They were instructed to wait until the appearance of the blank screen at the end of the trial before answering the question.

Each trial type was presented 48 times, with a total of 240 trials being presented to each subject, and trial order was randomised.

### *6.2.2.3 Imaging*

A 3T Siemens ALLEGRA system (Siemens, Erlangen) was used to acquire gradient-echo echo-planar T2* weighted images with Blood Oxygenation Level Dependent (BOLD) contrast. Each volume consisted of forty 3mm axial slices with in-plane resolution of 3x3 mm positioned to cover the whole brain with a TR of 2.6 seconds. Imaging was performed in one scanning run of 780 volumes. In each scanning run, six image volumes preceding presentation of the experimental conditions were discarded to allow for T1 equilibration effects. Eye movements were monitored continually during scanning using an ASL Eye-Tracking System (Applied Science Laboratories, Bedford) with remote optics (Model 504, sampling rate = 60Hz) that was custom-adapted for use in the scanner. Finally, a T1-weighted anatomical image was acquired from each subject.

#### *6.2.2.4 Statistical analysis of fMRI data*

Data were analysed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm). The initial six volumes were discarded, and subsequent image volumes then realigned, (Friston et al., 1995) spatially normalised (Ashburner and Friston, 1999) to the standard space defined by the Montreal Neurological Institute template (Mazziotta et al., 1995) and smoothed with a Gaussian kernel of 6mm full-width half maximum. Voxels activated during the experiment were identified using a general linear model that included the five experimental conditions. The gaze shifts were modelled as events with duration 120 ms, and the no gaze shift condition was modelled as an event with 120 ms duration at the time a gaze shift would normally have occurred. High-pass filtering removed low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. The resulting parameter estimates for each regressor at each voxel were then entered into a second level analysis where subject served as a random effect in a within-subjects ANOVA. The main effects and interactions between conditions were then specified by appropriately weighted linear contrasts and determined using the t-statistic on a voxel-by-voxel basis.

#### *6.2.2.5 Statistical analysis of eye-tracker data*

Eye-movement data were analysed using custom made Matlab scripts to ensure that subjects maintained fixation and that there were no differences in eye movements between conditions. The total length of scan path was compared across conditions. I also compared the mean distance between the eye position at each time point and the average eye position (a measure of fixation) across conditions.

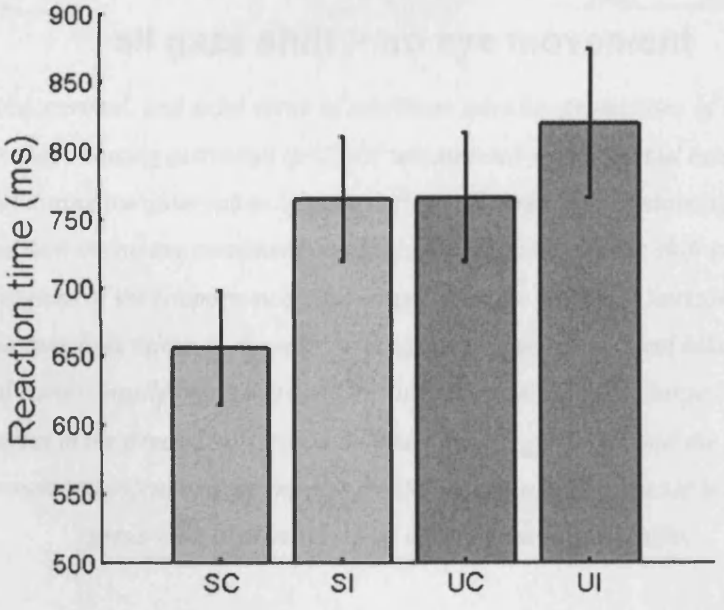
I also compared average eye position during each trial for different target locations, for the different locations (left or right side of screen) of the 'social' face, whether or not it made the gaze shift, for the different locations (left or right side of screen) of the face making the gaze shift, whether it was the 'social' or 'unsocial' face, and for the different end positions of the gaze shift.

## 6.3 Results

### 6.3.1 Behavioural experiment

Reaction times were significantly faster ($F_{(1,9)}$=44.0, p<0.000) when the gaze shifts were made by the 'social' face (mean RT = 710ms) rather than the 'unsocial' face (mean RT = 793ms). In addition reaction times were significantly faster ($F_{(1,9)}$= 18.1, p = 0.002) for 'correct' gaze shifts (mean RT = 711ms) compared to 'incorrect' gaze shifts (mean RT = 792ms; see Figure 6.2). There appeared to be an interaction between direction of gaze shift ('correct' v. 'incorrect') and face making the gaze shift ('social' vs. 'unsocial'), such that the effect of direction on reaction time is greater for the 'social' face than for the 'unsocial' face, and this interaction tended towards significance ($F_{(1,9)}$= 4.08, p=0.074).

***Figure 6.2 – Results of behavioural study***



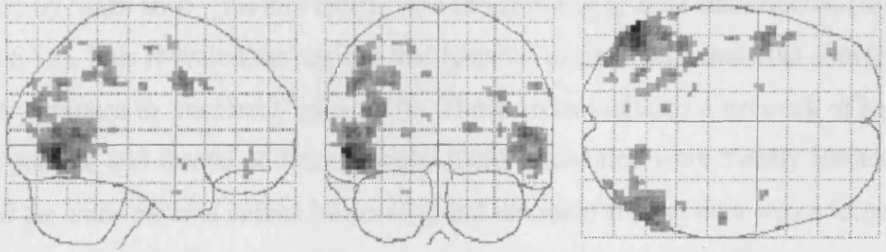

*Mean reaction time averaged across subjects for each of the four conditions: 'social' face makes a 'correct' gaze shift (SV); 'social' face makes an 'incorrect' gaze shift (SI); 'unsocial' face makes a 'correct' gaze shift (UV); 'unsocial' face makes an 'incorrect' gaze shift (UI).*

### 6.3.2 fMRI experiment

#### *6.3.2.1 All types of gaze shift minus no eye-movement*

The main effect of observing gaze shifts, i.e. all conditions with a gaze shift – no eye-movement condition (thresholded at $p<0.05$ FDR-corrected), revealed bilateral activation in a large region of the occipito-temporal cortex, from the posterior horizontal segment of the superior temporal sulcus to the inferior occipital sulcus (see Figure 6.3).

***Figure 6.3 - Regions activated by observation of gaze shifts***




*Saggittal, coronal, and axial views of maximum intensity projections of a statistical parametric map showing activation ($p<0.001$ uncorrected with a spatial extent threshold of 3 voxels) during the observation of gaze shifts in all conditions containing a gaze shift compared with the no eye movement condition. Observation of gaze shift activated large bilateral regions of the temporo-occipital cortex, from the posterior horizontal segment of the superior temporal sulcus to the inferior occipital sulcus, and several bilateral clusters in the parietal cortex, mostly located around the intra-parietal sulcus. A large region in the left frontal cortex in the precentral gyrus and middle frontal gyrus, around the junction of the inferior precentral sulcus and the inferior frontal sulcus, and in a cluster in the left orbital gyrus were also activated by observation of gaze shifts.*

Several clusters in the parietal cortex, mostly located around the intra-parietal sulcus, were also activated bilaterally. Observing gaze shifts also activated a large region in the left frontal cortex in the precentral gyrus and middle frontal gyrus, around the junction of the inferior precentral sulcus and the inferior frontal sulcus, and a cluster in the left orbital gyrus. The left parahippocampal gyrus was also activated, as was a cluster in the right lateral fissure.

#### *6.3.2.2 'Incorrect' gaze shift minus 'correct' gaze shifts (see Figure 6.4)*

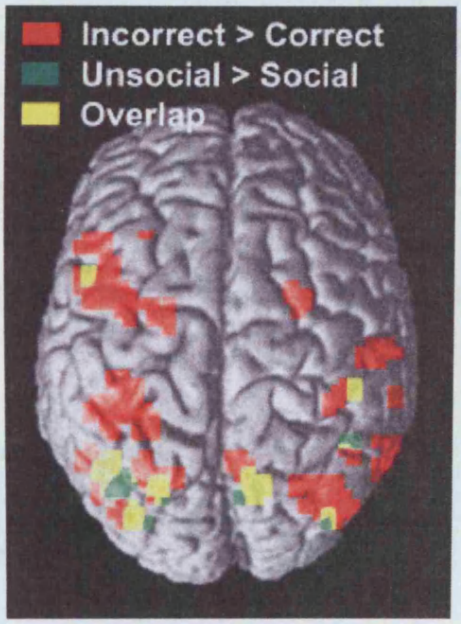
Conditions where the person made an 'incorrect' gaze shift, i.e. shifted their gaze but not to the target location, were compared to conditions where the person made the 'correct' gaze shift, i.e. shifted their gaze towards the target, at $p<0.001$ uncorrected. This revealed areas in the parietal and frontal cortices that showed greater activation to the perception of 'incorrect' gaze shift than to 'correct' gaze shifts.

I had hypothesised that regions activated by gaze shifts would show greater activation to 'incorrect' gaze shifts compared to 'correct' gaze shifts. Therefore I examined the contrast 'incorrect – correct' at a threshold of $p<0.05$ uncorrected, masked by 'gaze shift – no movement' at a threshold of $p<0.01$ uncorrected (see Table 6.1a). This revealed the regions that respond to gaze shift that also showed a greater response to 'incorrect' gaze shifts. These areas included a network of regions in the parietal and frontal cortices. Parietal regions revealed were mostly located around the intra-parietal sulcus bilaterally, and the main frontal area was a large cluster around the left pre-central gyrus and the middle frontal gyrus. Areas in the occipito-temporal lobe also showed greater activation to 'incorrect' gaze shifts. These included an area around the anterior part of lateral occipital sulcus, the superior part of the middle occipital gyrus, and parts of the posterior horizontal segment of the STS. (See Table 6.1a for full details of activated loci).

#### *6.3.2.3 'Unsocial' gaze shifts minus 'social' gaze shifts (see Figure 6.4)*

Conditions where the gaze shift was made by the 'social' face were compared to conditions where the gaze shift was made by the 'unsocial' face. The contrast 'unsocial – social' ($p<0.05$ uncorrected), masked by 'gaze shift – no eye-movement' ($p<0.01$ uncorrected), revealed regions activated by gaze shifts that showed greater activation to gaze shifts made by the 'unsocial' face than to gaze shifts made by the 'social' face (see Table 6.1b). These areas included the several clusters in the superior parietal cortex bilaterally, and the left posterior horizontal STS. The lateral occipital sulcus, and the middle occipital gyrus, and the left inferior pre-central sulcus areas also showed this pattern of activation, as did the left anterior thalamic nucleus. (See Table 6.1b for full details of activated loci).

***Figure 6.4 – Fronto-parietal attention network showing greater activation to 'incorrect' gaze shifts and to gaze shifts made by the 'unsocial' face***




*Superior view of a standard T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template, with loci showing a greater response to 'incorrect' compared to 'correct' gaze shifts (I-V ($p<0.05$ uncorrected) masked by GS – NM($p<0.01$ uncorrected), with spatial extent threshold of 3 voxels) shown superimposed in red on the rendered image. Regions showing a greater response to gaze shifts made by the 'unsocial' compared to the 'social' face (U-S thresholded at $p<0.05$ (uncorrected) masked by GS – NM, thresholded at $p<0.01$ (uncorrected)) with spatial extent threshold of 3 voxels) are shown superimposed in green on the rendered image. Regions of overlap, which show a greater response to 'incorrect' gaze shifts and to 'unsocial' gaze shifts are shown in yellow).*

#### *6.3.2.4 Areas activated by 'incorrect' gaze shifts and 'unsocial' gaze shifts*

I examined whether the regions that show a significant response to 'incorrect' versus 'correct' gaze shifts, were also activated more strongly when gaze shifts were made by the 'unsocial' than the 'social' face. The contrast 'unsocial – social' ($p<0.05$) masked by 'incorrect – correct' ($p<0.01$) revealed areas in the parietal, occipital and frontal cortices that show greater activation to 'incorrect' versus 'correct' gaze shifts, that also show a greater response to gaze shifts made by the 'unsocial' compared to the 'social' face. The parietal areas showing this pattern of activation included the right superior parietal gyrus, the right junction of the traverse and intra parietal sulci,

the right supramarginal gyrus, and the left IPS. In the occipital lobe the region around the left lateral occipital sulcus was revealed by this contrast. In the frontal cortex the areas showing this pattern of activation included the right middle frontal gyrus, and the left inferior frontal sulcus. (See Table 6.1c and Figure 6.4).

**Table 6.1 – Regions activated by incorrect gaze shifts & unsocial gaze shifts**

| | x | y | z | p-unc | Z |
|---|---|---|---|---|---|
| ***a) Incorrect > correct (p<0.05 uncor)masked by GS>NM (p=0.01 uncor)*** | | | | | |
| TPS / SPG / IPS | 12 | -69 | 54 | 0 | 3.81 |
| TPS/SPG/IPS | -18 | -69 | 51 | 0.027 | 1.93 |
| IPS / supramarginal / angular gyrus | -33 | -45 | 39 | 0 | 3.5 |
| supramarginal gyrus / IPS | 48 | -33 | 48 | 0.001 | 3.07 |
| posterior lateral fissure | -48 | -42 | 27 | 0.002 | 2.9 |
| IPS | -24 | -69 | 33 | 0 | 3.47 |
| pSTSh / angular gyrus / superior MOG | 39 | -75 | 33 | 0.001 | 3.25 |
| pSTSh (and MOG) | -39 | -81 | 30 | 0.008 | 2.43 |
| pSTSh | 48 | -60 | 9 | 0.016 | 2.14 |
| STG | 63 | -39 | 18 | 0.003 | 2.78 |
| LOS | -48 | -66 | 0 | 0.004 | 2.68 |
| LOS | 60 | -63 | -6 | 0.006 | 2.51 |
| postcentral gyrus / inferior postcentral sulcus | 51 | -21 | 36 | 0.003 | 2.72 |
| precentral gyrus / IPCS / MFG / IFS | -39 | 0 | 39 | 0.002 | 2.96 |
| MFG / inferior frontal sulcus | -45 | 21 | 33 | 0.003 | 2.75 |
| MFG | -36 | -6 | 66 | 0.006 | 2.52 |
| superior precentral sulcus | -45 | 3 | 54 | 0.016 | 2.14 |
| superior frontal sulcus | 27 | -3 | 51 | 0.003 | 2.72 |
| superior frontal sulcus | -21 | -6 | 54 | 0.009 | 2.36 |
| Superior frontal gyrus | -24 | -9 | 75 | 0.012 | 2.26 |
| short insular gyri | -33 | 21 | 0 | 0.015 | 2.17 |

***Abbreviations:*** *middle occipital gyrus (MOG); lateral occipital sulcus (LOS); middle temporal gyrus (MTG); superior temporal gyrus (STG); horizontal segment of posterior superior temporal sulcus (pSTSh); intra-parietal sulcus (IPS); superior parietal gyrus (SPG); traverse parietal sulcus (TPS); middle frontal gyrus (MFG); superior frontal gyrus (SFG); inferior frontal sulcus (IFS); inferio r precentral sulcus (IPCS);*

**Table 6.1 cont – Regions activated by incorrect gaze shifts & unsocial gaze shifts**

| | x | y | z | p-unc | Z |
|---|---|---|---|---|---|
| ***b) Unsocial > social (p<0.05 uncor) masked by GS> NM (p=0.01 uncor)*** | | | | | |
| TPS/SPG/IPS | 12 | -69 | 54 | 0.002 | 2.96 |
| IPS | -24 | -72 | 36 | 0.007 | 2.43 |
| supramarginal gyrus | 48 | -33 | 48 | 0.008 | 2.4 |
| angular gyrus | -36 | -81 | 33 | 0.026 | 1.95 |
| pSTSh | -42 | -69 | 15 | 0.025 | 1.97 |
| sulcus lunatus/MOG/pSTSh | -36 | -81 | 18 | 0.004 | 2.69 |
| MOG (between pSTSh and LOS) | 39 | -81 | 24 | 0.01 | 2.31 |
| Inferior MOG/LOS | -42 | -69 | -3 | 0.002 | 2.91 |
| LOS | 48 | -54 | -3 | 0.005 | 2.57 |
| Inferior precentral sulcus | -54 | 9 | 27 | 0.005 | 2.55 |
| anterior thalamic nucleus | -9 | -3 | 6 | 0.01 | 2.32 |
| ***c) Unsocial > social (p<0.05 uncor) masked by incorrect > correct (p=0.01 uncor)*** | | | | | |
| TPS/SPG/IPS | 12 | -69 | 54 | 0.002 | 2.96 |
| IPS | -24 | -72 | 36 | 0.007 | 2.43 |
| supramarginal gyrus | 51 | -33 | 48 | 0.007 | 2.45 |
| MFG | 45 | 15 | 45 | 0.004 | 2.63 |
| Inferior MFG | 48 | 33 | 30 | 0.014 | 2.2 |
| IFS | -42 | 21 | 27 | 0.02 | 2.05 |
| LOS | -45 | -66 | -3 | 0.017 | 2.11 |

### *6.3.2.5 'Correct' gaze shifts minus 'incorrect' gaze shifts*

The contrast of 'correct' gaze shifts and 'incorrect' gaze shifts (p<0.001 uncorrected) revealed regions that showed greater activation to 'correct' gaze shifts than 'incorrect' gaze shifts, largely in the medial frontal cortex. These areas include the cingulate gyrus bilaterally, the medial superior frontal gyrus bilaterally, the left posterior orbital gyrus, the right fronto-polar gyrus, the left medial orbital gyrus and olfactory sulcus, and the gyrus rectus bilaterally. The left middle temporal gyrus and the right fusiform gyrus also showed greater activation for 'correct' compared to 'incorrect' gaze shifts. (See Table 6.2a for full details of activated loci).

### *6.3.2.6 'Social' gaze shifts minus 'unsocial' gaze shifts*

The contrast 'social – unsocial' ($p<0.05$), masked by 'gaze shift – no eye-movement' ($p<0.05$), revealed regions that are activated by gaze shifts that show a greater response to gaze shifts made by the 'social' face, than to gaze shifts made by the 'unsocial' face, mainly in the frontal and occipital cortices. The frontal regions included the superior frontal gyrus bilaterally, the lateral orbital gyrus bilaterally, and the left superior pre-central sulcus, while the occipital areas included the left calcarine sulcus, the middle occipital gyrus and lateral occipital sulcus bilaterally. Parts of the temporal lobe also showed this pattern of activation including the middle temporal gyrus bilaterally, and a cluster in right superior temporal gyrus/sulcus. The right hippocampus/parahippocampal gyrus also showed greater bilateral activation to gaze shifts made by the 'social' face. The only parietal region showing this pattern of activation was a cluster in the angular gyrus. (See Table 6.2b for full details of activated loci).

**Table 6.2 – Regions activated by correct gaze shifts & correct gaze shifts**

| | x | y | z | p-unc | Z |
|---|---|---|---|---|---|
| ***a) Correct > Incorrect (p<0.001 uncorrected)*** | | | | | |
| cingulate gyrus | 9 | 30 | -12 | 0 | 4.17 |
| cingulate gyrus | -6 | 33 | -9 | 0 | 3.59 |
| medial superior frontal gyrus | -6 | 63 | 21 | 0 | 4.05 |
| superior frontal gyrus | 15 | 48 | 21 | 0 | 3.41 |
| posterior orbital gyrus | -30 | 36 | -12 | 0 | 3.7 |
| medial orbital gyrus/olfactory sulcus | -12 | 45 | -15 | 0 | 3.49 |
| frontopolar gyri | 3 | 60 | 0 | 0 | 3.49 |
| gyrus rectus | -3 | 42 | -21 | 0 | 3.42 |
| circular insular sulcus | -33 | -15 | 27 | 0 | 3.31 |
| MTG | -66 | -24 | -6 | 0 | 4.34 |
| middle occipital gyrus | 42 | -87 | 0 | 0 | 3.7 |
| fusiform gyrus | 36 | -69 | -12 | 0 | 3.34 |

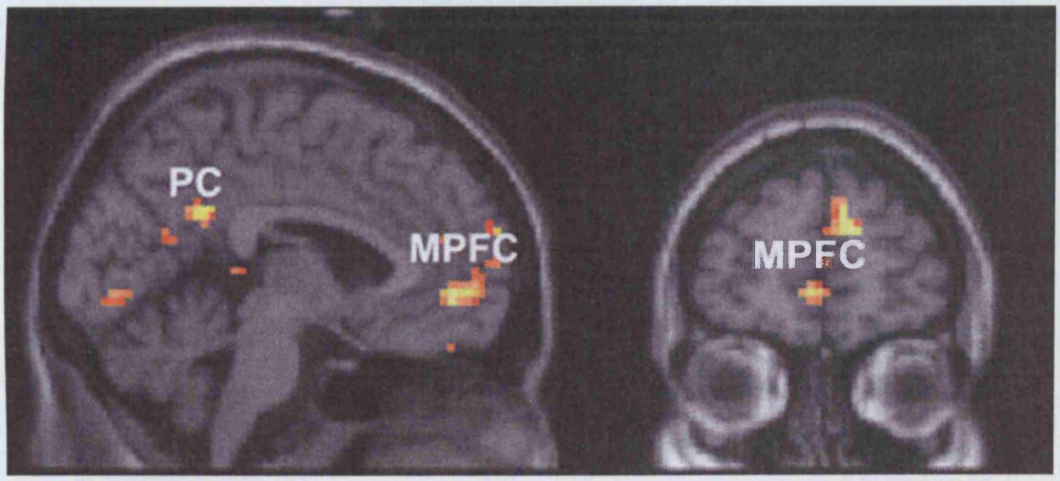
**Table 6.2 cont– Regions activated by correct gaze shifts & social gaze shifts**

| | x | y | z | p-unc | Z |
|---|---|---|---|---|---|
| ***b) Social > unsocial (p<0.05 uncor) masked by GS > NM (p=0.01 uncor)*** | | | | | |
| calcarine sulcus | -18 | -63 | 3 | 0 | 3.74 |
| parahippocampal gyrus/hippocampus | 30 | -36 | -3 | 0.003 | 2.8 |
| lateral orbital gyrus | -39 | 42 | -15 | 0.004 | 2.67 |
| lateral orbital gyrus/orbital sulcus | 33 | 39 | -9 | 0.015 | 2.17 |
| MTG | -57 | -42 | -6 | 0.004 | 2.63 |
| MTG | 51 | -42 | 0 | 0.009 | 2.36 |
| MOG | -48 | -81 | 3 | 0.009 | 2.37 |
| MOG | 48 | -75 | 0 | 0.023 | 1.99 |
| Inferior MOG | -48 | -81 | -6 | 0.013 | 2.22 |
| LOS/inferior MOG | 48 | -72 | -9 | 0.008 | 2.41 |
| LOS | 39 | -69 | 6 | 0.008 | 2.4 |
| superior frontal gyrus | -12 | -9 | 78 | 0.011 | 2.28 |
| superior frontal gyrus | 15 | -24 | 78 | 0.012 | 2.27 |
| superior precentral sulcus | -45 | 12 | 45 | 0.014 | 2.21 |
| superior temporal gyrus/next to STS | 66 | -33 | 6 | 0.027 | 1.92 |
| angular gyrus between pSTSh and IPS | 33 | -69 | 27 | 0.04 | 1.75 |
| ***c) Social > unsocial (p<0.05 uncor) masked by correct > incorrect (p=0.01 uncor)*** | | | | | |
| medial precuneus/cingulated gyrus | 0 | -51 | 30 | 0.001 | 2.97 |
| medial precuneus | 3 | -60 | 18 | 0.013 | 2.21 |
| supraorbital sulcus/SFG/cingulate sulcus | -3 | 48 | -3 | 0.002 | 2.96 |
| SFG | 9 | 54 | 24 | 0.003 | 2.75 |
| SFG/frontopolar gyri | -6 | 63 | 9 | 0.011 | 2.29 |
| SFG | -12 | 39 | 45 | 0.012 | 2.27 |
| gyrus rectus | 0 | 30 | -30 | 0.009 | 2.39 |
| gyrus rectus | 0 | 48 | -24 | 0.018 | 2.09 |
| H-shaped orbital sulcus | -27 | 33 | -9 | 0.011 | 2.3 |
| Inferior temporal gyrus/sulcus | 45 | 0 | -33 | 0.005 | 2.58 |
| MTG | -66 | -21 | -9 | 0.02 | 2.05 |
| anterior MTG | -60 | -3 | -18 | 0.015 | 2.16 |
| lingual gyrus | -3 | -84 | -3 | 0.014 | 2.19 |
| intra/traverse occipital sulcus | -27 | -87 | 3 | 0.026 | 1.94 |

### *6.3.2.7 Areas activated by 'correct' gaze shifts and 'social' gaze shifts*

I examined whether the regions that showed a greater response to the 'correct' than to 'incorrect' gaze shifts, were also activated more strongly when gaze shifts were made by the 'social' than the 'unsocial' face. The contrast 'social – unsocial' ($p<0.05$) masked by 'correct – incorrect' ($p<0.01$) revealed areas that showed this pattern of activation. Several clusters in the medial prefrontal cortex showed this pattern of activation. (See Figure 6.5 and Table 6.2c for full details of activated loci). The medial precuneus, close to the posterior cingulate gyrus and parieto-occipital fissure also showed this pattern of activation, as did two clusters in the left middle temporal gyrus, a cluster in the traverse-occipital sulcus, and a cluster in the right inferior temporal gyrus/sulcus.

***Figure 6.5 – Medial prefrontal cortex and medial precuneus show a greater response to 'correct' gaze shifts and to gaze shifts made by the 'social' face***




*Activity revealed by the contrast between conditions where the gaze shift was made by the 'social' face and those where the 'unsocial' face made the gaze shift, (i.e. S – U) thresholded at $p<0.05$ uncorrected, masked by the contrast between 'incorrect' and 'correct' gaze shifts (i.e. I – V), thresholded at $p<0.01$ (uncorrected), overlaid on a Saggittal and a coronal slice of the standard T1 weighted structural image in the standard space defined by the Montreal Neurological Institute template. The colour scale reflects the t value at each voxel. Regions revealed by this contrast showed greater activation to 'correct' compared to 'incorrect' gaze shifts and also show greater activation to gaze shifts made by the 'social' compared to 'unsocial' face. These regions include the medial prefrontal cortex (MPFC) and the medial precuneus (PC).*

#### *6.3.2.8 Interactions*

I hypothesised that the effects of goal directedness (i.e. 'correct' versus 'incorrect' gaze shifts) on the response to gaze shifts might be greater for gaze shifts made by the 'social' face than for gaze shifts made by the 'unsocial' face due to the greater salience of the social face. Therefore I looked for areas showing an interaction between the direction of the gaze shift and the face making the gaze shift within the regions showing an effect of the goal directedness of the gaze shift, such that this effect was greater for the social face.

Areas showing a greater increase in response to 'incorrect' compared to 'correct' gaze shifts for 'social' than for 'unsocial' faces were revealed by masking the interaction contrast '(SI-SC)-(UI-UC)' ($p<0.05$ uncorrected) with 'incorrect – correct' ($p<0.01$ uncorrected). A few small clusters showing this pattern of activation were found located in the right superior parietal gyrus where the intra and traverse parietal sulci meet, the supramarginal gyrus bilaterally, the right inferior frontal sulcus, and the right precentral gyrus, all of which are part of the fronto-parietal attentional network.

Areas showing a greater increase in response to 'correct' compared to 'incorrect' gaze shifts for 'social' than for 'unsocial' faces were revealed by masking the interaction contrast '(SC-SI)-(UC-UI)' ($p<0.05$) with 'correct – incorrect' ($p<0.01$). One region located around the right middle frontal gyrus and superior frontal sulcus showed this pattern of activation.

### 6.3.3 Eye-tracker data analysis

There were no significant differences between experimental conditions on length of scan path, mean distance between the eye position at each time point, and average eye position. Subject's therefore fixated equally well in all conditions. There was no effect of target location, of the location of the 'social' face, nor of the position of the face making the gaze shift on average eye position. There was also no effect of gaze shift end position on eye position. Differences in eye movements between conditions therefore cannot account for my results.

## 6.4 Discussion

### 6.4.1 Behavioural experiment

As hypothesised, I found a significant effect of both the direction of the gaze shift and of the sociability of face making the shift on reaction times (see Figure 6.2). Faster reaction times in the 'correct' condition suggest that the appearance of the target acted as an exogenous cue that directs attention covertly towards the target location. Consequently subjects were able to detect gaze shift towards this location more quickly and accurately than gaze shifts towards another location. Faster reaction times in the 'social' condition suggests that subjects' attention was covertly attracted to the 'social' face, thus enabling faster detection of the direction of gaze shifts made by the 'social' face. This supports my hypothesis that subjects would be engaged more by the 'social' face than the 'unsocial' face, and the notion that direct gaze is a strongly engaging social stimulus (Von Grunau and Anston, 1995).

### 6.4.2 fMRI experiment

Observation of gaze shifts activated large regions of the temporo-occipital cortex, from the posterior horizontal segment of the superior temporal sulcus to the inferior occipital sulcus, plus several bilateral clusters in the parietal cortex, mostly located around the intra-parietal sulcus (see Results and Figure 6.3). Observing gaze shifts also activated a large region in the left frontal cortex in the precentral gyrus and middle frontal gyrus, around the junction of the inferior precentral sulcus and the inferior frontal sulcus, and a cluster in the left orbital gyrus. Thus, the regions activated by observing gaze shifts in my study included the fronto-parietal network of regions that is activated by shifts of spatial attention (Corbetta et al., 1998;Grosbras et al., 2005;Kato et al., 2001;Nobre et al., 1997) and by making eye-movements (Grosbras et al., 2005). The posterior STS was also activated by gaze perception in my study. Activation of these regions by gaze shifts is consistent with the results of several other studies of gaze perception including a meta analysis of eight other studies (Grosbras et al., 2005;Hoffman and Haxby, 2000;Hooker et al., 2003;Pelphrey et al., 2003;Pelphrey et al., 2004b;Puce et al., 1998;Wicker et al., 1998). Thus, my findings are consistent with the notion that gaze perception involves

the face responsive region in the STS and the spatial attention network in the parietal and frontal cortices (Haxby et al., 2002).

Activation of the occipito-temporal lobe, including the middle temporal gyrus, is most likely a simple response to the motion (of the eyes) in the gaze shift condition, as my baseline lacked any such motion. This region of activation is consistent with the location of area V5/MT, which responds to visual motion (Zeki et al., 1991).

I sought to examine whether the neural response to gaze shifts was modulated by two factors: the social context of the gaze shift (i.e. whether it was made by the socially engaging face or by the 'unsocial' face); and the goal directedness of the gaze shift (i.e. whether it was towards the target or not). I was specifically interested in examining modulation of gaze-perception related activity in the STS, as the STS has already been shown to respond to the perceived intentionality of actions (Pelphrey et al., 2004a), and to have a greater response to gaze shifts when these are not made towards a visible target (Pelphrey et al., 2003). In addition, I identified two different networks that were modulated by these factors in different ways: first, a fronto-parietal network involved in gaze perception, eye movements and shifts of attention described above; second, a network consisting of a set of medial prefrontal regions, and a region in the posterior parietal/cingulate cortex.

#### *6.4.2.1 Superior temporal sulcus*

Bilateral regions of the posterior horizontal segment of the STS, and adjacent middle occipital gyrus, showed a greater response to 'incorrect' compared to 'correct' gaze shifts ($p<0.05$ un-corrected masked by 'gaze shift – no eye movement' at $p<0.01$). This is consistent with the results of Pelphrey et al. (Pelphrey et al., 2003), who found that activity in the STS lasted significantly longer for gaze shifts towards empty locations in space than for gaze shifts towards a target. The posterior STS is involved in predicting the actions of others (Ramnani and Miall, 2004) and Pelphrey and colleagues propose that prolonged activation of the STS observed for 'incorrect' gaze shifts reflects violation of the observer's prediction (Pelphrey et al., 2003). The observer predicts that the face will look towards the target when it appears, and when this occurs their expectations are met. However, when the face shifts its gaze to

another location, the observer's prediction is violated, leading to increased STS activity, perhaps due to reformulation of the observer's expectations about the other's behaviour, or due to the prediction of a second gaze shift from the empty location to the target (Pelphrey et al., 2003). The increased activity in the STS could also reflect the prediction error between the observer's prediction of what the actor is going to do and the actual action observed. This effect appears to be less strong in my experiment than for Pelphrey and colleagues (2003), perhaps because the maximum distance between the target and the end point of an 'incorrect' gaze shift was 90° in my study, whereas in Pelphrey's experiment the target and the end point of an 'incorrect' gaze shift could be as much as 180° apart. A greater discrepancy between the target and the gaze shift could cause even greater activation in the STS.

The left posterior horizontal segment of the STS, and the bilateral middle occipital gyrus, just below the STS, also showed greater activation to gaze shifts made by the 'social' face versus the 'unsocial' face. As with the increased activity for 'incorrect' gaze shifts this increase in activity for the 'unsocial' face can be explained in terms of expectation violation. Eye-contact can signal the intention to communicate (Kampe et al., 2003;Saxe, 2006) and as such the observer might expect the face looking at them to indicate the presence of the target by looking at it, more than they expect the 'unsocial' face to do so. When the 'social' face makes the eye movement this expectation is met, but when the 'unsocial' face makes the gaze shift the expectation is violated leading to increased activity in the STS, which could either reflect the generation of new predictions or the prediction error.

The increased activation of the STS during the 'unsocial' and 'incorrect' conditions is consistent with Kilner's predictive model of the mirror system, which includes the STS (Kilner et al. in submission).

#### *6.4.2.2 Fronto-parietal network*

Activity in a network of parietal and frontal regions, mainly located around the intra parietal sulcus and the precentral gyrus and sulcus, was greater in response to 'incorrect' gaze shifts, than to gaze shifts that correctly acquired the target ('correct' gaze shifts) ($p<0.05$ uncorrected masked by 'gaze shift – no eye movement' at

$p<0.01$). This is consistent with Pelphrey et al. (2003) where a greater response was found in the intra parietal sulcus to 'incorrect' versus 'correct' gaze shifts. A similar network of fronto-parietal regions also showed greater activation for gaze shifts made by the unsocial, compared to the 'social' face ($p<0.05$ uncorrected masked by 'gaze shift – no eye movement' at $p<0.01$).

This fronto-parietal network is also activated by execution of eye movements, and is thought to be part of an oculomotor "mirror system" (Grosbras et al., 2005). It therefore appears that this oculomotor mirror system showed a greater response to 'incorrect' gaze shifts, and greater activation to gaze shifts when they were made by the 'unsocial' face (though to a lesser extent than for 'incorrect' gaze shifts) (see Figure 6.4). If as proposed by Kilner and colleagues the mirror system acts in a predictive manner, the increased activation in this front-parietal network could reflect either a reformulation of the observer's prediction or the prediction error when the observer's expectation is violated in the 'incorrect' and 'unsocial' conditions, as does the increased activation observed in the STS in these conditions.

However, many studies have also shown that this fronto-parietal network is involved in shifting spatial attention (Corbetta et al., 1998;Grosbras et al., 2005;Kato et al., 2001;Nobre et al., 1997). (See Figure 6.3). Thus, the difference in activation seen in this attentional network between the different conditions can simply be accounted for by the number of shifts of attention that occur in each condition.

In both 'correct' and 'incorrect' conditions the subject's covert attention was exogenously shifted to the target location by the appearance of the target (see behavioural results). Gaze automatically induces reflexive shifts in spatial attention in the direction of gaze, thus the gaze shift that follows the appearance of the target will automatically shift the subject's attention in the direction of the gaze shift (Driver et al., 1999;Langton and Bruce, 1999). In the 'correct' condition, the gaze shift directs the subject's attention towards the target location, but 'incorrect' gaze shifts direct attention away from the target. Thus the 'incorrect' condition involves a second reallocation of attention, which could account for the increased activity seen in the spatial attention network.

Some parts of the fronto-parietal attentional network also showed an interaction between the effects of gaze shift direction and the face making the gaze shift, such that the increase in activity seen during 'incorrect' compared to 'correct' gaze shifts is greater when the gaze shifts are made by the 'social' face. The social face is an extremely salient stimulus, thus it is likely that gaze shifts made by the social face attract the subject's attention more strongly that gaze shifts made by the unsocial face, leading to a stronger reallocation of attention from the target location in the direction of the gaze shift, in the social condition, and thus a greater increase in activation in these attentional areas.

The increased activation to gaze shifts made by the 'unsocial' face, compared to the 'social' face, that I observed, may also be accounted for by a difference in the number of shifts of attention occurring in the two conditions. The direct gaze of the 'social' face is a very salient stimulus and attracts attention (Von Grunau and Anston, 1995), regardless of which face makes the gaze shift (as demonstrated by my behavioural data). The subject's attention is then attracted by the gaze shift. In the 'unsocial' condition this involves a shift of attention from the 'social' to the 'unsocial' face, but when the 'social' face makes the gaze shift this additional attentional shift does not occur as attention is already on the 'social' face. Reallocation of attention from the 'social' to the 'unsocial' face could account for the increased activity seen in areas involved in spatial attention in response to gaze shifts made by the 'unsocial' face.

Unfortunately, in this experiment, it is not possible to distinguish between these two alternative explanations for the increased activity seen in the fronto-parietal occulomotor network during the 'incorrect' and 'unsocial' gazeshifts.

#### *6.4.2.3 Medial prefrontal cortex*

It has been proposed that the medial prefrontal cortex is involved in representing shared attention and goals, and more specifically "triadic relations between Me, You, and This", i.e. the subject, a second person, and an object (Saxe, 2006). The only relevant neuroimaging study to date found that joint attention is associated with activity in the medial prefrontal cortex (Williams et al., 2005). Activation of a medial

prefrontal network by 'correct' (compared to 'incorrect') gaze shifts in my experiment is consistent with this region's involvement in joint attention, because during the 'correct' conditions the attention of both the subject and the face stimulus were directed towards the target, so the subject experiences joint attention with the face. This joint attention is covert as the subjects maintained fixation and did not move their eyes towards the target. In contrast, in the 'incorrect' condition the subject's attention was attracted to the target but then the face stimuli shifted their eyes, and by implication their attention, to a different location. Thus, in this situation, the subject did not experience joint attention, so activity in the medial prefrontal cortex might not be expected.

Similar regions were activated by 'correct', compared to 'incorrect', gaze shifts and by gaze shifts made by the 'social' versus the 'unsocial' face. These included areas in the medial prefrontal cortex and also a cluster in the medial precuneus (see Figure 6.5). Like the medial prefrontal cortex, the medial precuneus was also activated by joint attention in the experiment described above (Williams et al., 2005). Thus is appears that the network of areas involved in joint attention were activated when the face made 'correct' gaze shifts and also when gaze shifts were made by the 'social' face.

Such modulation of prefrontal activity by the sociability of the face is consistent with a previous experiment where virtual characters on a screen looked at the subject or at an imaginary other, and made socially relevant, for example a smile, or arbitrary facial movements (Schilbach et al., 2005). The facial movements made by the character looking at the subject, the equivalent to the 'social' face in my experiment, elicited greater activation in the anterior dorsal medial prefrontal cortex than movements made by the face with averted gaze, equivalent to my 'unsocial' face. Thus activation in the medial prefrontal cortex appears to reflect the feeling of personal involvement.

Direct gaze is a very salient and engaging social stimulus (Von Grunau and Anston, 1995) and it indicates that you are the object of another's attention. Direct or mutual gaze is a case of joint attention, involving just the two individuals, (dyadic attention), and often signals the intention to communicate, leading to triadic joint attention

(Saxe, 2006). Thus, perhaps the direct gaze of the 'social' face in my experiment makes the gaze shifts made by that face feel like intentional communicative gestures (Kampe et al., 2003), enhancing the feeling of joint attention, whereas when the 'unsocial' face makes a gaze shift there is no apparent intention to communicate. Perhaps the greater activity in the medial prefrontal cortex for gaze shifts made by the 'social' face reflects this perception of the gaze shift as an intentional communicative gesture.

## 6.5 Conclusion

I have demonstrated that both behavioural and neural responses to gaze shifts are modulated by the social context and the goal directedness of that gaze shift. Reaction times were significantly faster in response to 'correct' and 'social', compared to 'incorrect' and 'unsocial', gaze shifts respectively. I found significantly greater activation in the fronto-parietal network, and in parts of the posterior STS, in response to 'incorrect' and 'unsocial', compared to 'incorrect' and 'social', gaze shifts respectively. I suggest that the increased STS activity occurs because the 'incorrect' and 'unsocial' gaze shifts are unexpected, and that it reflects a reformulation of the observer's prediction or the prediction error, consistent with the proposal that the mirror system acts in a predictive manner. The increased activity in the fronto-parietal network may also reflect the prediction error or the generation of new predictions. Alternatively, the increase fronto-parietal activation may simply have occurred because 'incorrect' and 'unsocial' gaze shifts induce additional shifts of attention compared to 'correct' and 'social' gaze shifts. Further work will be needed to distinguish between these two possible explanations. Conversely I found greater activation in the MPFC and precuneus, in response to 'correct' and 'social' compared to 'incorrect' and 'unsocial' gaze shifts respectively. I suggest that this activity reflects the experience of joint attention elicited by 'correct' and 'social' gaze shifts. By having both the 'social' and the 'unsocial' face on screen at all times, I was able to control for the presence of direct and averted gaze, and specifically examine the effects of social context on the response to gaze shifts.

# CHAPTER 7: THE SAME BRAIN AREAS ARE INVOLVED IN MONITORING THE CONSEQUENCES OF YOUR OWN AND ANOTHER PERSON'S ACTIONS

## 7.1 Introduction

As described in the Introduction, there is much evidence animals use an efference copy of their motor commands sent from the motor areas controlling the actions, in parallel with the motor signals, to predict and attenuate the sensory consequences of their own actions and to distinguish the sensory consequences of their own actions from externally produced sensory stimuli (Wolpert and Miall, 1996). As well as being able to predict the consequences of their own actions and thus recognise and attenuate self-produced sensory stimuli, animals should also be able to monitor and predict the actions of others, and the sensory consequences of these actions. Such an ability would serve to distinguish them from sensory stimuli with an environmental cause, as events caused by others will have different implications to events with an environmental cause. In this study I therefore sought to examine whether the same neural systems are involved in monitoring the sensory consequences of our own actions and in monitoring the sensory consequences of another's actions. I also sought to examine whether the response to sensory stimuli differed depending on whether the stimulus is self- generated, generated by another person, or externally generated.

Subjects performed a task in which they had to monitor the relationship between an auditory stimulus and an action, namely a button press, which was either performed by themselves or another person (the experimenter). The degree of temporal contingency between the button press and the sound was manipulated. Subjects were asked to judge whether the sounds they heard, in a block of 10 trials, were contingent upon the timing of the button press, i.e. were the sounds predictable on the basis of the timing of the button press. There were three levels of predictability/contingency: 'predictable', 'partially predictable', and 'unpredictable'. To control for the effects of contingency/predictability per se, subjects were also presented with blocks of externally-generated sounds, where they had to judge the degree of contingency between the sounds and the disappearance of a white dot on screen. Thus, my

experiment consisted of a 3 x 3 factorial design, with 2 independently manipulated factors: agency and contingency/predictability, enabling us to examine effects of self- and other-generated actions on the response to sensory stimuli beyond any effect of stimulus predictability, and to examine the effects of stimulus predictability/contingency per se, and to examine interactions between the two.

Observation of the actions of others is known to activate the same brain regions involved in action execution (Buccino et al., 2001;Rizzolatti and Craighero, 2004), and there is also evidence that the action control system is involved in anticipating or predicting the actions of others (Kilner et al., 2004;Ramnani and Miall, 2004). In addition, several studies have demonstrated modulation of sensory activity during action observation (Avikainen et al., 2002;Grezes et al., 2003;Mottonen et al., 2005;Pekkola et al., 2005;Rossi et al., 2002). Therefore, I hypothesised that the regions involved in monitoring our own actions and their sensory consequences, would also be engaged when monitoring the sensory consequences of the actions of others.

Several studies have demonstrated attenuation of the response to self-produced auditory stimuli (Curio et al., 2000;Martikainen et al., 2005;Numminen et al., 1999;Schafer and Marcus, 1973). Thus, I hypothesised that activation of the auditory cortex would be greater in response to externally generated tones compared to self-generated tones. There is evidence that the degree of attenuation depends on the closeness of the match between the sensory consequences of the action predicted by the internal forward model and the actual sensory feedback from that action. Blakemore and colleagues found that the perceived intensity of tactile stimulation increased as the discrepancy, in time and space, between an action and its sensory consequences increased (Blakemore et al., 1999a). Thus I hypothesised that auditory cortex activation would vary with the degree of contingency between the button press and the tone, when the subject pressed the button. There is also evidence that the attenuation of the response to self-generated sensory stimuli is due in part to stimulus predictability (Blakemore et al., 1998a;Schafer et al., 1981). Any attenuation due to stimulus predictability per se should be equally present in the self-generated, other-generated, and externally generated conditions.

I had no prior hypothesis about the auditory response to other-generated stimuli. Previous studies have demonstrated modulation of the activity in sensory cortices by action observation in the absence of sensory stimulation (Avikainen et al., 2002;Grezes et al., 2003;Mottonen et al., 2005;Pekkola et al., 2005;Rossi et al., 2002), supporting the idea that the mirror system uses the same forward model used to predict the sensory consequences of our own action to predict the sensory consequences of the actions of others (Kilner et al. in submission). (See General Introduction for a review). However, these studies did not directly address how this sensory prediction may modulate the response to other-generated stimuli. It may be that sensory stimuli generated by the actions of others is of greater significance than externally generated stimuli, perhaps because they may be caused by predators or prey or potential mates, in which case the response to stimuli caused by others may be enhanced, rather than attenuated. Or it may be that sensory stimuli caused by others that I can predict is attenuated in a similar way to self-generated sensory stimuli, enabling us to concentrate our attention on unexpected sensory stimuli.

## 7.2 Materials and Methods

### 7.2.1 Subjects

Fourteen normal volunteers (7 male and 7 female, aged 19 to 31, mean 24.7, SD 3.7) gave written informed consent to participate in the study, which was approved by the Institute of Neurology and National Hospital for Neurology and Neurosurgery Joint Ethics Committee.

### 7.2.2 Paradigm

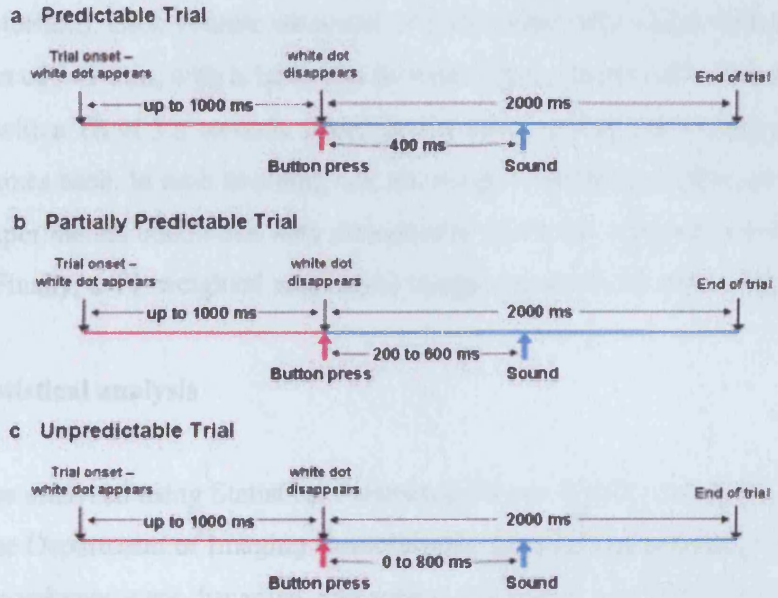
Two experimental factors were manipulated independently in a blocked design: 1) the predictability of the tone; and 2) agency, i.e. whether the subject, another person, or no one made a self generated movement.

Each block consisted of 10 trials. At the start of each trial a white dot appeared and remained on the screen for up to 1 second. During this time either the subject ('subject' condition), or the experimenter ('other' condition), were required to make a self-generated button press, or no one made a button press ('no agent' condition). The experimenter sat next to the subject in the scanner room, and their hand rested next to the subject's hand on a tray-table positioned over the subject's body. The subject was able to see both their own hand and the experimenter's hand at all times during the experiment. In the 'subject' and 'other' condition the white dot disappeared following the button press. In the 'no agent' condition the white dot would spontaneously vanish at a random time up to 1 second after its appearance. There was then a 800ms time window, before the end of the trial, during which a sound was presented. The sound heard consisted of 0.2 seconds of Gaussian noise with a frequency of 44100 Hz (created in Matlab from a normal distribution with mean zero, variance one and standard deviation one).

The predictability of the timing of the sound relative to the button press/ disappearance of the white dot varied between blocks. The sound could be totally predictable ('predictable' blocks), in which case it occurred exactly 400 ms after the button press in the 'subject' and 'other' conditions, or the disappearance of the white

dot in the 'no agent' conditions. Or the sound could be unpredictable to a varying degree: in some blocks (partially predictable blocks) the sound occurred 200 – 600ms (fixed distribution) after the button press or the disappearance of the white dot, and in some blocks (unpredictable blocks) the sound occurred randomly at any time up to 800 ms after the button press or the disappearance of the white dot. There was then a pause and the next trial began 3 seconds after the onset of the previous trial.

***Figure 7.1 – Trial Structure***




The experiment thus consisted of nine conditions constituting a 3 x 3 factorial:

| Agency | Predictability of Sound | | |
|---|---|---|---|
| | Predictable (P) | Partially (PP) | Unpredictable (U) |
| Subject (S) | **S P** | **S PP** | **S U** |
| Other (O) | **O P** | **O PP** | **O U** |
| No Agent (N) | **N P** | **N PP** | **N U** |

Each type of block was presented twice per scanning run. At the end of each block of ten trials, subjects were asked, in a forced choice task, whether or not the sounds in the block had been contingent on the button press, in the 'subject' and 'other'

conditions, or on the disappearance of the white dot in the 'no agent' conditions. Subjects responded by pressing 'yes' or 'no' on a keypad, and their responses were recorded.

### 7.2.3 Imaging

A 1.5T Siemens ALLEGRA system (Siemens, Erlangen) was used to acquire gradient-echo echo-planar T2* weighted images with Blood Oxygenation Level Dependent (BOLD) contrast. (See Chapter 2: fRMI Methods for details of BOLD signal detection). Each volume consisted of forty 2 mm axial slices with in-plane resolution of 3x3 mm, with a 1mm gap between slices, positioned to cover the whole cortexn with a TR of 3.6 seconds. Imaging was performed in three scanning runs of 150 volumes each. In each scanning run, six image volumes preceding presentation of the experimental conditions were discarded to allow for magnetic saturation effects. Finally, a T1-weighted anatomical image was acquired from each subject.

### 7.2.4 Statistical analysis

Data were analysed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm). The initial six volumes were discarded, and subsequent image volumes then realigned (Friston et al., 1995), spatially normalised (Ashburner and Friston, 1999) to the standard space defined by the Montreal Neurological Institute template (Mazziotta et al., 1995) and smoothed with a Gaussian kernel of 6 mm full-width half maximum. (See Chapter 2: fMRI Methods for details of realignment, normalisation and smoothing). Voxels activated during the experiment were identified using a general linear model that included the nine experimental conditions and the question at the end of each block. The sounds were modelled as events with duration 200 ms. The question was modelled as a boxcar waveform of a few seconds in length (the exact length depended on the subject's response time). Voxels activated during the experiment were identified using a statistical model that comprised ten delayed boxcar waveforms for each scanning run. These represented the mean activity evoked in the nine experimental conditions, and the mean activity during the question at the end of each block. High-pass filtering (cut-off 128 s) removed low-

frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. (See Chapter 2: fMRI Methods for details of statistical analysis). The resulting parameter estimates for the nine regressors, representing the nine block types, at each voxel were then entered into a second level analysis where subject served as a random effect in a within-subjects ANOVA. The main effects and interactions between conditions were then specified by appropriately weighted linear contrasts and determined using the t-statistic on a voxel-by-voxel basis. A statistical threshold of $p<0.05$, corrected for multiple comparisons across the entire brain volume, was used except for regions that were hypothesized a priori, where a threshold of $p<0.001$, uncorrected for multiple comparisons was used.

## 7.3 Results

### 7.3.1 Behavioural ratings

In a forced-choice task at the end of each block subjects were asked to say whether the sounds they heard were contingent upon the button press or the disappearance of the white dot, i.e. whether the sounds were predictable or not. Subject's had to answer either 'yes' or 'no' using a key pad and their answers were recorded.

**Table 7.1 – Proportion of times (%) each type of block was rated as 'contingent upon button press or disappearance of white dot' i.e. as predictable, by the subject, (i.e. proportion of times subjects answered 'yes').**

| Sub. No. | Predictable | | | Partially Predictable | | | Unpredictable | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Subject* | *Other* | *No agent* | *Subject* | *Other* | *No agent* | *Subject* | *Other* | *No agent* |
| 1 | *100* | *100* | *100* | *50* | *83* | *100* | *0* | *0* | *0* |
| 2 | *100* | *100* | *100* | *75* | *75* | *75* | *0* | *0* | *25* |
| 3 | *100* | *100* | *25* | *0* | *50* | *25* | *0* | *0* | *50* |
| 4 | *100* | *100* | *67* | *67* | *67* | *67* | *17* | *67* | *50* |
| 5 | *75* | *75* | *50* | *0* | *75* | *25* | *25* | *0* | *0* |
| 6 | *100* | *100* | *100* | *33* | *67* | *50* | *0* | *17* | *0* |
| 7 | *67* | *100* | *67* | *50* | *33* | *67* | *17* | *50* | *0* |
| 8 | *100* | *75* | *100* | *100* | *75* | *50* | *50* | *0* | *25* |
| 9 | *100* | *100* | *83* | *33* | *50* | *67* | *17* | *33* | *50* |
| 10 | *100* | *83* | *67* | *83* | *67* | *33* | *33* | *50* | *50* |
| 11 | *100* | *100* | *100* | *67* | *83* | *33* | *17* | *33* | *50* |
| 12 | *83* | *100* | *83* | *0* | *17* | *83* | *17* | *17* | *17* |
| 13 | *83* | *50* | *100* | *83* | *33* | *33* | *0* | *33* | *17* |
| 14 | *100* | *67* | *33* | *33* | *67* | *17* | *17* | *0* | *17* |
| mean | 93 | 89 | 77 | 48 | 60 | 52 | 15 | 21 | 25 |
| **mean** | **86.5** | | | **53.4** | | | **20.4** | | |

'Predictable' blocks, where the sound occurred exactly 400ms after the button press or disappearance of the white dot, were rated as contingent/predictable on 86.5% of occasions (SD = 19.9%). In contrast 'unpredictable' blocks, where the sound

occurred anytime up to 800ms after the button press or the disappearance of the white dot, were rated as contingent/predictable on 20.4% of occasions (SD=19.9%). 'Partially predictable' blocks, where the sound occurred between 200 and 400 ms after the button press or the disappearance of the white dot, were rated as contingent/predictable on 53.4% of occasions (i.e. at chance level) (SD=26.5%). A 3 x 3 ANOVA showed a significant effect of predictability on the proportion of times each block type was rated as 'contingent/predictable' ($F=103.73$, $p = 0.000$). These behavioural results show that my manipulation of the predictability of the sound within a block, by varying the time delay between the sounds and the button press/disappearance of white dot, worked as expected. The same 3 x 3 ANOVA revealed no significant effect of agency on contingency rating ($F=1.14$, $p=0.33$), nor any significant interaction between predictability and agency ($F=1.68$, $p = 0.19$).

### 7.3.2 fMRI results

#### 7.3.2.1 Effects of agency

##### *7.3.2.1.1 Subject > no agent*

Comparison of the conditions when the subject pressed the button to trigger the sound, with the 'no agent' conditions, when neither the subject nor the experimenter pressed the button, and the white dot spontaneously disappeared, revealed several regions showing significantly ($p<0.05$ FDR-corrected) greater activation during the 'subject' versus 'no agent' conditions. The main areas showing this pattern of activation were motor regions including the right primary motor cortex (M1), the right premotor cortex (PMC), the bilateral supplementary motor area (SMA), and the cerebellum (mostly medially). The left insula, dorsal medial prefrontal cortex (dMPFC) (the anterior superior frontal gyrus), the right temporal pole, the right lateral orbital gyrus, the caudate, and the left post central gyrus also showed greater activation during the 'subject' conditions compared to the 'no agent' conditions. (See Table 7.2 for full details of all activated loci). The opposite contrast revealed no regions that showed significantly greater activation during the 'no agent' conditions than during the 'subject' conditions, even when the threshold was lowered to $p<0.001$ uncorrected.

**Table 7.2 - Subject > No Agent (p<0.05 FDR-corrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| cerebellum (lateral) | -36 | -51 | -33 | 0.019 | 0 | 4.1 |
| precentral gyrus (PMC) | 39 | -12 | 51 | 0.022 | 0 | 4 |
| precentral gyrus (PMC) | 27 | -15 | 51 | 0.027 | 0 | 3.91 |
| precentral gyrus (PMC) | 45 | -18 | 63 | 0.045 | 0 | 3.63 |
| precentral gyrus/central sulcus (M1) | 36 | -27 | 57 | 0.027 | 0 | 3.91 |
| posterior superior frontal gyrus (SMA) | -3 | -3 | 54 | 0.012 | 0 | 4.82 |
| cerebellum (medial) | 3 | -69 | -12 | 0.007 | 0 | 5.16 |
| cerebellum | -21 | -57 | -15 | 0.03 | 0 | 3.85 |
| cerebellum | -33 | -69 | -24 | 0.037 | 0 | 3.73 |
| cerebellum | 42 | -54 | -30 | 0.048 | 0 | 3.58 |
| cerebellum | -12 | -42 | -36 | 0.05 | 0 | 3.53 |
| insuka | -36 | 0 | 15 | 0.015 | 0 | 4.6 |
| superior frontal gyrus (dMPFC) | 9 | 60 | 27 | 0.017 | 0 | 4.3 |
| superior frontal gyrus (dMPFC) | -3 | 42 | 48 | 0.022 | 0 | 4.01 |
| superior frontal gyrus ( near cingulate sulcus) | 12 | 48 | 18 | 0.04 | 0 | 3.7 |
| inferior temporal gyrus(temporal pole) | 45 | 6 | -42 | 0.017 | 0 | 4.22 |
| middle temporal gyrus(temporal pole) | 54 | 9 | -36 | 0.04 | 0 | 3.69 |
| precuneus (subparietal sulcus) | 15 | -51 | 39 | 0.042 | 0 | 3.67 |
| central sulcus/post central gyrus | -54 | -24 | 45 | 0.017 | 0 | 4.19 |
| superior post central sulcus | 24 | -45 | 63 | 0.033 | 0 | 3.79 |
| angular gyrus | 45 | -51 | 42 | 0.038 | 0 | 3.72 |
| lateral orbital gyrus | 42 | 48 | -6 | 0.019 | 0 | 4.09 |
| hippocampus | -33 | -33 | -6 | 0.029 | 0 | 3.87 |
| caudate | 18 | 3 | 21 | 0.035 | 0 | 3.76 |
| pulvinar | 24 | -30 | 3 | 0.039 | 0 | 3.71 |

#### *7.3.2.1.2 Subject > Other*

Comparison of the conditions, when the subject pressed the button, compared to the conditions when the experimenter pressed the button, revealed regions that showed greater activation during the 'subject' versus 'other' conditions. The main regions

showing this pattern on activation included the SMA (i.e. the posterior superior frontal gyrus, down to the cingulate sulcus), the right primary (M1) and pre-motor cortex (PMC), the cerebellum, the pars opercularis of inferior frontal gyrus bilaterally, and the insula bilaterally.

**Table 7.3 - Subject > Other (p<0.05 FDR-corrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| posterior superior frontal gyrus (SMA) | -3 | -6 | 57 | 0.001 | 0 | 5.64 |
| posterior superior frontal gyrus (SMA) | 9 | -6 | 75 | 0.048 | 0 | 3.58 |
| precentral gyrus (central sulcus) (M1) | 48 | -12 | 57 | 0.014 | 0 | 4.13 |
| precentral gyrus (PMC) | 33 | -18 | 69 | 0.015 | 0 | 4.07 |
| inferior frontal gyrus (vPM) | 60 | 12 | 12 | 0.010 | 0 | 4.28 |
| inferior frontal gyrus (vPM) | -60 | 3 | 12 | 0.080 | 0.001 | 4.04 |
| cerebellum (medial) | 3 | -66 | -12 | 0.001 | 0 | 5.08 |
| cerebellum (medial) | 21 | -60 | -21 | 0.001 | 0 | 4.99 |
| cerebellum | -24 | -57 | -30 | 0.040 | 0 | 3.69 |
| cerebellum | -48 | -54 | -36 | 0.050 | 0 | 3.56 |
| circular insular sulcus | -51 | 0 | 3 | 0.014 | 0 | 4.1 |
| short insular gyri | 51 | 3 | -3 | 0.016 | 0 | 4.05 |
| central sulcus (post central gyrus) | 33 | -27 | 57 | 0.005 | 0 | 4.51 |
| supramarginal gyrus | 63 | -33 | 45 | 0.033 | 0 | 3.78 |
| parahippocampal gyrus/hippocampus | 21 | -6 | -36 | 0.040 | 0 | 3.69 |
| cuneus | 0 | -84 | 18 | 0.044 | 0 | 3.64 |
| putamen | 33 | 3 | 0 | 0.050 | 0 | 3.57 |

#### *7.3.2.1.3 Subject > Other and Subject > No Agent (see Figure 7.2a & b)*

Similar regions were revealed by the contrasts 'subject' – 'other' and 'subject' – 'no agent' ,thus I specifically looked for areas that showed significantly greater activation to 'subject' compared with 'other' conditions and to 'subject' compared with 'no agent' conditions as revealed by the contrast [('subject' – 'other') masked by ('subject' - 'no agent')]. The main regions showing this pattern of activation were the cerebellum, the insula bilaterally, the SMA (i.e. the medial posterior superior

frontal gyrus), and the right premotor and primary motor cortex. (See Table 7.4 for full details of activated loci).

**Table 7.4 - Subject - Other (p<0.001 uncor) masked by Subject – No Agent (p<0.01 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| posterior superior frontal gyrus (SMA) | -3 | -6 | 57 | 0.001 | 0 | 5.64 |
| posterior superior frontal gyrus (SMA) | 9 | -6 | 75 | 0.048 | 0 | 3.58 |
| central sulcus (M1) | 33 | -27 | 57 | 0.005 | 0 | 4.51 |
| central sulcus (M1) | 45 | -24 | 63 | 0.032 | 0 | 3.79 |
| precentral gyrus (PMC) | 48 | -12 | 57 | 0.014 | 0 | 4.13 |
| precentral gyrus (PMC) | 33 | -18 | 69 | 0.015 | 0 | 4.07 |
| cerebellum (medial) | 3 | -66 | -12 | 0.001 | 0 | 5.08 |
| cerebellum | 21 | -60 | -21 | 0.001 | 0 | 4.99 |
| cerebellum | -24 | -57 | -30 | 0.04 | 0 | 3.69 |
| cerebellum | 48 | -51 | -36 | 0.051 | 0 | 3.56 |
| cerebellum | -9 | -51 | -18 | 0.076 | 0 | 3.32 |
| cerebellum | -9 | -66 | -30 | 0.081 | 0.001 | 3.28 |
| insula | -51 | 0 | 3 | 0.014 | 0 | 4.1 |
| Short insular gyri | 51 | 3 | -3 | 0.016 | 0 | 4.05 |
| supramarginal gyrus | 63 | -33 | 45 | 0.033 | 0 | 3.78 |
| parahippocampal gyrus/hippocampus | 21 | -6 | -36 | 0.04 | 0 | 3.69 |

#### *7.3.2.1.4 Other > No Agent*

Areas showing greater activation in the 'other' condition compared to the 'no agent' condition were revealed by the contrast ['other' – 'no agent']. Large areas of the occipito-temporal cortex showed this pattern of activation bilaterally, including the middle occipital gyrus, the lateral occipital sulcus, the middle temporal gyrus, the superior temporal sulcus and the posterior calcarine sulcus. Other regions showing greater activation during the 'other' condition, than during the 'no agent' condition, included a large cluster in the medial precuneus, several clusters in the parietal lobe, the dorsal medial prefrontal cortex (dMPFC) (the anterior prefrontal gyrus) and the cerebellum. (See Table 7.5 for full details of activated loci.)

**Table 7.5 - Other > No Agent (p<0.05 FDR-corrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| middle occipital gyrus/los | 51 | -78 | 0 | 0 | 0 | 6.37 |
| middle occipital gyrus | 30 | -93 | 9 | 0.002 | 0 | 4.44 |
| middle occipital gyrus/los | -54 | -66 | 18 | 0 | 0 | 5.75 |
| middle occipital gyrus | -18 | -99 | 21 | 0 | 0 | 5.28 |
| superior occipital gyrus | 24 | -90 | 33 | 0.001 | 0 | 4.78 |
| superior occipital gyrus | -15 | -87 | 42 | 0.005 | 0 | 4.17 |
| calcarine sulcus/gyrus descendens(V3) | 12 | -87 | 3 | 0.002 | 0 | 4.49 |
| gyrus descendens/calcarine sulcus(V3) | -9 | -96 | 0 | 0.007 | 0 | 3.99 |
| lingual gyrus | 12 | -78 | -12 | 0.001 | 0 | 4.91 |
| lingual gyrus | -12 | -87 | -15 | 0.013 | 0 | 3.67 |
| collateral sulcus/fusiform gyrus | 27 | -69 | -6 | 0.002 | 0 | 4.49 |
| collateral sulcus/fusiform gyrus | -27 | -69 | -3 | 0.025 | 0 | 3.34 |
| fusiform gyrus/cerebellum | -42 | -54 | -21 | 0.008 | 0 | 3.93 |
| Cerebellum | 6 | -75 | -24 | 0.009 | 0 | 3.88 |
| Cerebellum | 48 | -63 | -27 | 0.009 | 0 | 3.87 |
| Cerebellum | -24 | -87 | -24 | 0.007 | 0 | 3.95 |
| superior parietal gyrus/ips | 12 | -63 | 66 | 0.003 | 0 | 4.34 |
| ips/superior parietal gyrus | -36 | -45 | 60 | 0.003 | 0 | 4.27 |
| superior parietal gyrus | -30 | -54 | 66 | 0.009 | 0 | 3.88 |
| angular gyrus | 51 | -69 | 42 | 0.01 | 0 | 3.83 |
| angular gyrus | 33 | -78 | 36 | 0.034 | 0.001 | 3.18 |
| pSTS/angular gyrus | 57 | -60 | 18 | 0.005 | 0 | 4.16 |
| superior temporal sulcus | 60 | -36 | 3 | 0.009 | 0 | 3.84 |
| middle temporal gyrus | -54 | -30 | -6 | 0.005 | 0 | 4.14 |
| STS (temporal pole) | -39 | 3 | -24 | 0.006 | 0 | 4.07 |
| STG (temporal pole) | 30 | 18 | -33 | 0.015 | 0 | 3.61 |
| precuneus/subparietal sulcus | 3 | -63 | 42 | 0.001 | 0 | 4.78 |
| superior frontal gyrus (dMPFC) | 3 | 57 | 21 | 0.007 | 0 | 3.97 |
| superior frontal gyrus (dMFPC) | 3 | 48 | 36 | 0.011 | 0 | 3.77 |
| superior frontal gyrus | 12 | 39 | 54 | 0.003 | 0 | 4.34 |
| superior frontal gyrus | 15 | 15 | 66 | 0.018 | 0 | 3.51 |
| cingulate gyrus | 0 | -21 | 42 | 0.009 | 0 | 3.84 |
| subcentral gyrus | 51 | -21 | 21 | 0.011 | 0 | 3.77 |
| middle frontal gyrus | 42 | 3 | 57 | 0.025 | 0 | 3.35 |

The opposite comparison revealed a few regions which showed less activation during the 'other' compared to 'no agent' conditions. These clusters were found in the cuneus, the inferior frontal gyrus and the post central gyrus. However these clusters were not significant at $p<0.05$ FDR corrected.

#### *7.3.2.1.5 Other > Subject*

Large areas of the occipito-temporal cortex bilaterally showed significantly greater activation to the 'other' compared to 'subject' conditions (as revealed by the contrast ['other' - 'subject']), including the middle occipital gyrus, superior occipital gyrus, lateral occipital sulcus, lingual gyrus, collateral sulcus, middle temporal gyrus, and the superior temporal sulcus. Several parietal regions also showed this pattern of activation bilaterally, including the parieto occipital fissure, superior parietal gyrus, the angular gyrus, and the intra-parietal sulcus. (See Table 7.6 for full details of activated loci).

#### *7.3.2.1.6 Other > Subject and Other > No Agent (see Figure 7.2a)*

Similar regions were revealed by the contrasts 'other' –'no agent' and 'other' – 'subject', thus I specifically looked for areas that showed significantly greater activation to 'other' compared with 'subject' conditions and to 'other' compared 'no agent' conditions as revealed by the contrast [('other' – 'subject') masked by ('other' - 'no agent')]. This contrast revealed large bilateral regions of the occipito-temporal cortex, largely around the middle occipital and posterior middle temporal gyri, which showed this pattern on activation. Several clusters in the parietal cortex also showed this pattern of activation bilaterally. (See Table 7.7 for full details of activated loci).

**Table 7.6 - Other > Subject (p<0.05 FDR-corrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| middle occipital gyrus (V5) | 48 | -75 | 3 | 0 | 0 | 5.74 |
| middle occipital gyrus (V5) | -48 | -72 | 6 | 0 | 0 | 5.48 |
| middle occipital gyrus | -45 | -75 | -9 | 0.02 | 0 | 3.69 |
| middle occipital gyrus | 30 | -93 | 12 | 0.001 | 0 | 5.15 |
| middle occipital gyrus | -24 | -99 | 6 | 0.001 | 0 | 5.14 |
| middle occipital gyrus | -30 | -84 | 18 | 0.03 | 0 | 3.48 |
| superior occipital gyrus | 24 | -93 | 27 | 0.003 | 0 | 4.61 |
| parieto-occipital fissure | -21 | -72 | 36 | 0.001 | 0 | 4.96 |
| gyrus descendens/calcarine sulcus(V3) | -12 | -102 | 3 | 0.001 | 0 | 5.04 |
| lingual gyrus | 18 | -102 | -12 | 0.006 | 0 | 4.19 |
| lingual gyrus | 30 | -84 | -15 | 0.004 | 0 | 4.37 |
| lingual gyrus | -24 | -84 | -18 | 0.014 | 0 | 3.84 |
| collateral sulcus/fusiform gyrus | 27 | -69 | -6 | 0.009 | 0 | 4.04 |
| collateral sulcus/fusiform gyrus | -24 | -75 | -6 | 0.034 | 0 | 3.41 |
| middle temporal gyrus | -54 | -30 | -6 | 0.004 | 0 | 4.53 |
| middle temporal gyrus | 48 | -51 | 6 | 0.025 | 0 | 3.57 |
| pSTS/STG | -60 | -54 | 24 | 0.009 | 0 | 4.03 |
| pSTS | 42 | -57 | 21 | 0.015 | 0 | 3.82 |
| middle occipital gyrus/pSTSh | -45 | -78 | 21 | 0.032 | 0 | 3.44 |
| superior temporal sulcus | 48 | -3 | -18 | 0.046 | 0.001 | 3.26 |
| superior parietal gyrus/ips | 27 | -60 | 63 | 0.006 | 0 | 4.27 |
| superior parietal gyrus | -30 | -57 | 66 | 0.005 | 0 | 4.34 |
| ips/superior parietal gyrus | -27 | -57 | 51 | 0.006 | 0 | 4.2 |
| superior parietal gyrus | -18 | -51 | 54 | 0.046 | 0.001 | 3.27 |
| ips/angular gyrus | -36 | -45 | 57 | 0.009 | 0 | 4.06 |
| superior parietal gyrus/precuneus | 12 | -60 | 69 | 0.003 | 0 | 4.64 |
| precuneus/subparietal sulcus | 6 | -51 | 42 | 0.01 | 0 | 4.01 |
| middle frontal gyrus/superior frontal sulcus | -30 | -6 | 54 | 0.018 | 0 | 3.74 |
| superior frontal sulcus /gyrus | -24 | -9 | 63 | 0.02 | 0 | 3.68 |
| Cerebellum | -42 | -78 | -18 | 0.021 | 0 | 3.67 |

**Table 7.7 - Other - Subject (p<0.001 uncor) masked by Other – No Agent (p<0.01 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| middle occipital gyrus (V5) | 48 | -75 | 3 | 0 | 0 | 5.74 |
| middle occipital gyrus (V5) | -48 | -72 | 6 | 0 | 0 | 5.48 |
| middle occipital gyrus | 30 | -93 | 12 | 0.001 | 0 | 5.15 |
| middle occipital gyrus | -24 | -99 | 6 | 0.001 | 0 | 5.14 |
| middle occipital gyrus | -45 | -75 | -9 | 0.02 | 0 | 3.69 |
| pSTS | 63 | -42 | 9 | 0.003 | 0 | 4.58 |
| pSTS | -60 | -54 | 24 | 0.009 | 0 | 4.03 |
| pSTS | 42 | -57 | 21 | 0.015 | 0 | 3.82 |
| superior occipital gyrus/intra occipital sulcus | 24 | -93 | 27 | 0.003 | 0 | 4.61 |
| parieto-occipital sulcus/superior occipital gyrus | -21 | -72 | 36 | 0.001 | 0 | 4.96 |
| gyrus descendens/calcarine sulcus (V3) | -12 | -102 | 3 | 0.001 | 0 | 5.04 |
| lingual gyrus/calcarine sulcus/cuneus (V3) | 18 | -93 | -3 | 0.008 | 0 | 4.1 |
| lingual gyrus | 30 | -84 | -15 | 0.004 | 0 | 4.37 |
| lingual gyrus | -24 | -84 | -18 | 0.014 | 0 | 3.84 |
| collateral sulcus/fusiform gyrus | -24 | -75 | -6 | 0.034 | 0 | 3.41 |
| collateral sulcus/fusiform gyrus | 27 | -69 | -6 | 0.009 | 0 | 4.04 |
| superior parietal gyrus/ips | 27 | -60 | 63 | 0.006 | 0 | 4.27 |
| superior parietal gyrus/ips | -30 | -57 | 66 | 0.005 | 0 | 4.34 |
| ips/angular gyrus | -36 | -45 | 57 | 0.009 | 0 | 4.06 |
| middle temporal gyrus | -54 | -30 | -6 | 0.004 | 0 | 4.53 |
| superior parietal gyrus/precuneus | 12 | -60 | 69 | 0.003 | 0 | 4.64 |
| precuneus/subparietal sulcus | 6 | -51 | 42 | 0.01 | 0 | 4.01 |
| Middle frontal gyrus/superior frontal sulcus | -30 | -6 | 54 | 0.018 | 0 | 3.74 |
| Cerebellum | -42 | -78 | -18 | 0.021 | 0 | 3.67 |

*7.3.2.1.7 Subject > No Agent and Other > No Agent (see Figure 7.2a & c)*

Similar regions were also revealed by the contrasts 'subject' – 'no agent' and 'other' – 'no agent' ,thus I specifically looked for regions that showed significantly greater activation to both 'subject' compared to 'no agent' conditions and to 'other' compared to 'no agent' conditions as revealed by the contrast [('other' – 'no agent') masked by ('subject' – 'no agent')]. This contrast revealed two main areas showing this pattern of activation: the medial precuneus, and the dorsal medial prefrontal cortex (dMPFC). The posterior superior temporal sulcus and angular gyrus bilaterally also showed this pattern of activation as did a few other small clusters. (See Table 7.8 for full details of all activated loci).

**Table 7.8 - Other – No Agent (p<0.001 uncor) masked by Subject – No Agent (p<0.01 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| superior frontal gyrus (dMPFC) | 3 | 57 | 21 | 0.007 | 0 | 3.97 |
| precuneus | 6 | -54 | 39 | 0.001 | 0 | 4.68 |
| precuneus/parieto-occipital fissure | 3 | -69 | 39 | 0.003 | 0 | 4.32 |
| precuneus/superior parietal gyrus | -6 | -54 | 42 | 0.002 | 0 | 4.56 |
| pSTS/angular gyrus | -48 | -57 | 30 | 0.023 | 0 | 3.39 |
| pSTS/angular gyrus | 57 | -60 | 30 | 0.009 | 0 | 3.86 |
| angular gyrus | 51 | -69 | 42 | 0.01 | 0 | 3.83 |
| cerebellum | 48 | -63 | -27 | 0.009 | 0 | 3.87 |
| superior frontal gyrus (anterior dorsal) | 12 | 39 | 54 | 0.003 | 0 | 4.34 |
| cingulate gyrus (central) | 0 | -21 | 42 | 0.009 | 0 | 3.84 |
| superior post central sulcus/ gyrus | 24 | -45 | 63 | 0.016 | 0 | 3.6 |
| middle occipital gyrus | -42 | -75 | -6 | 0.001 | 0 | 4.92 |
| lingual gyrus | 12 | -78 | -12 | 0.001 | 0 | 4.91 |
| Pulvinar | 15 | -21 | 6 | 0.008 | 0 | 3.9 |

### 7.3.2.2 Effects of predictability

#### *7.3.2.2.1 Predictable > Unpredictable*

Areas showing greater activation to 'predictable' conditions, when the sound occurred exactly 400ms after the button press or the disappearance of the white dot, compared to 'unpredictable' conditions, when the sound occurred randomly any time up to 800ms after the button press or the disappearance of the white dot, were revealed by the contrast ('predictable' – 'unpredictable'). Several clusters in the orbital medial prefrontal cortex (oMPCF), showed this pattern of activation, as did a few voxels in the angular gyrus. (See Table 7.9 for full details of activated loci). However, none of these activations reached significance when corrected for multiple comparisons.

**Table 7.9 - Predictable – Unpredictable (p<0.001 uncorrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| gyrus rectus/cingulate sulcus/gyrus (oMPFC) | 3 | 21 | -18 | 0.696 | 0 | 4.23 |
| sub callosal gyrus (oMPFC) | 6 | 12 | -6 | 0.975 | 0 | 3.79 |
| cingulate gyrus (oMPFC) | 6 | 45 | -6 | 0.975 | 0.001 | 3.29 |
| Supraorbital sulcus/cingulate sulcus (oMPFC) | -9 | 45 | -9 | 0.975 | 0 | 3.74 |
| superior frontal gyrus | -12 | 66 | 9 | 0.975 | 0 | 3.36 |
| angular gyrus | -36 | -84 | 36 | 0.975 | 0 | 3.44 |

#### *7.3.2.2.2 Predictable > Partially Predictable*

The contrast 'predictable' – 'partially predictable' revealed areas showing greater activation to 'predictable' conditions, when the sound occurred exactly 400ms after the button press or the disappearance of the white dot, compared to 'partially predictable' conditions, when the sound occurred 200 to 600ms after the button press or the disappearance of the white dot. The main region showing this pattern of activation was the orbital medial prefrontal cortex (oMPFC). Parts of the dorsal medial prefrontal cortex (dMPFC) also showed this pattern of activation, as did the

medial precuneus. A few other clusters also showed this pattern of activation, mostly in the temporal lobe, (See Table 7.10 for full details of all activated loci). However, none of these activations reached significance when corrected for multiple comparisons.

**Table 7.10 - Predictable – Partially Predictable (p<0.001 uncorrected)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| gyrus rectus (oMPFC) | 3 | 42 | -21 | 0.056 | 0 | 4.7 |
| supraorbital sulcus (oMPFC) | -6 | 54 | -6 | 0.132 | 0 | 3.9 |
| sub callosal/cingulate gyrus (oMPFC) | 0 | 24 | -3 | 0.162 | 0 | 3.73 |
| superior frontal gyrus (dMPFC) | -6 | 54 | 18 | 0.099 | 0 | 4.14 |
| superior frontal gyrus (dMPFC) | 6 | 57 | 36 | 0.199 | 0 | 3.42 |
| middle temporal gyrus | -66 | -21 | -18 | 0.099 | 0 | 4.01 |
| temporo-occipital sulcus / inferior temporal sulcus | -51 | -39 | -12 | 0.151 | 0 | 3.81 |
| precentral gyrus | -15 | -30 | 69 | 0.162 | 0 | 3.74 |
| middle temporal gyrus (temporal pole) | -54 | 6 | -27 | 0.172 | 0 | 3.6 |
| mtg/sts (at temporal pole) | 42 | 12 | -33 | 0.199 | 0 | 3.45 |
| preceuneus / cingulate gyrus | -9 | -51 | 24 | 0.195 | 0 | 3.51 |
| preceuneus / cingulate gyrus | 3 | -57 | 27 | 0.195 | 0 | 3.49 |
| pSTSh | 57 | -66 | 24 | 0.195 | 0 | 3.51 |
| anterior calcarine sulcus | -6 | -60 | 9 | 0.199 | 0 | 3.42 |
| Putamen | -30 | -12 | -9 | 0.202 | 0 | 3.35 |

#### *7.3.2.2.3 Partially Predictable > Unpredictable*

A few regions were revealed that showed greater activation to 'partially predictable' compared to 'unpredictable' trials. The main areas showing this pattern of activation was the cerebellum. The cingulate sulcus, right inferior frontal gyrus, and circular insula sulcus, and the left intra- parietal/occipital sulcus, also showed greater activation to 'partially predictable' compared to 'unpredictable' trials. (See Table 7.11 for full details of activated loci). However, these activations were not significant when corrected for multiple comparisons.

**Table 7.11 - Partially Predictable – Unpredictable (p<0.001 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| Cerebellum | -6 | -63 | -18 | 0.907 | 0 | 3.77 |
| Cerebellum | 12 | -57 | -9 | 0.907 | 0 | 3.42 |
| Cerebellum | -6 | -69 | -9 | 0.907 | 0 | 3.41 |
| cingulate sulcus | -12 | -18 | 45 | 0.907 | 0 | 3.53 |
| circular insula sulcus/inferior frontal gyrus | 48 | 9 | 6 | 0.907 | 0 | 3.46 |
| ips/intra-occipital sulcus | -24 | -78 | 33 | 0.907 | 0.001 | 3.24 |

#### *7.3.2.2.4 Predictable > Partially Predictable > Unpredictable*

I looked for regions that showed greater activation to 'predictable' compared to 'partially predictable' trials , as well as showing greater activation to 'partially predictable' compared to 'unpredictable' trials, using the contrast 'predictable' – 'partially predictable' (p<0.001 uncorr) masked by 'partially predictable' – 'unpredictable' (p<0.01 uncorr), and the contrast 'partially predictable' – 'unpredictable' (p<0.001 uncorr) masked by 'predictable' – 'partially predictable' (p<0.01). Neither of these contrasts revealed any regions showing significantly greater activation to 'predictable' compared to 'partially predictable' trials, and significantly greater activation to 'partially predictable' compared to 'unpredictable' trials. Thus no regions showed a linear increase in activation from 'unpredictable', to 'partially predictable', through to 'predictable' trials.

#### *7.3.2.2.5 Predictable > Partially Predictable and Predictable > Unpredictable*

However, the regions revealed by the contrasts 'predictable' – 'unpredictable' and 'predictable' – 'partially predictable' appeared very similar, thus I specifically looked for regions that showed greater activation to 'predictable' compared to 'partially predictable' conditions, as well as greater activation to 'predictable' compared to 'unpredictable' conditions. Such areas were revealed by the contrast [('predictable' – 'partially predictable') masked by ('predictable' – 'unpredictable')]. The only regions showing greater activation to 'predictable' conditions both when compared to 'partially predictable' conditions and when compared to 'unpredictable' conditions were in the orbital medial prefrontal cortex. (See Figure 7.3 and Table

7.12 for full details of activated loci.). Though these activations do not quite reach significance when corrected for multiple comparisons they will nevertheless be discussed.

**Table 7.12 - Predictable - Partially Predictable (p<0.001 uncor) masked by Predictable – Unpredictable (p<0.01 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| gyrus rectus (oMPFC) | 3 | 42 | -21 | 0.056 | 0 | 4.7 |
| cingulate sulcus/gyrus /supraorbital sulcus (oMPFC) | 0 | 45 | -12 | 0.099 | 0 | 4.03 |
| sub callosal/cingulate gyrus (oMPFC) | 0 | 24 | -3 | 0.162 | 0 | 3.73 |
| cingulate sulcus/gyrus (oMPFC) | -3 | 30 | -15 | 0.195 | 0 | 3.52 |

**Table 7.13 – Unpredictable – Predictable (p<0.001 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| inferior frontal gyrus / lateral fissure | 48 | 24 | -3 | 0.001 | 0 | 5.44 |
| posterior lateral fissure/supramarginal gyrus | 54 | -36 | 39 | 0.106 | 0 | 4.09 |
| middle frontal gyrus | 42 | 57 | 9 | 0.106 | 0 | 4.07 |
| subcentral gyrus (between inferior precentral sulcus and central sulcus) | -39 | -6 | 27 | 0.106 | 0 | 4.06 |
| lateral fissure/circular insular sulcus | 30 | 21 | -12 | 0.145 | 0 | 3.92 |
| superior frontal gyrus | 9 | 27 | 57 | 0.151 | 0 | 3.89 |
| superior frontal gyrus | 3 | 15 | 57 | 0.321 | 0 | 3.32 |
| lateral orbital gyrus | 42 | 51 | -6 | 0.208 | 0 | 3.73 |
| Superior temporal sulcus | -51 | -27 | 3 | 0.226 | 0 | 3.58 |
| Superior temporal sulcus | 66 | -36 | 0 | 0.287 | 0 | 3.39 |
| Cerebellum | -30 | -57 | -33 | 0.226 | 0 | 3.58 |

#### *7.3.2.2.6 Unpredictable > Predictable*

The contrast 'unpredictable' – 'predictable' revealed areas showing greater activation to 'unpredictable' trials compared to 'predictable' trials. The regions showing this pattern of activation were mostly located in the right lateral frontal cortex (right superior, middle and inferior frontal gyri, right lateral fissure and right insula). The superior temporal sulcus also showed this pattern of activation bilaterally, as did the

right posterior lateral fissure, the left sub-central gyrus, and the left cerebellum. (See Table 7.13 for full details of activated loci). However, most of these activations were not significant when corrected for multiple comparisons.

#### *7.3.2.2.7 Unpredictable > Partially Predictable*

Areas, showing a greater response to unpredictable compared to partially predictable trails, were revealed in the medial prefrontal cortex (ventral and dorsal), the medial precuneus, the left precentral gyrus, and in several locations in the temporal lobes bilaterally, including the temporal poles. (See Table 7.14 for full details of activated loci). However, these activations are not significant when corrected for multiple comparisons.

**Table 7.14 – Unpredictable – Partially Predictable (p<0.001 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| precentral gyrus/sulcus | -57 | -9 | 30 | 0.332 | 0 | 4.34 |
| precentral gyrus/paracentral lobule | -15 | -27 | 69 | 0.373 | 0 | 3.97 |
| gyrus rectus (vMPFC) | -3 | 45 | -18 | 0.332 | 0 | 4.24 |
| inferior temporal sulcus (temporal pole) | -45 | 9 | -39 | 0.373 | 0 | 4.09 |
| inferior temporalsulcus (temporal pole) | 54 | -3 | -30 | 0.373 | 0 | 3.48 |
| Isthmus | -15 | -33 | 0 | 0.373 | 0 | 3.86 |
| middle temporal gyrus / superior temporal sulcus | 66 | -45 | 6 | 0.373 | 0 | 3.83 |
| superior temporal sulcus | 51 | -30 | 3 | 0.373 | 0 | 3.57 |
| middle temporal gyrus | -57 | -24 | -9 | 0.373 | 0 | 3.58 |
| middle temporal gyrus (temporal pole) | 45 | 12 | -36 | 0.373 | 0 | 3.46 |
| inferior temporal gyrus (anterior) | -48 | -15 | -33 | 0.373 | 0 | 3.68 |
| inferior frontal gyrus | 57 | 27 | 6 | 0.373 | 0 | 3.61 |
| cingulate sulcus | 18 | 45 | 0 | 0.373 | 0 | 3.59 |
| posterior orbital gyrus | 27 | 18 | -18 | 0.373 | 0 | 3.47 |
| Pulvinar | -15 | -27 | 0 | 0.373 | 0 | 3.46 |
| superior frontal gyrus (dMPFC) | 3 | 54 | 33 | 0.373 | 0 | 3.4 |
| lateral orbital gyrus | -39 | 33 | -12 | 0.389 | 0 | 3.36 |
| tail of hippocampus | 18 | -36 | 9 | 0.389 | 0.001 | 3.27 |
| preceuneus / cingulate gyrus | -9 | -51 | 24 | 0.389 | 0.001 | 3.25 |

#### *7.3.2.2.8 Partially Predictable > Predictable*

Areas showing greater activation to 'partially predictable' compared to 'predictable' trials were revealed by the contrast 'partially predictable' – 'predictable'. These regions were located mainly in the right lateral frontal cortex, around the right middle frontal gyrus, and right inferior frontal gyrus. Other areas showing this pattern of activation included the left precentral gyrus, the right central sulcus, right posterior STS, the left IPS, the right posterior lateral fissure, the left cerebellum, the left insula and the right cingulate gyrus. (See Table 7.15 for full details of activated loci). Most of these activations were not significant when corrected for multiple comparisons.

**Table 7.15 - Partially Predictable – Predictable (p<0.001 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| Subcentral gyrus / precentral gyrus (near inferior precentral sulcus) | -36 | -3 | 30 | 0.014 | 0 | 5.01 |
| precentral gyrus/central sulcus | -48 | -6 | 48 | 0.243 | 0.001 | 3.28 |
| inferior frontal sulcus | 30 | 42 | 18 | 0.014 | 0 | 4.89 |
| inferior frontal sulcus | 45 | 36 | 30 | 0.229 | 0 | 3.35 |
| inferior frontal gyurs | 51 | 15 | 9 | 0.062 | 0 | 4.28 |
| inferior frontal gyrus | 63 | 21 | 12 | 0.096 | 0 | 4.07 |
| inferior frontal gyrus / lateral fissure | 48 | 24 | -3 | 0.104 | 0 | 3.98 |
| central sulcus | 33 | -15 | 39 | 0.038 | 0 | 4.56 |
| middle frontal gyrus/inferior frontal sulcus | 51 | 48 | 9 | 0.038 | 0 | 4.51 |
| middle frontal gyrus | 42 | 48 | 24 | 0.192 | 0 | 3.61 |
| angular gyrus/pSTS | 33 | -54 | 30 | 0.104 | 0 | 4.01 |
| intraparietal sulcus | -21 | -54 | 36 | 0.104 | 0 | 4.01 |
| Cerebellum | -33 | -60 | -24 | 0.129 | 0 | 3.84 |
| Cerebellum | -3 | -72 | -33 | 0.22 | 0 | 3.49 |
| calcarine sulcus | 30 | -69 | 9 | 0.146 | 0 | 3.74 |
| supramarginal gyrus/posterior lateral fissure | 57 | -39 | 42 | 0.184 | 0 | 3.65 |
| Short insular gyri | -36 | 12 | 3 | 0.22 | 0 | 3.4 |
| cingulate gyrus | 6 | -30 | 48 | 0.243 | 0.001 | 3.29 |

#### *7.3.2.2.9 Unpredictable > Partially Predictable > Predictable*

I looked for regions that showed greater activation to 'unpredictable' compared to 'partially predictable' trials , as well as showing greater activation to 'partially predictable' compared to 'predictable' trials, using the contrast 'unpredictable' – 'partially predictable' ($p<0.001$ uncorr) masked by 'partially predictable' – 'predictable' ($p<0.01$ uncorr), and the contrast 'partially predictable' – 'predictable' ($p<0.001$ uncorr) masked by 'unpredictable' – 'partially predictable' ($p<0.01$). Neither of these contrasts revealed any regions showing significantly greater activation to 'unpredictable' compared to 'partially predictable' trials, and significantly greater activation to 'partially predictable' compared to 'predictable' trials. Thus no regions showed an increase in activation from 'predictable', to 'partially predictable', through to 'unpredictable' trials.

#### *7.3.2.2.10 Partially Predictable > Predictable and Unpredictable > Predictable*

However, the regions revealed by the contrasts 'unpredictable' – 'predictable' and 'partially predictable' – 'predictable' appeared very similar, thus I specifically looked for regions that showed greater activation to 'partially predictable' compared to 'predictable' conditions, as well as greater activation to 'unpredictable' compared to 'predictable' conditions. Such regions were revealed by the contrast [('partially predictable' – 'predictable') masked by ('unpredictable' – 'predictable')] (see Figure 7.3). Areas showing this pattern of activation were mainly located in the right lateral frontal cortex (in the right middle frontal gyrus and in the right inferior frontal gyrus next to the lateral fissure. The left precentral gyrus, right central sulcus, right calcarine sulcus and right supramarginal gyrus also showed this pattern ofactivation. (See Table 7.16 for full details of activated loci.) Though not all these activations reach significance when corrected for multiple comparisons they will nevertheless be discussed.

**Table 7.16 - Partially Predictable - Predictable (p<0.001 uncor) masked by Unpredictable - Predictable (p<0.01 uncor)**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| Subcentral gyrus / precentral gyrus (next to inferior precentral sulcus) | -36 | -3 | 30 | 0.014 | 0 | 5.01 |
| central sulcus | 33 | -15 | 39 | 0.038 | 0 | 4.56 |
| inferior frontal sulcus | 30 | 42 | 18 | 0.014 | 0 | 4.89 |
| middle frontal gyrus/inferior frontal sulcus | 51 | 48 | 9 | 0.038 | 0 | 4.51 |
| middle frontal gyrus | 42 | 48 | 24 | 0.192 | 0 | 3.61 |
| inferior frontal gyrus | 63 | 21 | 12 | 0.096 | 0 | 4.07 |
| inferior frontal gyrus /lateral fissure | 48 | 24 | -3 | 0.104 | 0 | 3.98 |
| inferior frontal gyrus /lateral fissure | 48 | 18 | 9 | 0.132 | 0 | 3.79 |
| calcarine sulcus | 30 | -69 | 9 | 0.146 | 0 | 3.74 |
| supramarginal gyrus/posterior lateral fissure | 57 | -39 | 42 | 0.184 | 0 | 3.65 |

### 7.3.2.3 Interactions

I looked for regions whose response showed an interaction between the effect of the predictability of the trials and the effect of agency, such that the effect of predictability was modulated by the agent, or that effect of agency was modulated by the predictability of the trial. I used an F-contrast to reveal brain regions showing any type of interaction between these two factors: agency and predictability. This revealed two regions showing an interaction between agency and predictability: the cerebellum and the inferior parietal gyrus. (See Table 7.17 for details), but the interaction in these cluster did not reach significance at the corrected level.

**Table 7.17 - Interactions F-test**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| Cerebellum | 3 | -60 | -15 | 1 | 0 | 4.11 |
| supramarginal gyrus/inferior parietal gyrus | -57 | -27 | 21 | 1 | 0 | 3.53 |

I also conducted T-tests to test for specific interactions as such T-tests are more sensitive than the above F-test. Since the effects of contingency were mostly observed between the 'predictable' condition and the 'partially predictable' and 'unpredictable' conditions, I looked for an interaction between the effect of 'predictable' compared with 'partially predictable' and 'unpredictable' conditions, and the effects of agency. This revealed an interaction between predictability and agency in several small clusters (see Table 7.18), however none of these activations were significant when corrected for multiple comparisons.

**Table 7.18 – Interaction T-tests**

| | x | y | z | p-FDR | p-unc | Z |
|---|---|---|---|---|---|---|
| ***(P – PP - U) x (subject – no agent)*** | | | | | | |
| superior frontal gyrus (dMPFC) | 9 | 48 | 21 | 0.999 | 0 | 3.75 |
| Cerebellum | 9 | -54 | -21 | 0.999 | 0 | 3.5 |
| ***(P – PP – U) x (no agent – subject)*** | | | | | | |
| Right STS | 60 | -30 | 3 | 0.832 | 0 | 3.99 |
| Right ITS | 57 | -9 | -30 | 0.832 | 0 | 3.62 |
| ***(P – PP – U) x (subject – other)*** | | | | | | |
| MFG | 33 | 42 | 42 | 0.973 | 0.001 | 3.19 |
| ***(P – PP – U) x (other – subject)*** | | | | | | |
| Nothing | | | | | | |
| ***(P – PP – U) x (other – no agent)*** | | | | | | |
| Nothing | | | | | | |
| ***(P – PP – U) x (no agent – other)*** | | | | | | |
| Short insular gyri | 36 | 18 | -12 | 0.877 | 0 | 3.48 |
| putamen | 21 | 15 | -9 | 0.877 | 0 | 3.44 |
| STG(planum polare)/lateral fissure/circular insular sulcus | 48 | -9 | -3 | 0.877 | 0 | 3.36 |
| inferior temporal gyrus | -51 | -21 | -30 | 0.877 | 0.001 | 3.24 |
| inferior temporal gyrus | 36 | -15 | -33 | 0.877 | 0.001 | 3.12 |

I also looked specifically for interactions within the regions that showed a main effect of agency or contingency, by conducting the same interaction T-tests (see Table 7.18 for details of T-tests conducted) masked inclusively by the main effects of

agency or contingency. I found no significant interactions ($p<0.001$ uncorrected), between contingency ('predictable' v. 'partially predictable' + 'unpredictable') and agency ('subject' v. 'no agent', 'subject' v. 'other', and 'other' v. 'no agent') within areas that show an effect of agency (F-test $p<0.01$ uncorrected). Neither did I find any significant interactions ($p<0.001$ uncorrected) between contingency ('predictable' v. 'partially predictable' + 'unpredictable') and agency ('subject' v. 'no agent', 'subject' v. 'other', and 'other' v. 'no agent'), within areas that show an effect of contingency (F-test $p<0.01$ uncorrected).

## 7.4 Discussion

### 7.4.1 Behavioural ratings

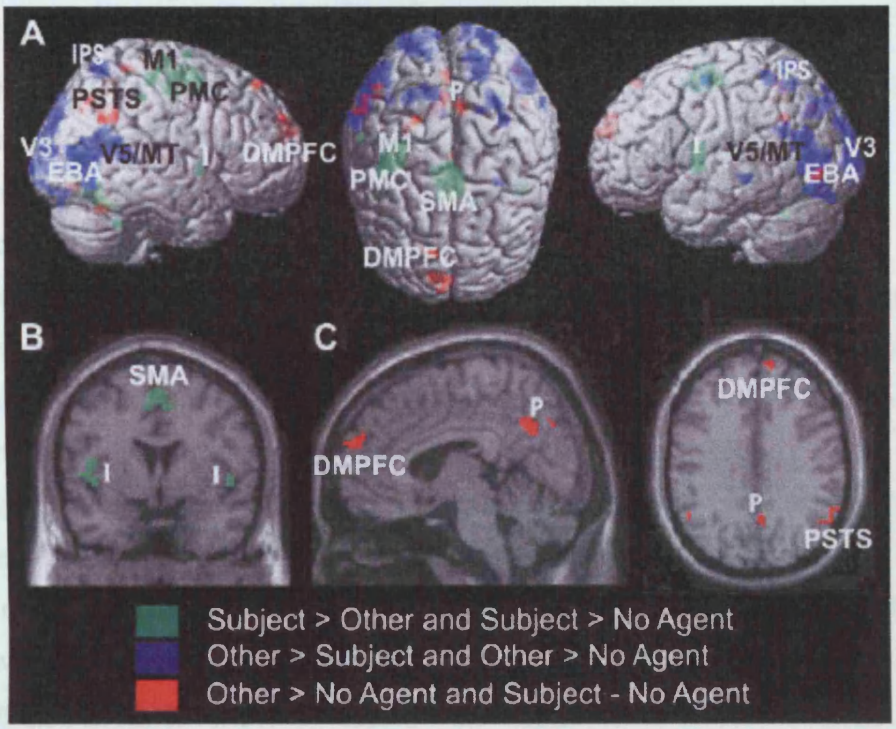
In 'predictable' blocks the sounds, which occurred exactly 400 ms after the button press or disappearance of the white dot, were rated as being contingent/predictable on 86.5% of occasions. The sounds in 'partially predictable' blocks were rated as being contingent/predictable on only 53.4% of occasions, (i.e. at chance level), and in 'unpredictable blocks' the sounds were rated as predictable/contingent on 20.4% of occasions. This shows that my manipulation of the time delay between the button press, or disappearance of the white dot, and the occurrence of the sound, modified the perceived predictability of the sound as expected.

### 7.4.2 fMRI data

#### 7.4.2.1 Effects of Agency

Contrary to my hypothesis I did not find a difference between the response to self-generated ('subject' condition) and externally generated ('no agent' condition) auditory stimuli in the auditory cortex. This may be due to the presence of background scanner noise. Previous studies of attenuation of auditory responses have mainly used MEG and EEG, which are silent technologies, unlike fMRI. It may be that my auditory stimuli do not activate the auditory cortex sufficiently, relative to auditory activation caused by the scanner noise, for a difference between the self- and externally-generated conditions to be detected. This may also explain the absence of a difference in the auditory cortex between the 'other' and 'no agent' conditions, and between the 'other' and 'subject' conditions. Thus I can not conclude that agency does not affect the response to auditory stimuli, (a conclusion which in the case of self-produced stimuli would be contrary to many previous studies). I did however find many other brain regions showing significant effects of agency.

***Figure 7.2 – Effects of agency***




**A.** *Left lateral, right lateral, and superior views of a standard T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template. Regions showing significant effects of agency are shown superimposed on the rendered image (spatial extent threshold of 3 voxels was used for display purposes). Areas in green show greater activation for the 'subject' condition, compared to the 'other' and 'no agent' conditions (subject > other $p < 0.001$ uncorrected, masked by subject > no agent $p<0.01$ uncorrected). Areas in blue, show greater activation for the 'other' condition, compared to the 'subject' and 'no agent' conditions (other > subject $p < 0.001$ uncorrected, masked by other > no agent $p<0.01$ uncorrected). Areas in red show greater activation for the 'subject' and 'other' conditions, compared to the 'no agent' condition (other > no agent $p < 0.001$ uncorrected, masked by subject > no agent $p<0.01$ uncorrected).* **B.** *Activity revealed by the contrast 'subject' – 'other' ($p<0.001$), masked by 'subject' – 'no agent' ($p<0.01$), overlaid on a coronal slice of the standard T1 weighted structural image in the standard space defined by the Montreal Neurological Institute template.* **C.** *Activity revealed by the contrast 'other' – 'no agent' ($p<0.001$), masked by 'subject' – 'no agent' ($p<0.01$), overlaid on a sagittal and a coronal slice of the standard T1 weighted structural image in the standard space defined by the Montreal Neurological Institute template. M1=Primary Motor Cortex, PMC=Premotor Cortex, SMA=Supplementary Motor Area, I=Insula, EBA=Extrastriate Body Area, IPS=intraparietal sulcus, DMPFC=dorsal medial Prefrontal Cortex, pSTS=posterior superior temporal sulcus, P=Precuneus.*

#### *7.4.2.1.1 Motor regions*

As expected motor regions, including the right primary motor cortex (M1), the right premotor cortex (PMC), the supplementary motor area (SMA), the right supramarginal gyrus, and the cerebellum, were activated during the 'subject' conditions, during which the subject pressed a button at the start of each trial, compared to the 'other' and 'no agent' trials during which the subject did not make a button press (see Figure 7.2a & b, areas in green). The locations of the motor regions activated by the button presses in the 'subject' condition are consistent with previous studies identifying human motor regions (Fink et al., 1997), including a meta-analysis of eight other studies (Grezes and Decety, 2001). The inferior frontal gyrus (*pars opercularis)* bilaterally showed greater activation during the subject condition but only when compared to the 'other' conditions. It has previously been shown to be activated by actions (Fink et al., 1997;Grezes and Decety, 2001), and may correspond to the macaque ventral Premotor Area (Fink et al., 1997).

#### *7.4.2.1.2 Insula*

The insula also showed greater activation during the 'subject' compared to both the 'other' and 'no agent' conditions. (See Figure 7.2a & b). Activation of the insula by the 'subject' condition is consistent with previous studies of willed actions (Blakemore et al., 1998a;Fink et al., 1997). More recent work suggests that rather than being involved in making movements per se, the insula is involved in the experience of agency (Farrer et al., 2003;Farrer and Frith, 2002). Subjects used a joystick to move a circle on the screen, but in some conditions they were told that the circle would be controlled by the experimenter rather than their own movement. Awareness of causing the movement of the circle on the screen activated the insula, to a greater extent than when another person controlled the movement seen on screen, although the subject performed the same arm actions in both conditions (Farrer and Frith, 2002). Similarly, activity in the insula decreased with the degree of discrepancy between the hand movements made by the subject, and the movements made by a virtual hand on screen. Thus, activity in the insula decreased as the degree of control felt by the subject decreased (Farrer et al., 2003). Thus, rather than merely reflecting motor activation, the insula activation seen in my study during the

'subject' condition may reflect the subject's sense of agency and control over the sounds heard in the 'subject' conditions. The variation in the time delay between the predictable, partly predictable and unpredictable trials is probably not great enough to abolish the subject's sense of agency as in all 'subject' conditions the sound occurs within 1 second of the button press.

#### *7.4.2.1.3 Parietal cortex*

Whereas the insula is activated by the attribution of agency to the self, attribution of agency to another person activates the inferior parietal cortex (Farrer and Frith, 2002). Similarly activity in the inferior parietal lobe increases as the discrepancy between the subject's hand movement and visual feedback from that movement increases. In other words activity in the inferior parietal cortex increases as the sense of personal agency decreases (Farrer et al., 2003). The activation of a parietal region around the intra-parietal sulcus and angular gyrus, observed during the 'other' condition, compared to both the 'subject' and 'no agent' conditions, (see Figure 7.2a), in my experiment could reflect the attribution of agency to another person during the 'other' condition, as in the 'other' condition the sounds appear to be caused by the experimenter's button press. Alternatively, the increased activity seen in this region during the 'other' compared to the 'no agent' condition could be due to the presence of a hand movement, and the intra-parietal cortex is known to respond to the observation of hand and arm movements (Buccino et al., 2001). The increased activation during the 'other' compared to 'subject' conditions could be due to the subject paying greater visual attention to the experimenter's hand movements than to their own, as they do not need to watch their own hand to know when it is moving.

#### *7.4.2.1.4 Occipito-temporal cortex*

The 'other' condition, when subjects watched the experimenter press the button at the begining of each trial, also activated several regions in the occipito-temporal cortex when compared to both the 'subject' conditions and the 'no agent' conditions. These activations form two main lateral occipito-temporal clusters (covering the middle occipital gyrus, middle temporal gyrus and lateral occipital sulcus), one in each hemisphere, the anterior part of which appears to correspond to V5/MT (Zeki et

al., 1991), while the posterior part of the cluster could correspond to a region of the occipital cortex that is activated by observation of human body parts, known as the Extrastriate Body Area (EBA) (Downing et al., 2001). (See Figure 7.2a, areas in blue). Though both the subject's hand and the experimenter's hand were within the subject's field of view throughout the experiment, increased activation in the EBA during the 'other' condition could be due to the subject paying greater attention to the experimenter's hand during the 'other' conditions as they need to pay close attention to the timing of the experimenter's hand movement, whereas in the 'subject' and 'no agent' conditions subject's do not need to visually monitor their own or the experimenter's hand movements. Increased activation in V5/MT, which responds to visual motion, could be due to the subjects paying close attention to the movement of the experimenter's hand during the 'other' conditions but not during the 'subject' or 'no agent' conditions. The observed increased activation in a posterior occipital region, which may correspond to area V3 (Hasnain et al., 1998), during the 'other' condition, could have a similar explanation. In macaques V3 cells exhibit complex motion responsive properties (Gegenfurtner et al., 1997), and compared to other visual areas, V3 appears to be particularly suited to the analysis of motion stimuli like V5/MT(Felleman and Van Essen, 1987).

This cluster extends up to the superior temporal sulcus. This part of the STS is activated by biological motion (Allison et al., 2000), and its increased activation in the 'other' condition may be due to the subject paying greater attention to experimenter's moving hand in the 'other' condition than they do to their own hand in the 'subject' condition, and due to the lack of any hand motion in the 'no agent' condition. A similar explanation may apply to the observed activation of the fusiform gyrus, on the banks of the posterior collateral sulcus, in the 'other' compared to the 'subject' and 'no agent' conditions, as the fusiform gyrus has been shown to respond to biological motion (Bonda et al., 1996;Grezes et al., 1998).

#### *7.4.2.1.5 Social cognition areas*

I found a set of regions that are activated by both the 'subject' and the 'other' conditions compared to the 'no agent' conditions, including the medial prefrontal cortex, the medial precuneus and posterior cingulate, the posterior STS, and the

temporal poles. (See Figure 7.2a, c & d, areas in red). These regions are commonly activated in a variety of tasks involving thinking about one's own and other people's actions and mental states, i.e. social cognition (Amodio and Frith, 2006;Saxe, 2006). For example, the medial prefrontal cortex is activated during self-monitoring tasks (McGuire et al., 1996a;McGuire et al., 1996b), and when subjects play games with another person, in which the subjects think about the other person's actions and intentions, compared with playing against a computer (Gallagher et al., 2002;McCabe et al., 2001). In both the 'subject' and 'other' conditions the subject had to monitor an action and its consequences in order to judge at the end of the block whether the sound heard was predictable/contingent upon the button press. In the 'no agent' condition subjects did not have to monitor an action but just had to assess whether the sound heard was predictable/contingent upon the disappearance of the white dot. I suggest that the activation seen in the dorsal medial prefrontal cortex during the 'subject' and 'other' conditions reflects this monitoring of actions and their consequences, whether they are made by the subject or the experimenter, in these conditions. In a recent review of the medial frontal cortex, Amodio and Frith suggest that the posterior rostral medial frontal cortex, the location of which is consistent with the location of the dorsal medial prefrontal activation observed in this study, is involved in the internal monitoring of our own actions and their outcomes (Amodio and Frith, 2006). My results suggest that it is also involved in monitoring the actions of others. In support of this notion, anticipating the action of another person has been shown to activate the dMPFC, in a location consistent with that activated by the 'other' and 'subject' compared with the 'no agent' condition in my experiment (Ramnani and Miall, 2004). In addition, the error-related negativity, an ERP signal that arises when one makes an error (Gehring et al., 1993), and which has been localised to the MPFC (Dehaene et al., 1994), has recently been shown to also arise when one observes another person making an error (Bates et al., 2005;van Schie et al., 2004).

I suggest that the activation of the posterior STS in both the 'other' and 'subject' conditions, compared to the 'no agent' condition, also reflects the monitoring of an action and its consequences in these two conditions. The posterior STS is involved in the analysis of biological motion (Allison et al., 2000) and more specifically it is believed to be involved in representing goal-directed actions (Bonda et al.,

1996;Castelli et al., 2000;Grezes et al., 1998). Recently the posterior STS has been implicated in predicting/monitoring the actions of others (Pelphrey et al., 2003;Pelphrey et al., 2004a;Ramnani and Miall, 2004). My results suggest that the posterior STS is involved in monitoring our own actions and their consequences as well as those of others.

The temporal poles and the region around the precuneus and posterior cingulate also showed greater activation to both the 'other' and the 'subject' conditions compared to the 'no agent' condition, suggesting that they are also involved in monitoring actions and their outcomes, which is consistent with their activation in many tasks involving thinking about other peoples actions (Fletcher et al., 1995;Gallagher et al., 2000). However, the precuneus was significantly more active during the 'other' compared to the 'subject' condition, suggesting that this region is primarily involved in monitoring the actions of others. This is consistent with a previous study, which found that imagining yourself performing an action activated the precuneus, but to a lesser extent than imagining someone else performing the same action (Ruby and Decety, 2001).

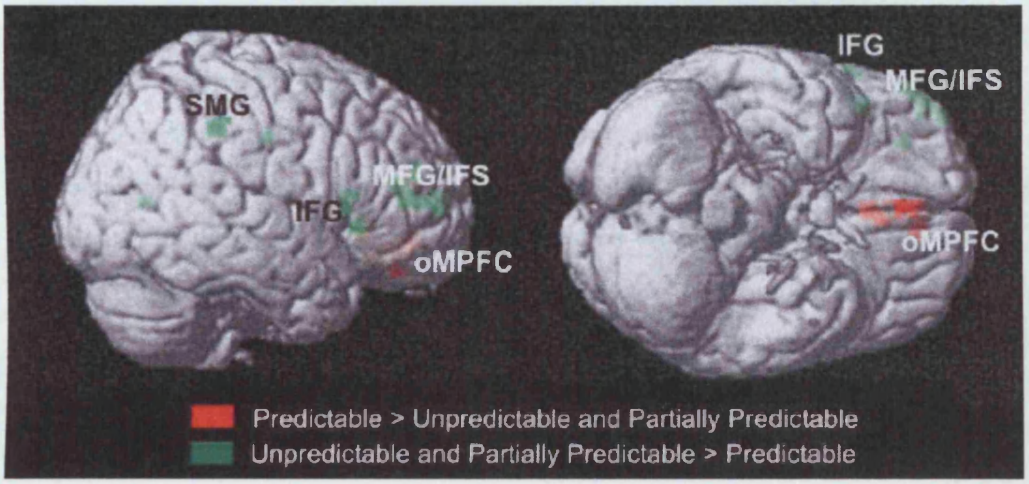
A cluster in the right lateral cerebellum showed significant activation during the 'other' conditions compared to the 'no agent' condition, as well as during the 'subject' compared to the 'no agent' condition. The right lateral cerebellum has previously been implicated in predicting the sensory consequences of our own actions (Blakemore et al., 1998b;Blakemore et al., 2001). Activation of this region in the 'other' as well as the 'subject' condition suggests that the cerebellum may also be involved in monitoring the consequences of other people's actions.

#### 7.4.2.2 Effects of predictability

I did not find any effect of contingency/predictability in the auditory cortex. This may be due to back ground scanner noise concealing any more subtle effects in the auditory cortex, or it may be because the difference in the time delay between the tone and the button press/disappearance of the white dot, in the 'predictable', 'partially predictable' and 'unpredictable' conditions, was insufficient to cause differential activation in the auditory cortex. Shafer and Marcus demonstrated that

attenuation of the response to self-produced auditory stimuli persisted even with delays of up to 4 seconds between the tone and the button press. All my stimuli occurred within 1 second of the button press, perhaps explaining why I did not see an effect of predictability in the auditory cortex. However, I did identify effects of stimulus predictability/contingency in the orbital medial prefrontal cortex, the lateral frontal cortex, and the supramarginal gyrus (see Figure 7.3).

***Figure7. 3 – Effects of contingency/predictability***




*Right lateral and ventral views of a standard T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template. Regions showing significant effects of predictability/contingency are shown superimposed on the rendered image (spatial extent threshold of 3 voxels was used for display purposes). Areas in green, including the inferior frontal gyrus (IFG), the Middle Frontal Gyrus(MFG) and Inferior Frontal sulcus (IFS), and the Supramarginal gyrus (SMG), show greater activation for the 'unpredictable' and 'partially predictable' conditions, compared to the 'predictable' condition (partially predictable > predictable $p < 0.001$ uncorrected, masked by unpredictable > predictable $p<0.01$ uncorrected). The orbital medial prefrontal cortex (oMPFC), in red, shows significantly greater activation for the predictable' condition, compared to the 'partially predictable' and 'unpredictable' conditions (predictable > partially predictable $p < 0.001$ uncorrected, masked by predictable > unpredictable $P<0.01$ uncorrected).*

#### *7.4.2.2.1 Orbital medial prefrontal cortex*

While the dorsal medial prefrontal cortex showed greater activation to the 'subject' and 'other' conditions compared to the 'no agent' conditions, the orbital medial prefrontal cortex (oMPFC) showed greater activation to the 'predictable' conditions, compared with the 'partially predictable' and the 'unpredictable' conditions, across agency conditions. It has been proposed that the medial orbito-frontal cortex is involved in monitoring and learning associations between stimuli, responses and outcomes (Elliott et al., 2000;Rolls, 2004). Amodio and Frith propose that while the dMPFC is involved in monitoring actions, the oMPFC is involved in monitoring outcomes (Amodio and Frith, 2006). In my study, subjects had to monitor the association between an outcome, the sound, and an action (a button press) or a visual stimulus (another person making a button press or the disappearance of the white dot). Thus the activation of the oMPFC in my study is consistent with its proposed role in monitoring the relationship between a stimulus and an outcome. My findings suggest that the oMPFC shows greater activation when the degree of contingency, between the stimulus and the outcome, is greater.

#### *7.4.2.2.2 Lateral frontal regions*

Two main lateral frontal regions showed greater activity during the 'unpredictable' and 'partially predictable' conditions compared to the 'predictable' conditions: a region around the right middle frontal gyrus and inferior frontal sulcus, and the right inferior frontal gyrus, where it meets the lateral fissure and insula. Both of these areas have been implicated in temporal processing in several studies (Coull et al., 2004;Ferrandez et al., 2003;Lewis and Miall, 2003;Livesey et al., 2006;Smith et al., 2003;Tregellas et al., 2006), and activity in these regions increases with task difficulty (Tregellas et al., 2006). In my experiment, at the end of each block, subjects had to judge whether the tones heard in that block were contingent upon the button press or the disappearance of the white dot. This was essentially a timing task as the subjects had to monitor and compare the time intervals between the button press, or disappearance of the white dot, and the subsequent tones in each block in order to complete the task. The increased activity seen in these time perception regions during the 'partially predictable' and 'unpredictable' conditions may reflect

increased task difficulty in these two conditions compared to the 'predictable' condition. The task was inherently more difficult in the 'partially predictable condition' as the stimuli in this condition were designed so that the sounds would not be perceived as clearly contingent or non-contingent by the subjects, and that instead the subjects' responses would be at chance level. The task also appears to have been more difficult in the 'unpredictable' condition compared to the 'predictable' condition as subjects' responses were 87% accurate in the 'predictable' blocks but only 80% accurate in 'unpredictable' blocks, though this difference did not reach significance ($p=0.087$). If these areas are responding to task difficulty I would expect to see more activity in these regions during the 'partially predictable' than during the easier 'unpredictable' condition. Comparison of the 'partially predictable' and 'unpredictable' conditions reveals greater activity in the right inferior frontal gyrus during the 'partially predictable' condition. Similarly, plotting the betas for the peak voxels in the right middle frontal gyrus/inferior sulcus reveals higher activation for the 'partially predictable' than the 'unpredictable' condition, though this difference does not appear to be significant.

#### *7.4.2.2.3 Supramarginal gyrus*

The right inferior parietal cortex, in the supramarginal gyrus also showed significantly greater activation during the 'partially predictable' and 'unpredictable' conditions. The right inferior parietal lobe, and the supramarginal gyrus specifically, has also been implicated in timing (Assmus et al., 2003;Livesey et al., 2006), (though in these studies it was the left rather than the right supramarginal gyrus that was activated). Activity in this region is greatest during the 'partially predictable' condition suggesting that the increased activity seen in this region reflects the difficulty of the task as does the activity in the lateral frontal cortex.

## 7.5 Conclusion

I found that a set of brain regions, namely the dorsal medial prefrontal cortex, precuneus, and posterior STS, previously implicated in monitoring and predicting our own actions and those of others, are also involved in monitoring and predicting the sensory consequences of those actions. I also identified an orbital medial prefrontal region, previously implicated in learning and outcome monitoring, that shows an increased response as the degree of contingency between and event and its outcome increases.

# CHAPTER 8: SOMATOSENSORY ACTIVATIONS DURING THE OBSERVATION OF TOUCH

## 8.1 Introduction

During the observation of action, a significant proportion of the brain's motor system becomes active (Rizzolatti et al., 2001;Rizzolatti and Craighero, 2004). In monkeys, neurons in ventral premotor cortex fire both when the monkey executes grasping actions and when it observes another individual (human or monkey) performing the same action (Gallese et al., 1996;Rizzolatti et al., 1996a). There is growing evidence that a similar mirror system also exists in the human brain (see General Introduction for a review of the evidence). For example, observing actions leads to somatotopic activation of the premotor cortex, with the mouth represented laterally and the foot medially (Buccino et al., 2001). There is also accumulating evidence that action observation modulates activity in the sensory cortices in the absence of sensory stimulation (see General Introduction). This activity may represent the predicted sensory consequences of the observed action. In addition, a number of brain systems with 'mirror' properties have recently been described. Common regions are activated by the experience and mere observation of disgust (Wicker et al., 2003), emotional facial expression (Carr et al., 2003), and pain (Singer et al., 2004).

Here I sought to investigate whether in addition to representing actions of other in our own motor system, and representing the sensory consequences of these actions in our sensory cortices, we also represent the sensations experienced by others in a similar manner. A recent study has demonstrated that the observation of touch to someone else's legs activates similar regions in the secondary somatosensory cortex (SII) in the observer's brain as when the observer's own legs are touched (Keysers et al., 2004), suggesting the existence of the touch mirror system, equivalent to the action mirror system. However, this SII activation was also found during the observation of touch to an object, and no primary somatosensory cortex activity was found in either condition.

I also describe a female subject (C) for whom the observation of another person being touched is experienced as tactile stimulation on the equivalent part of her own

body, and investigate the neural basis of this experience. C experiences touch from purely visual input. She experiences tactile stimulation on the part of her body that mirrors the body part she observes being touched. C has spent the whole of her life experiencing touch when she observes touch on others, unaware that the vast majority of the population does not experience similar sensations. She was surprised to discover that her perception of touch on observing others being touched is unusual.

There are various possible causes of C's mirror-touch sensation. One possibility is that it is due to over activation of somatosensory regions normally activated during the observation of touch (the putative tactile mirror system; (Keysers et al., 2004)). Perhaps this system is activated above a threshold for conscious tactile perception in C when she observes touch to another person so that she perceives the touch as if she is the object of it. In most people, this system would be active below a certain threshold, resulting in no conscious perception of tactile stimulation. In the visual system, there is evidence that stimulus processing with awareness is associated with greater activity in ventral visual cortex than processing without awareness (Beck et al., 2001;Rees et al., 2002). One crucial difference between C's phenomenology and the results of the fMRI experiment described above (Keysers et al., 2004) is that C reports no experience of tactile perception when she observes objects being touched. Therefore, her touch mirror system should not be activated more than normal when she observes objects being touched.

A second possible explanation of C's mirror-touch sensation is that it reflects direct connectivity between visual and somatosensory regions that is unique to C. In this account, C's mirror-touch experience would not depend upon the same mechanisms that are believed to be involved in the observation of touch in the rest of the population. A third possible explanation is that bimodal cells in the parietal cortex, specifically the intraparietal sulcus, which respond to both visual and tactile stimuli (Bremmer et al., 2001;Macaluso et al., 2003), are activated above the threshold for tactile perception during the observation of touch in C.

The aims of the current study were twofold. First, the experiment was designed to investigate neural interactions between visually perceived touch and tactile perception in the normal population. Secondly, I investigated the neural systems

underlying C's mirror-touch experience. I used fMRI to compare brain activity while the C and a group of 'normal control' subjects observed people being touched and objects being touched.

To investigate whether brain activity during observation of touch follows a somatotopic organization, I compared brain activity during the observation of touch to different areas of the body (human neck and face, and similar regions on an object) and to different sides of the body. There were three reasons why the face and neck were chosen as regions of stimulation in both the videos and the touch conditions. First, the face was chosen because of the known somatotopic representation of this region in primary somatosensory cortex (SI). Although the exact representation of the neck in human SI is unknown, the neck was chosen because it is physically close to the face but does not activate the face area of SI. Secondly, the face and neck were chosen because of the desire to match as closely as possible the human face and neck with an object with face- and neck-like properties (e.g. an electric fan) in the observation conditions. Finally, C reported being particularly sensitive to the observation of touch to another person's face and neck.

Activations during the observation of touch were compared with activations during tactile stimulation to the subject's own face and neck. I made several predictions. First, I predicted that, in the control subjects and in C, observation of touch to another human would activate somatosensory regions more than observation of touch to an object. Secondly, I predicted that SI activity to the observation of touch would be related to the region of the body observed being touched in a somatotopic manner. Finally, I predicted that these observation-related activations would be significantly higher in C than in the control subjects. In addition, there may be additional regions of C's brain that are activated by the observation of touch which are not activated in the control group. This could account for why observed touch is not perceived as touch in most people.

## 8.2 Materials and Methods

### 8.2.1 Subjects

A female, right-handed subject (C, age 41 years), who experienced tactile stimulation on her own body when seeing another person being touched, as well as 12 right-handed control participants (seven females; mean age 28.75 ± 2.66 years), gave informed consent and participated in the study, which was approved by the National Hospital for Neurology and Neurosurgery Ethics Committee.

C, who appears to be neurologically and psychologically normal in every other way, claims always to have perceived observed touch on other people as touch to her own body. Although always having experienced touch when she observes touch on others, she was unaware that the vast majority of the population do not experience similar sensations until July 2003 when the authors were talking with her about observed touch and the mirror system. She was surprised to discover that her perception of touch on observing others being touched is unusual. C's reported perception of touch when observing touch on other people seems to be reliable over time: the words and phrases she uses to describe the observed touch, its intensity and exact location on herself are highly consistent.

### 8.2.2 Stimuli

#### *8.2.2.1 Touch session*

During the touch session, the subjects lay on the MRI bed with their eyes shut, while the experimenter applied a tactile stimulus to the subjects' neck or face (cheek area). There were four touch conditions defined according to the site of tactile stimulation: 1) touch to left side of neck (tLN); 2) touch to right side of neck (tRN); 3) touch to left side of face (tLF); and 4) touch to right side of face (tRF). In addition there was a Baseline condition during which no touch occurred. The tactile stimulus device consisted of a 2-inch rigid piece of felt attached to the end of a wooden rod (length ~1m). The rod reached into the scanner bore and could be positioned by the experimenter such that the felt-tip touched the subject's neck or cheek (or neither in

the baseline condition). In each block, the subject was stroked for 20 seconds on one of the four areas. Over the session there were five blocks of each tactile stimulus condition and five blocks of the rest baseline. The order of conditions was alternated between Face and Neck on either side.

#### *8.2.2.2 Video sessions*

The experiment also involved two video sessions, during which subjects were scanned while viewing short video clips. Each video clip lasted 4.5 seconds. Half the clips (the "human" videos) showed the head and shoulders of a person being touched on their neck or face by the finger of another person. Three different people, one male and two female, featured in these videos and only their head and shoulders were visible. The other half (the "object" videos) showed inanimate objects (a lamp, an electric fan and a loud speaker) being touched on their equivalent 'neck' or 'face' regions. The object conditions were designed to control for the presence of visual stimulation and movement of the toucher's hand and arm and any other non-specific visual factors in the films.

The design was factorial with 3 factors: 1) Focus of the observed touch (human or object), 2) side of observed touch (left or right) and 3) location of observed touch (face or neck). This resulted in 8 conditions, as shown in Table 8.1. In addition, a fixation baseline condition was included.

**Table 8.1 - Experimental conditions in video sessions**

| | | **Human** | **Object** |
|---|---|---|---|
| **Right** | **Neck** | *Human Right Neck (HRN)* | *Object Right Neck (ORN)* |
| | **Face** | *Human Right Face (HRF)* | *Object Right Face (ORF)* |
| **Left** | **Neck** | *Human Left Neck (HLN)* | *Object Left Neck (OLN)* |
| | **Face** | *Human Left Face (HLF)* | *Object Left Face (OLF)* |

The videos were presented in 23-sec blocks. Each block contained four different video clips from the same condition. The order in which the four video clips were presented within each block was random. At the end of each block, following the four videos, subjects were asked to rate the intensity of the touch applied to the

person or object in the most recent video. A screen appeared for 5 seconds displaying the words "hard", "medium" and "soft". Subjects indicated their answer by pressing one of three buttons on a keypad held in their right hand. The intensity of the touch in the videos was not in fact deliberately varied between the different clips. The question was designed to ensure that the subjects paid attention to the touch stimulus in the videos for its duration.

During each of the video sessions, there was a total of 27 blocks, comprising three repetitions of each of the eight video conditions (see Table 8.1) and three repetitions of the 23-sec fixation baseline block. The order of presentation of the blocks was counterbalanced within and between subjects.

### 8.2.3 Imaging

A Siemens ALLEGRA system (Siemens, Erlangen) operating at 3 T was used to acquire both multi-slice axial gradient-echo, echo-planar T2* weighted image volumes with blood oxygenation level dependent (BOLD) contrast and axial T1 weighted fast-field echo structural images for anatomical co-registration. (See Chapter 2: fMRI Methods for details of functional imaging). Data were acquired in 3 functional imaging sessions. A total of 205 volumes was acquired in the *Touch* session, and 250 volumes were acquired in each of the following two *Video* sessions. Each session began with 8 "dummy" volumes, which were subsequently discarded, to allow for T1 equilibration effects. Each functional image volume comprised 40 2mm axial slices with in-plane resolution of 3 x 3 mm positioned to cover the whole brain. Volumes were acquired continuously every 2.6 seconds throughout each session (TR = 2.6).

The acquisition of a T1-weighted anatomical image occurred after the three functional sessions and lasted approximately 12 minutes. The total duration of the experiment was approximately 45 minutes.

### 8.2.4 Perceptual Ratings

After scanning, subjects were asked whether they felt the observed touch in any of the conditions. If they responded that they did, they were asked to watch 32 video clips comprising four exemplars of each of the eight conditions, selected at random from the video clips used in the scanning experiment. The order of presentation of the clips was random. Subjects were asked to rate the intensity of the tactile stimulation they felt on their own face or neck when they watched each video on a scale from 0 (indicating 'no perceived tactile sensation') to 5 (indicating 'very intense tactile sensation').

### 8.2.5 Statistical analysis

Functional imaging analysis used Statistical Parametric Mapping, implemented in SPM2 (Wellcome Department of Cognitive Neuroscience, www.fil.ion.ucl.ac.uk/spm). For each subject, the fMRI scans were realigned to correct for inter-scan movement, using sinc interpolation (Friston et al. 1995), and subsequently stereotactically normalised using affine registration followed by non-linear registration (Ashburner and Friston, 1999). The data were resampled using sinc interpolation, with a resolution of 3 x 3 x 3 $mm^3$, into the standard space of the Montreal Neurological Institute brain. The scans were then smoothed with a Gaussian kernel of 6mm full-width half maximum. (See Chapter 2: fMRI Methods for details of realignment, normalisation and smoothing).

The analysis of functional imaging data entails the creation of statistical parametric maps that represent a statistical assessment of hypothesised condition specific effects (Friston et al., 1994a). Condition specific effects were estimated with the General Linear Model with a delayed box-car waveform. (See Chapter 2: fMRI Methods for details of statistical analysis). Low frequency sine and cosine waves modelled and removed subject-specific, low frequency drifts in signal, and global changes in activity were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. For the group of control subjects, the resulting parameter estimates for each regressor at each voxel were then entered into a second level analysis where subject served as a random effect in a within-subjects

ANOVA. For both the group of control subjects (at the second level) and C (at the first level), the main effects and interactions between conditions were then specified by appropriately weighted linear contrasts and determined using the t-statistic on a voxel-by-voxel basis.

Statistical analysis was performed on the data from the Touch session to examine the main effects of tactile stimulation versus the no tactile stimulation baseline ({tRN+tLN+tRF+tLF} – baseline). Because of my specific hypothesis concerning somatotopic representation of observing the face being touched, analysis was performed to examine the main effects of touching the subject's face versus neck ({tRF+tLF} – {tRN+tLN}), left versus right side ({tLF+tLN} – {tRF+tRN}) and right versus left side ({tRF+tRN} – {tLF+tLN}). In addition to a group analysis, individual subject analyses were performed to investigate the somatotopy of the activations during each touch condition.

The data from the video sessions were analysed to examine the main effects for which *a priori* predictions were made. These were the main effects of watching videos ({HRF+HLF+HRN+HLN+ORF+OLF+ORN+OLN} – baseline) and observing touch to a human compared with touch to an object ({HRF+HLF+HRN+HLN} – {ORF+OLF+ORN+OLN}) (see Table 8.1 for an explanation of the abbreviations). In addition, analysis of the human video conditions was performed to examine the main effects of observation of touch to the face ({HRF+HLF} – {HRN+HLN}), to the left side ({HLF+HLN} – {HRF+HRN}) and to the right side ({HRF+HRN} – {HLF+HLN}). For each of these latter contrasts, the resulting images were inclusively masked (at $p<0.05$ uncorrected) with the equivalent contrast in the Touch experiment to investigate common activations during tactile stimulation and the observation of tactile stimulation.

These statistical contrasts were used to create an SPM{t}, which was transformed into an SPM{Z} and thresholded at $p<0.05$ (corrected on the basis of the theory of random Gaussian fields for multiple comparisons across the whole brain volume examined). I report those regions that survive correction at $p<0.05$ plus those regions surviving an uncorrected threshold of $p<0.001$ for which I had an *a priori* hypothesis for their activation, namely somatosensory areas and the mirror neuron system.

#### *8.2.5.1 Comparison between C and control subjects*

At the second level, a between-subjects ANOVA was used to test the significance of the interaction between group (control vs. C) and condition (observing human vs. observing object). This analysis was performed to test the hypothesis that there would be significantly greater activity in somatosensory and premotor regions when C, relative to the control subjects, observed humans being touched relative to objects being touched.

## 8.3 Results

### 8.3.1 Perceptual ratings

None of the control subjects reported feeling the observed touch on their own face or neck during any of the video conditions. C was asked to rate the intensity of the tactile stimulation she felt on her own face or neck when she watched each video on a scale from 0 (indicating 'no perceived tactile sensation') to 5 (indicating 'very intense tactile sensation'). Table 8.2 shows C's perceptual ratings. C reported feeling no sensation on her own face or neck during the object videos.

**Table 8.2 - C's mean ratings for the perception of touch on her own face or neck during the observation of touch to another person or object's face and neck.**

| Observation condition | C's mean ratings |
|---|---|
| Human right neck (HRN) | 3.88 |
| Human right face (HRF) | 3.50 |
| Human left neck (HLN) | 3.67 |
| Human left face (HLF) | 4.33 |

### 8.3.2 fMRI data: touch session

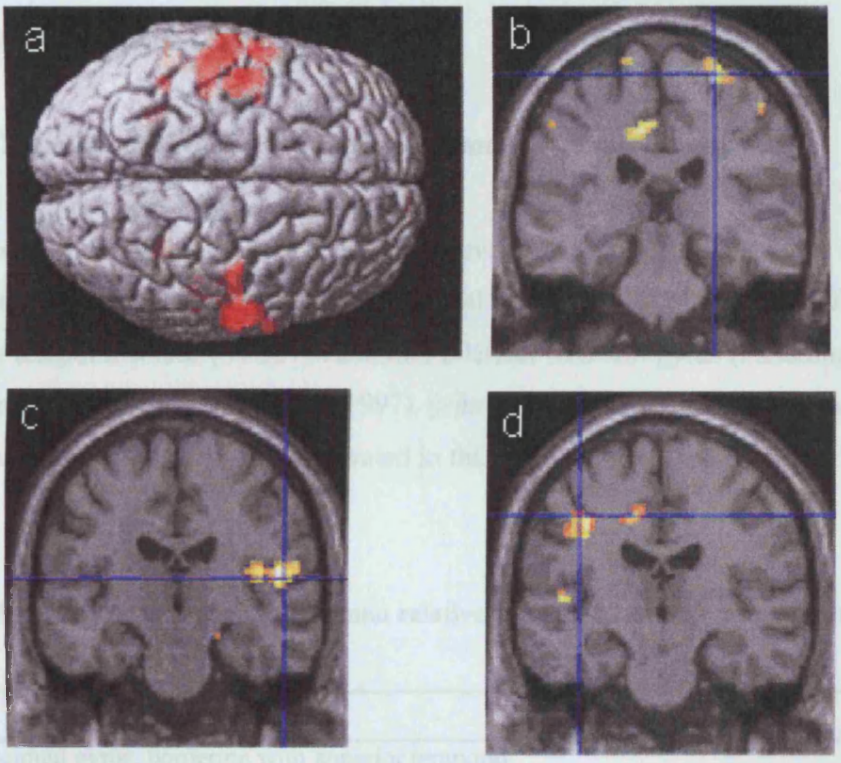
#### 8.3.2.1 Main effect of touch – baseline:

Comparison of the four touch conditions relative to baseline ({tRN+tRF+tLN+tLF} – baseline) in the group of control subjects and in C resulted in activation of a number of somatosensory regions, including primary somatosensory cortex (SI) and secondary somatosensory cortex (SII), and motor and premotor regions. (See Figure 8.1a).

### 8.3.2.2 Main effect of touch to the face vs. neck:

Comparison of the two touch-face conditions relative to the two touch-neck conditions ({tRF+tLF} – {tRN+tLN}) in the group of control subjects and in C resulted in activation of regions in SI corresponding to the head area, SII and the parietal cortex. (See Figure 8.1b).

***Figure 8.1 - Activations due to tactile stimulation in the control group***




*a) somatosensory activations resulting from the comparison of the four touch conditions relative to rest baseline superimposed on T1 weighted image rendered in the standard space defined by the Montreal Neurological Institute template. b) SI activation resulting from the comparison of the two touch-face conditions relative to the two touch-neck conditions on a coronal section of a TI MR image at y = -27. c) right SII activation resulting from the comparison of the two touch-left side conditions relative to the two touch-right side conditions on a coronal section of a TI MR image at y = -18. d) shows left SI and SII activation resulting from the comparison of the two touch-right side conditions relative to the two touch-left side conditions shown on a coronal section of a TI MR image at y = -18. Activatios are thresholded at p<0.001 uncorrected with spatial extent threshold of 5 voxels.*

#### 8.3.2.3 Main effect of touch to the right vs. left:

Comparison of the two touch-left side conditions relative to the two touch-right side conditions ({tLF+tLN}-{tRF+tRN}) in the group of control subjects and in C resulted in right-sided activation of SI and SII. (See Figure 8.1c). The contrast of the two touch-right side conditions relative to the two touch-left side conditions ({tRF+tRN}-{tLF+tLN}) resulted in left-sided activation of SI and SII. (See Figure 8.1d).

### 8.3.3 fMRI data: video sessions

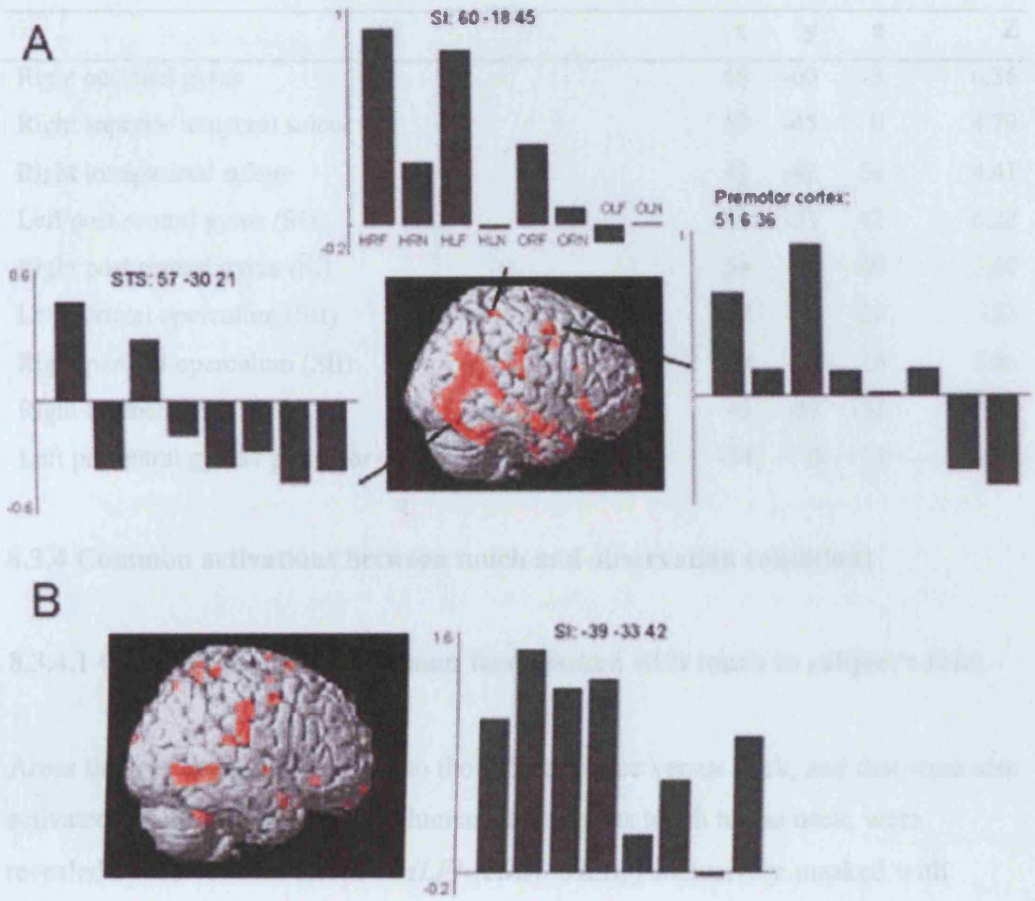
#### 8.3.3.1 Main effect of observing touch to humans vs. touch to objects:

In the control subjects, the main effect of observing touch to a human relative to observing touch to an object resulted in bilateral activation along the length of the superior temporal sulcus (STS). In addition bilateral fusiform gyrus (including the fusiform face area; Kanwisher et al. 1997), primary and secondary somatosensory cortex and premotor cortex were activated in this contrast. (See Table 8.3 and Figure 8.2A).

**Table 8.3 – Observing touch to a human relative to touch to an object in the control group**

| | x | y | z | Z |
|---|---|---|---|---|
| Left occipital gyrus, bordering with superior temporal sulcus | -45 | -72 | 3 | 4.17 |
| Right temporo-parietal junction, intraparietal sulcus and STS | 60 | -57 | 24 | 4.86 |
| Right fusiform gyrus | 45 | -57 | -27 | 4.24 |
| Precuneus bordering posterior cingulated | 3 | -57 | 36 | 4.42 |
| Right intraparietal sulcus | 42 | -36 | 60 | 3.11 |
| Left superior temporal sulcus | -60 | -21 | -12 | 4.03 |
| Right post central gyrus (SI) | 66 | -18 | 30 | 3.70 |
| Right parietal operculum (SII) | 63 | -18 | 15 | 3.97 |
| Right inferior frontal gyrus | 54 | 30 | -6 | 3.25 |
| Superior/middle frontal gyrus (premotor cortex) | 42 | 6 | 39 | 4.42 |

***Figure 8.2 – Observing touch to a human versus touch to an object***




*(A) In the control group the contrast ({HRF+HRN+HLF+HLN}-{ORF+ORN+OLF+ORF}) resulted in activation of bilateral STS at the temporo-parietal junction, fusiform gyrus, SI, SII and premotor cortex. (B) In C this contrast resulted in activation of the right STS, bilateral SI and SII, insula cortex, left anterior premotor cortex and right cerebellar cortex. These activations are shown superimposed on a rendered T1 structural MR image in the stereotactic space of Montreal Neurological Institute template. Activations are thresholded at $p<0.001$ uncorrected with spatial extent threshold of 5 voxels. The plot shows parameter estimates of the relative activation in each of the eight conditions in right SI, right STS and right premotor cortex in controls (A), and in left SI in C (B). Condition labels as in top plot can be found in Table 8.1.*

In C, this contrast resulted in activation of the right superior temporal sulcus (STS), bilateral primary and secondary somatosensory cortex, insular cortex, anterior premotor cortex and cerebellar cortex. (See Table 8.4 and Figure 8.2B).

**Table 8.4 – Observing touch to a human relative to touch to an object in C**

| | x | y | z | Z |
|---|---|---|---|---|
| Right occipital gyrus | 60 | -60 | -3 | 6.36 |
| Right superior temporal sulcus | 69 | -45 | 0 | 4.79 |
| Right intraparietal sulcus | 42 | -42 | 66 | 4.41 |
| Left post central gyrus (SI) | -39 | -33 | 42 | 6.28 |
| Right post central gyrus (SI) | 54 | -21 | 39 | 5.60 |
| Left parietal operculum (SII) | -57 | -30 | 21 | 5.53 |
| Right parietal operculum (SII) | 60 | -30 | 18 | 3.96 |
| Right cerebellum | 45 | -51 | -33 | 5.18 |
| Left precentral gyrus / premotor | -54 | 0 | 33 | 5.18 |

### 8.3.4 Common activations between touch and observation conditions

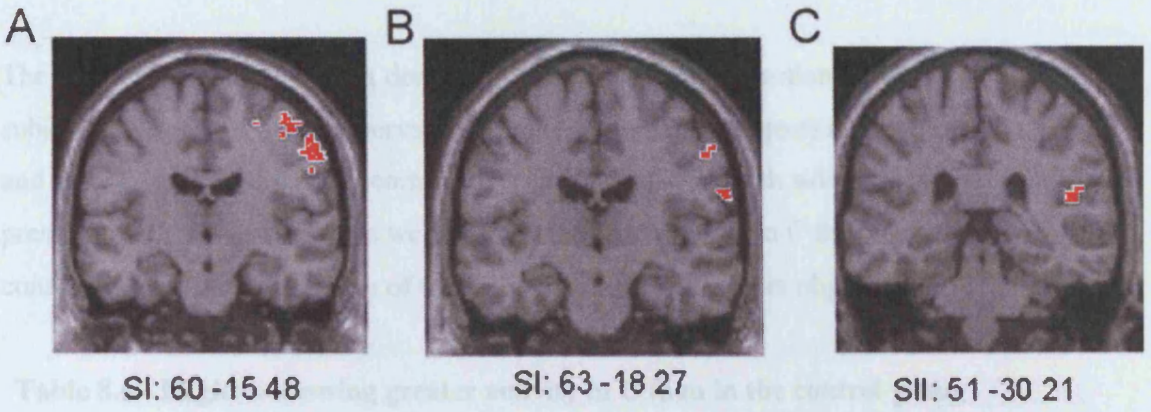
#### 8.3.4.1 Observing touch to a human face masked with touch to subject's face:

Areas that are activated by touch to the subject's face versus neck, and that were also activated by observing touch to a human face, versus touch to the neck, were revealed by the contrast *({HRF+HLF}-{HRN+HLN})* inclusively masked with *({tRF+tLF}–{tRN+tLN})* at $p<0.05$ uncorrected. This contrast revealed activation of the head area of SI located in the anterior wall of the right post central gyrus in the control group. The same contrast also revealed activation of the head area of SI located in the anterior wall of the right post central gyrus in C. (See Table 8.5 and Figure 8.3A & B).

**Table 8.5 - Observing touch to human face masked by touch to subject's face**

| ***control group*** | x | y | z | Z |
|---|---|---|---|---|
| Right post central gyrus (SI head area) | 30 | -48 | 66 | 4.05 |
| Right precentral gyrus | 57 | -15 | 45 | 3.92 |
| Right superior frontal gyrus | 27 | -9 | 69 | 3.44 |
| ***C*** | | | | |
| Right post central gyrus (SI) | 63 | -18 | 27 | 2.38 |
| Right parietal operculum (SII) | 51 | -24 | 18 | 1.55 |
| Right precentral gyrus | 57 | -15 | 42 | 2.67 |

***Figure 8.3 - Common activations between touch and observation conditions***




*(**A**) Activations in SI head area resulting from the comparison of observing touch to a human face (relative to a human neck) at p<0.01 uncorrected masked with touch to the subject's face (relative to their neck) in the control group at p<0.05 uncorrected, shown on a coronal section of a T1 image at y = –15. (**B**) Activations in SI head area resulting from the comparison of observing touch to a human face (relative to a human neck) at p<0.01 uncorrected masked with touch to the subject's face (relative to neck) in C at p<0.05 uncorrected, shown on a coronal section of a T1 image at y = –18. (**C**) Activations in right SII resulting from the comparison of observing touch to the left side of a human (relative to the right side) at p<0.01 uncorrected masked with touch to the subject's left side (relative to their right side) in the control group at p<0.05 uncorrectd, shown on a coronal section of a T1 image at y = –30. A spatial extent threshold of 5 voxels was used..*

### 8.3.4.2 Observing touch to the left or right side of a human masked with touch to the subject's corresponding side:

Areas activated by touch to the subject's left, versus right, side that were also activated by the observation of touch to the left, versus right, side of a human were revealed by the contrast *({HLF+HLN}-{HRF+HRN})* inclusively masked by *({tLF+tLN}-{tRF+tRN})* at p<0.05 uncorrected. This contrast revealed activation of right secondary somatosensory areas in the control group. (See Figure 8.3C). The opposite contrast *({HRF+HRN}-{HLF+HLN})* inclusively masked by *({tRF+tRN}-{tLF+tLN})* at p<0.05 uncorrected, did not reveal any regions significantly activated by observing touch to the right side that were also activated by touch to the subject's right side. Neither of these masked contrasts revealed any significant activation in C, possibly because of lack of power.

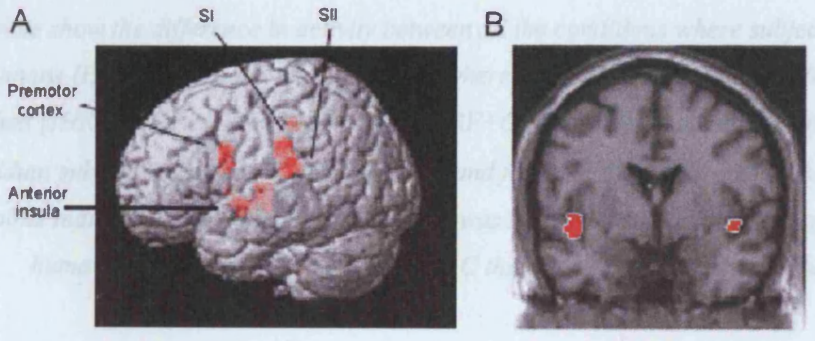
### 8.3.5 Comparison between C and control subjects

The between subjects ANOVA demonstrated a significant interaction between subject (control vs. C) and observation condition (human vs. object) in the primary and secondary somatosensory cortex, the anterior insular on both sides and the left premotor cortex. These regions were significantly more active in C than in the controls during the observation of touch to a human relative to an object.

**Table 8.6 - Regions showing greater activity in C than in the control group during the observation of touch to a human relative to an object**

| | x | y | z | Z |
|---|---|---|---|---|
| Left supramarginal gyrus | -60 | -27 | 30 | 3.52 |
| Left parietal operculum (SII) | -60 | -33 | 18 | 3.55 |
| Right parietal operculum (SII) | 60 | -30 | 18 | 2.95 |
| Left post central gyrus (SI) | -39 | -33 | 4 | 3.09 |
| Right post central gyrus / central sulcus | 54 | -24 | 39 | 3.29 |
| Left anterior insular cortex | -45 | -3 | -6 | 3.65 |
| Right anterior insular cortex | 45 | 0 | -3 | 2.95 |
| Left frontal operculum (Broca's area) | -60 | 6 | 18 | 3.31 |

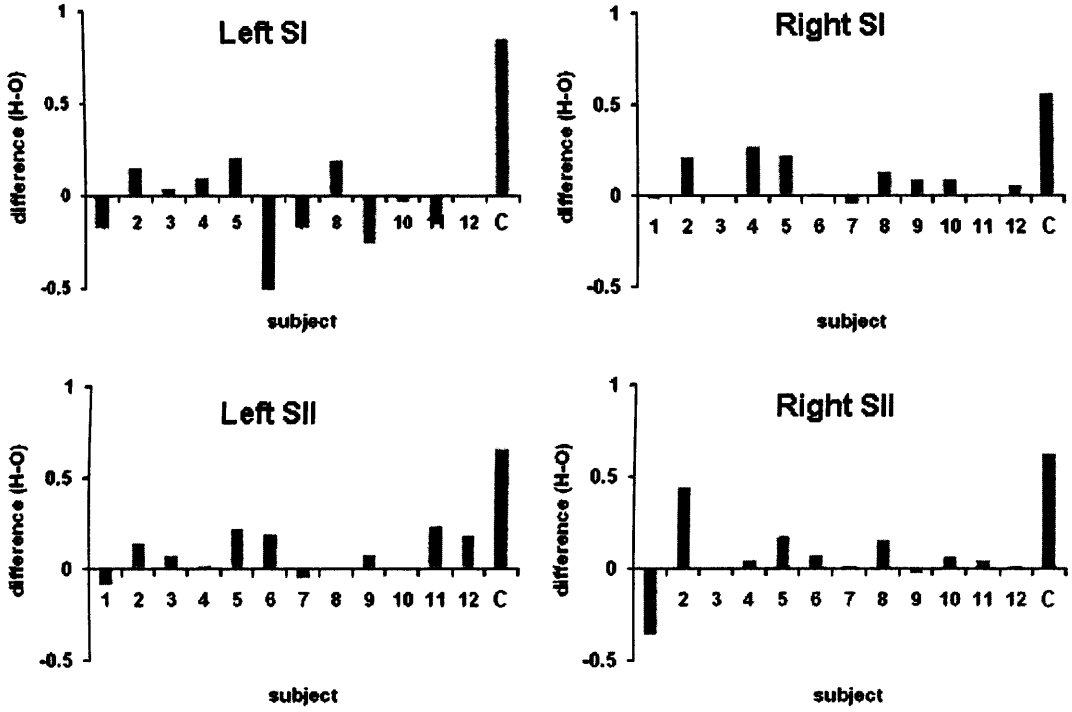
***Figure 8.4 – Areas that show greater activation to observation of touch to a human (versus observation of touch to an object) in C than in normal controls.***




*(A) Bilateral SI, SII, anterior insula and left premotor cortex were significantly more active in C than in the control group during the observation of touch to a human relative to an object ($p<0.001$ uncorrected). The left sided-activations are superimposed on a rendered MR image. (B) Bilateral insula activations resulting from this contrast superimposed on a coronal section of a T1 image. Spatial extent threshold of 5 voxels.*

To ensure that C's activations to the observation of touch to a human were not simply higher than the mean ofthe control group's activations, I plotted individualresponses in left and right SI and SII for each subject. (See Figure 8.5). This demonstrated that activity in these regions was higher in C than in any of the control subjects during the observation of touch to a human relative to touch to an object.

***Fig. 8.5 Plots showing individual subject neural activity during the conditions where subjects observed humans and objects being touched***




*The plots show the difference in activity between all the conditions where subjects observed humans (H) being touched and conditions where subjects observed objects (O) being touched ({HRN+HRF+HLN+HLF}-{ORN+ORF+OLN+OLF}). Activity is shown for each individual subject in the control group (1–12), and for C, in SI and SII in both hemispheres. The plots indicate that activity in these regions was higher during observation of touch to a human relative to touch to an object in C than in all the control individuals*

## 8.4 Discussion

In this study, I investigated the neural systems associated with the observation of touch in normal humans and in an individual who experiences mirror-touch sensations. The results of the fMRI study demonstrate that, in normal control subjects, a number of regions including the primary and secondary somatosensory cortices are activated by the mere observation of touch to another human (relative to observation of touch to an object). The somatosensory activations to the observation of touch were somatotopically organised, following the classical sensory homunculus in SI (Disbrow et al., 2000). In the control subjects, somatosensory activations were present in the absence of any perception of touch. However, in this study I also included a subject, C, who experiences tactile stimulation on her own body when she observes other people being touched. My fMRI study was designed to investigate the difference in the neural systems that are activated by the observation of touch C, who experiences observed touch as tactile stimulation on herself, compared with the control subjects who experience no such tactile sensations. The somatosensory activation induced by the observation of touch to a human was significantly greater in C, who felt the observed tactile stimulation on her own body, than in the control group. In addition, C showed a higher activation than in the control group in premotor cortex and insular cortex during the observation of touch to a human.

### 8.4.1 Observation of touch in the brain

My study demonstrates that the observation of touch to another person's head or neck activates the STS, especially on the right, fusiform gyrus (in the region of the fusiform face area; (Kanwisher et al., 1997)), bilateral SI and SII, and premotor cortex. These regions were activated more by the observation of a human's head or neck being touched than by the observation of a similarly shaped object being touched.

The fusiform gyrus and the STS are typically activated by the visual presentation of faces (Kanwisher et al., 1997). Single-cell studies in the monkey homologue of human STS have identified cells that respond selectively to faces (Baylis et al., 1985;Perrett et al., 1992). In the human brain, the STS is activated by faces, in

particular by facial movements (Puce et al., 1998;Wicker et al., 1998). The STS is often activated when subjects observe human action and biological motion (Grezes et al., 2001;Grossman et al., 2000), and as such is generally considered as part of the mirror system even though it is not activated by action execution (Rizzolatti et al., 2001). The STS activation in the current study was stronger in the right than in the left hemisphere, which is consistent with previous neuroimaging studies of biological motion (Grezes et al., 2001;Grossman et al., 2000).

The premotor cortex has similar mirror properties. In monkeys, the premotor cortex contains neurons that respond both to the execution and the observation of action (Gallese et al., 1996). The human premotor cortex has been activated in neuroimaging studies in which subjects observe a range of different actions (Buccino et al., 2001;Grafton et al., 1996;Rizzolatti et al., 1996b). It is interesting to note that, in the current experiment, the STS and premotor cortex were activated significantly more by the observation of a human head being touched than by objects being touched. Both the object and human videos contained movement of a human hand (doing the touching), the only difference being the presence of a human face in the human videos. This raises the intriguing possibility that mirror areas are preferentially activated by "social" actions, i.e. actions directed towards other humans. The selectivity of mirror areas for biological agents (rather than inanimate devices) has been suggested before (Tai et al., 2004). My results imply that mirror areas are not only selective for biological actors, but are also preferentially activated when the target of the action is biological.

The intraparietal sulcus contains bimodal cells responsive both to vision and tactile stimulation (Bremmer et al., 2001;Macaluso et al., 2003). The activation of the intraparietal sulcus during the observation of touch to a human might represent responses of these bimodal cells. Alternatively, it is possible that the intraparietal activations reflect activity of neurons that respond to visual stimulation only (Grefkes et al., 2002).

SI, comprising areas 1, 2 and 3 in the post central sulcus, and SII, located in the parietal operculum in the posterior insula, respond to tactile stimulation (Burton et al., 1993;Del Gratta et al., 2000;Disbrow et al., 2000). It is remarkable that both SI

and SII were activated by the mere observation of touch to a human in the current study. This is in line with a recent study demonstrating that observing touch to a person's legs activates SII (Keysers et al., 2004). However, there are several notable differences between the current study and the study by Keysers and colleagues (Keysers et al., 2004). First, the videos in the current study depicted touch to the face and neck, whereas the videos in the study by Keysers and colleagues depicted touch to the legs. Secondly, the somatosensory activations here were significantly higher for the observation of touch to a human than to an object. In contrast, SII activation in the study by Keysers and colleagues was found both for observation of touch to human legs and to cylindrical objects.

Furthermore, I found significant activation of SI to the observation of touch to a human. SI activation was somatotopically organised according to which area of the body was observed being touched. The head area of SI, located on the anterior wall of the post central gyrus, was activated both by being touched on the face (versus on the neck) and by observing another human being touched on the face (relative to the neck). Keysers and colleagues (Keysers et al., 2004) report a non-significant trend towards SI activation to the observation of touch. One possible explanation for the differences between the current study and the one by Keysers and colleagues is that the presence of a human face in the videos used here triggers especially strong and somatotopically organized somatosensory activations. (See Figure 8.2A).

The lateralisation that occurred when being touched to one side was also present in SI when observing touch to the same side. SI lateralisation to the observation of touch was same-sided rather than being the mirror image of the side being touched. In other words, observing touch to the left side of a human face or neck activated right SI, which is the same side of SI activated when being touched on the left side. Such a finding is consistent with studies recording motor evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS). MEP threshold is lowered specifically in those muscles that are activated during the observed action (Fadiga et al., 1995). Each hemisphere is more strongly activated when viewing actions conducted by a model's contralateral hand than when viewing actions conducted by an ipsilateral hand (Aziz-Zadeh et al., 2002). Larger MEPs were produced in the

right hand when right rather than left hand actions were observed, while left hand MEPs increased only during observation of left hand movements.

Given the existence of mirror systems in several modalities including action (Rizzolatti et al., 2001), emotion (Carr et al., 2003) and pain (Singer et al., 2004), my data suggest that similar mirror activity is found during the observation of touch. However, one possibility is that the somatosensory activity to the observation of touch merely represents tactile imagery. There is neuroimaging evidence that primary and secondary somatosensory cortices are activated by anticipation of touch in the absence of any tactile stimulation (Carlsson et al., 2000). However, no subject reported imagining the touch in any of the conditions. Whether the activations to the observation of touch in the current study represent a tactile mirror system or tactile imagery remains to be investigated.

### 8.4.2 Mirrored touch sensation

As in the control group, somatosensory, parietal and premotor activation in C was significantly higher during the observation of touch to a human than touch to an object. The somatosensory activation induced by the observation of touch to a human was significantly greater in C than in the control group. In addition, unlike the individuals in the control group, C experienced the observed touch to a human face or neck as tactile stimulation on her own face or neck.

In the introduction to this chapter, I outlined three possible explanations for C's mirror-touch experiences. First, there could be increased activity in the tactile mirror system, demonstrated in the control subjects in this study and by Keysers and colleagues (Keysers et al., 2004), above a threshold for conscious tactile perception. Secondly, the existence of direct connections between C's visual and somatosensory areas could account for the difference between C and the control subjects. Thirdly, hyperactivation of bimodal visual-tactile cells could be sufficient to give rise to illusory touch in C.

Although bimodal visual-tactile cells, for example in parietal cortex, may be important in giving rise to mirrored touch sensation, they are unlikely to be the only

cells involved because of the changes in activation observed elsewhere in the mirror-touch system, including SI regions. The second account also seems unlikely. If there were direct connections between visual and somatosensory cortices in C, then activity in somatosensory regions would be predicted in C but not necessarily activity in the other areas found here. Nor would I expect to see any somatosensory activation in the normal control subjects when they observe touch, as they would not have the hypothesized direct connections.

The first account is favoured on the basis of the empirical evidence from this study. In most people, it is possible that the somatosensory mirror system, which matches observed and felt touch, is involved in understanding the effect of tactile stimulation on others. This system is normally active below a certain threshold such that no conscious perception of tactile stimulation is experienced. One possibility is that this system is activated above that perceptual threshold in C whenever she observes touch to another person. In this case, rather than simply allowing C to understand the tactile stimulation she is observing, C perceives it as if she were the receiver of it. In support of this supposition, activity in bilateral SI and SII was higher in C's brain than in any of the control subjects during the observation of touch to a human relative to touch to an object. (See Figure 8.5). In other words, SI and SII activity in C was not only significantly higher than the mean activity in these regions in the control subjects; C's activations were also higher than all individuals within the control group.

In addition to somatosensory activity during the observation of touch to a human, C showed a higher activation in left premotor cortex, in the vicinity of Broca's area in the frontal operculum, in this contrast than did the control group. I propose that this higher activation of premotor cortex represents overactivity of the action mirror system in C. It is possible that, when C observes action, her mirror system is activated to a greater extent than in most people.

This idea of a threshold for conscious perception is supported by several studies showing that consciousness of visual stimuli is associated with greater activity in ventral visual cortex, but that unconscious processing also activates the same region (Beck et al., 2001;Rees et al., 2002). Given the somatotopic activation of SI and SII during the observation of touch in the control group as well as in C, however, this

threshold hypothesis may be too simple to account for why the control subjects, and indeed most people, never perceive observed touch. Presumably the touch mirror system could occasionally be activated above threshold even in normal control subjects. Even though C's somatosensory activations were significantly higher than the activations in the control group, this may not explain why C feels observed touch whereas there was no hint of feeling observed touch in any of the control subjects. It would be surprising if there were no special regions associated exclusively with the conscious experience of touch.

One possible region that mediates the conscious perception of touch on oneself during the observation of touch is the anterior insula. This region was bilaterally activated in C during the observation of touch, but was not activated during the same condition in the control group. The anterior insula contains tactile receptive fields (Burton et al., 1993;Olausson et al., 2002). Furthermore, the insula is associated with self-processing. The anterior insula was activated in neuroimaging studies in which subjects imagined themselves performing actions relative to someone else performing the same action (Ruby and Decety, 2001), looked at pictures of their own face (Kircher et al., 2001) or identified their own memories (Fink et al., 1996). Farrer and Frith found activation of a very similar region of the anterior insula cortex, in both hemispheres, when subjects attribute actions to themselves rather than to another person (Farrer and Frith, 2002). Given its role in attribution to the self, it is possible that the anterior insula activity found in C in my study, along with over activation of the touch mirror system, accounts for why she perceives herself as the direct target of the observed touch.

## 8.5 Conclusion

In this study, I investigated the neural systems associated with the observation of touch in normal humans and in an individual who experiences mirror-touch sensations. In normal subjects the primary and secondary somatosensory cortices were activated by the mere observation of touch to a human (relative to observation of touch to an object). This activation was somatotopically organized, following the classical sensory homunculus in SI (Disbrow et al., 2000), such that observation of touch to the face activated the head area of primary somatosensory cortex, whereas observation of touch to the neck did not. In normal subjects, the brain's mirror system—comprising premotor cortex, superior temporal sulcus and parietal cortex—was also activated by the observation of touch to another human more than to an object. This suggests that we use our own somatosensory system to predict and simulate the sensory experiences of others, similar to the way in which we use our own motor system to predict and simulate the actions of others.

The activation patterns observed in C, who experiences observed touch as tactile stimulation on herself, differed from those of the normal control subjects (who experience no such tactile sensations) in three ways. Activations in the somatosensory cortex were significantly higher in C when she observed touch. These results suggest that, in C, the mirror system for touch is overactive, above the threshold for conscious tactile perception. C also showed higher activation in premotor cortex, part of the action mirror system, and insular cortex than the control group during the observation of touch to a human.

## Acknowledgement

This study was carried out in collaboration with Jamie Ward, Sarah-Jayne Blakemore, and Geoffrey Bird. I designed and constructed the stimuli, ran the experiment and performed a preliminary analysis of the data. The data analysis was completed by Geoffrey Bird.

# CHAPTER 9: RECOGNISING THE SENSORY CONSEQUENCES OF THE ACTIONS OF OTHERS: A CROSS-MODAL REPRESENTATION OF VOWELS IN 2-3 MONTH OLD INFANTS

## 9.1 Introduction

As described in the General Introduction to this thesis, there is strong evidence that infants as young as 3-5 months can detect contingencies between their actions and a stimulus, and that they can distinguish between self-produced sensory stimuli and externally generated stimuli, on the basis of these contingencies between their actions and sensory input, as demonstrated by the differential responses they show to the two types of stimuli, i.e. by 3-5 months of age infants can recognise the consequences of their own actions (Bahrick and Watson, 1985;Field, 1979;Rochat, 1998;Rochat and Hespos, 1997;Rochat and Morgan, 1995;Schmuckler, 1996).

It also appears that, as well as being able to recognise the consequences of their own actions, infants can recognise the consequences of actions made by others from 2 months of age, at least in the context of speech. There is strong behavioural evidence that infants as young as two months of age can match observed articulatory movements, to the appropriate auditory phonemes. When presented with two videos of faces articulating vowels, 4.5 month old infants spent significantly longer fixating the video that matched the auditory vowels they were played (Kuhl and Meltzoff, 1982;Patterson and Werker, 1999). This finding has been replicated with 2 month old infants (Patterson and Werker, 2003). In an operant sucking paradigm, 4 month old infants will suck more to receive a face that matches the heard speech sound (Walton and Bower, 1993). As yet the neural mechanisms underlying infants' ability to match visual and auditory speech, remains is unknown. One possibility is that infants have a cross-modal representation of speech that is accessed by both heard and seen speech.

Supporting this possibility is the fact that, in adults, both seeing and hearing speech has been shown to activate regions involved in speech production (Skipper et al., 2005;Wilson et al., 2004). When subjects listen to or watch speech, muscle potentiation increases in the subject's own mouth muscles. MEPs were recorded in subject's tongue muscles in response to TMS of left motor cortex, while they listened

to speech sounds requiring different amount of tongue movement. MEPs were greatest when listening to sounds that required greater tongue movements (Fadiga et al., 2002). Similarly MEPs in the lip muscles, produced by TMS of the face area of the left motor cortex, were recorded while subjects heard speech sounds versus non speech sounds and watched speech related lip movements versus eye and brow movements. MEPs were greater while subjects listened to speech sounds compared to non-speech sounds, and when subjects saw lip movements compared to eye and brow movements (Watkins et al., 2003). In addition speech perception has been shown to activate the premotor regions involved in speech production using fMRI. Viewing silent articulatory mouth movements activates Broca's area (Calvert and Campbell, 2003). Listening to speech sounds also activates premotor areas involved in speech production (Wilson et al., 2004). Most recently observation of silently articulating faces, and listening to speech sounds have been shown to activate a network of brain regions involved in speech production including the premotor cortex, inferior frontal gyrus, primary motor cortex and superior temporal sulcus (Skipper et al., 2005). These findings demonstrate that speech perception, whether visual or auditory, activates the motor areas underlying speech production in the left hemisphere. Thus it appears that adults represent seen and heard speech in their motor systems. This is consistent with the motor theory of speech, which proposes that speech is primarily represented as articulatory gestures (Liberman and Mattingly, 1985;Liberman and Whalen, 2000).

There is some evidence of a correspondence between heard speech and motor production in infants. When infants, aged 12-20 weeks, listened to an adult speaker produce different vowels, they produced more vocalisations resembling that particular vowel (Kuhl and Meltzoff, 1996). Likewise, new born infants, aged from 1 to 7 days, make the appropriate mouth movement in response to speech sounds (Chen et al., 2004). This suggests that like adults, children represent heard speech in their motor system. Thus, perhaps infants' ability to match visual and auditory speech is based on a cross-modal representation of seen or heard speech in their motor system. Here, I sought to use high density electro-encephalography to examine whether infants have a cross- or a-modal neural representation of phonemes that is accessed by both auditory and visual speech.

I designed a habituation paradigm to examine whether infants' response to auditory speech could be habituated by the prior presentation of visual speech in a phoneme specific manner, i.e. does visual speech perception affect the processing of auditory speech. Repetition of a stimulus leads to decreased activity within the neural networks representing that stimulus, in both auditory (Miller et al., 1991) and visual (Ulanovsky et al., 2003) cortices, a phenomenon known as repetition suppression. Scalp potentials evoked by a stimulus and measured with EEG also show decreases amplitude with repetition (Woods and Elmasian, 1986). This response habituation with repetition is abolished by presentation of a new or deviant stimulus, due to activation of a new set of neurons by the deviant stimulus. Thus trials where a stimulus is repeated elicit a smaller response compared to when the stimulus changes. By manipulating what stimulus changes elicit a difference in the brain response (the ERP), it is possible to infer what counts as a 'repetition' for a particular neural network and thus the nature of the representation computed by the network. For example, a network encoding a phonetic representation should habituate to repetition of a phoneme irrespective of the speaker, and should show renewed activity to a phonetic change only. In infants the neuronal response to auditory phonetic stimuli decreases with repetition, even when different speakers are used, and presentation of a new phoneme restores the amplitude of the ERP (Dehaene-Lambertz and Baillet, 1998;Dehaene-Lambertz and Dehaene, 1994;Dehaene-Lambertz and Pena, 2001;Woods and Elmasian, 1986). This demonstrates that infants have a neural network dedicated to phonetic processing, that normalises across acoustical differences in the stimuli.

I hypothesised that if infants have a neural network encoding a cross-modal representation of phonemes, it should be possible to habituate the response of such a network to auditory phonetic stimuli by the prior presentation of visual speech. Any such habituation should be specific to the phoneme used for habituation, and a change of phoneme, compared to repeated presentation of the same phoneme, across modalities should elicit a greater neural response.

Sixteen full term French infants (4 boys; 12 girls) were tested between 9 and 12 weeks after birth (mean 10.5 weeks, SD=0.92 weeks). In each trial infants were presented with a short video clip of a person silently articulating a vowel, a French

/a/ or a French /i/, presented twice in succession (the context stimuli). This was followed by presentation of the test stimulus: an auditory only vowel, either a French /a/ or /i/. In half the trials the auditory test vowel was the same as the preceding visually presented vowels (vowel match trials), and in half the trials the alternative vowel was presented (vowel mismatch trials). I predicted that the response to vowel matched auditory test stimulus would be smaller than the response to the vowel mismatch auditory test stimuli.

As a control I also varied the gender of the speaker in the visual context and auditory test stimuli. Thus in half of each of the two trial types described above, (vowel match and vowel mismatch), the gender of the auditory test stimulus matched the gender of the speaker previously seen articulating vowels (gender match trials), and in half the trials the gender differed (gender mismatch trials). This resulted in four conditions overall (see Methods). I did not expect to see a difference in the auditory test stimulus ERP between gender match and gender mismatch trials, as infants below 6-8 months of age are not able to match gender information in face and voice (Patterson and Werker, 2002;Walker-Andrews et al., 1991) suggesting that infants as young as those I tested (2.4 months) do not yet have an amodal representation of gender.

## 9.2 Materials and Methods

### 9.2.1 Subjects

Sixteen full term infants (4 boys; 12 girls) were tested between 9 and 12 weeks after birth (mean age 10.5 weeks, SD = 0.92 weeks). Ten additional infants were tested but rejected for fussiness, excessive movement, or bad electrode recording.

### 9.2.2 Stimuli

Four male and four female actors were filmed articulating /a/ and /i/ against a white background to create the stimuli. There were four possible visual stimuli (the context stimuli): 1) a female articulating /a/, 2) a female articulating /i/, 3) a male articulating /a/, or 4) a male articulating /i/. One video clip of each vowel was selected for each actor. Four frames were extracted from each clip: i) mouth closed, ii) beginning of movement, iii) mouth semi-extended, iv) mouth fully extended. These 4 frames were presented at fixed time intervals (calculated from the original videos) to recreate natural looking articulatory movements.

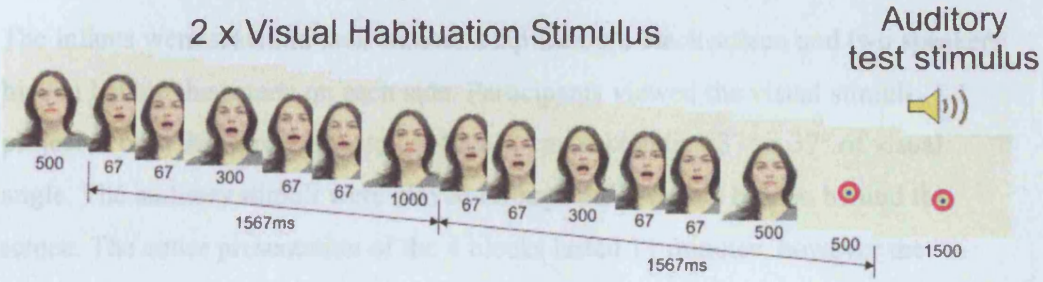
Similarly there were four possible auditory stimuli (the test stimuli): 1) a female spoken /a/, 2) a female spoken /i/, 3) a male spoken /a/, or 4) a male spoken /i/. Whereas several different actors were used to create the visual context stimuli, the four test stimuli were always the same. Only one female and one male speaker were recorded and only one of each vowel was used for each speaker. The auditory stimuli were recorded and edited using Cool Edit Pro (Syntrillium Software) (now renamed Adobe Audition). A single /a/ and /i/ lasting 190 ms were selected for the male and female speaker. The vowels were then matched for subjective intensity and volume.

### 9.2.3. Paradigm

Each trial consisted of three stimuli. Two visual vowels were presented in succession, (the context stimuli) and followed by an auditory vowel (the test stimulus) (see Fig 9.1). Each visual stimulus consisted of a short video clip of a person silently articulating a vowel. Each articulatory movement lasted 567ms, and

was preceded and followed by 500ms of the mouth being fully closed. The auditory test stimulus consists of a spoken vowel of duration 190ms. The two visual context stimuli and the auditory test stimuli were presented with a 1567 ms interval between the onset of each stimulus (onset of the two articulatory movements and onset of the sound). Figure 9.1 shows the trial structure. A brightly coloured 'bull's eye' was presented after the offset of the context stimuli, and during the presentation of the auditory test stimulus, in the same location as the mouth and nose in the visual stimuli, to keep the infant's attention on that location in readiness for the appearance of the visual stimuli in the next trial.

***Figure 9.1 – Trial Structure***




Stimuli were presented using Eprime (Psychology Software Tools, Inc.). Trials were presented in 4 blocks of 32 trials (trial length = 5134 ms) of the same context (1 block for each possible context), e.g. a female articulating /a/. Each of the 4 possible actors appeared 8 times in each block. In each trial the auditory test stimuli could either match the visual context stimuli in terms of the vowel produced, the gender of the speaker, both or neither. Thus there were four possible trial types/conditions:

1) vowel match, gender match (VM/GM)
2) vowel mismatch, gender match (VMM/GM)
3) vowel match, gender mismatch (VM/GMM)
4) vowel mismatch, gender mismatch (VMM/GMM)

| Visual Habituation stimuli | Auditory Test Stimuli | | | |
|---|---|---|---|---|
| | Female auditory /a/ | Female auditory /i/ | Male auditory /a/ | Male auditory /i/ |
| Female visual /a/ | **VM/GM** | **VMM/GM** | **VM/GMM** | **VMM/GMM** |
| Female visual /i/ | **VMM/GM** | **VM/GM** | **VMM/GMM** | **VM/GMM** |
| Male visual /a/ | **VM/GMM** | **VMM/GMM** | **VM/GM** | **VMM/GM** |
| Male visual /i/ | **VMM/GMM** | **VM/GMM** | **VMM/GM** | **VM/GM** |

Each trial type occurred 8 times in each block (twice following each individual actor), thus each trial type occurred 32 times during the whole experiment.

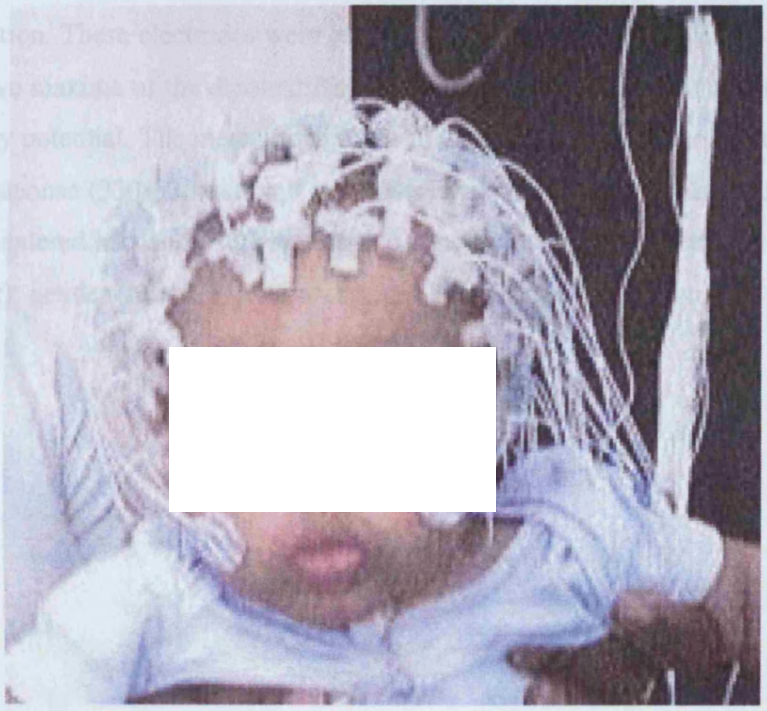
The infants were seated in their mother's lap facing a black screen and two speakers hidden behind the screen on each side. Participants viewed the visual stimuli projected onto this screen situated at 60 ±10 cm, subtending 37° x 37° of visual angle. The auditory stimuli were played through the speakers hidden behind the screen. The entire presentation of the 4 blocks lasted 11 minutes, however the presentation of trials was stopped whenever the infant looked away, and restarted once their attention returned to the screen. Pauses also occurred whenever the infant needed comforting. Once the infant's attention had returned to the screen, interrupted trials were restarted at their beginning.

### 9.2.4 ERP recording and data analysis

A continuous electro-encephalogram (EEG) was recorded with a Geodesic electrode net (EGI) referenced to the vertex (electrode 65). The net was positioned in anatomical reference to the vertex and the cantho-meatal line. (See Figure 9.2). Scalp voltages were recorded amplified, digitized at 125 Hz and filtered between 0.5 and 20 Hz. Segmentation, artefact detection and averaging was then carried out on the EEG using EEGlab toolbox (Delorme and Makeig, 2004). The EEG was segmented into epochs starting 500 ms before the onset of each auditory test stimulus and ending 1500 ms after stimulus onset. The epochs were then automatically checked for artefacts. Channels contaminated by eye or motion artefacts were automatically rejected. All trials with more than 50% contaminated channels were rejected. Any

electrodes contaminated in more than 70% of the retained trials were excluded from the analysis. The artefact free trials were averaged for each infant for each of the 4 possible conditions: 1) VMGM, 2) VMMGM, 3) VMGMM, and 4) VMMGMM. On average 26 trials were retained per infant for each condition (26.8, 25.9, 26.1, and 25.7 respectively). Averages were then baseline corrected, with baseline -200 to 0ms relative to stimulus onset, and an average reference transformation was applied to obtain reference-independent potentials. Two-dimensional reconstructions of scalp voltage at each time step were computed using spherical spline interpolation.

***Figure 9.2 –Infant wearing the Geodesic 64 electrode net***



### 9.2.5 Statistical analysis

#### *9.2.5.1 Vowel match versus vowel mismatch*

To examine the effect of vowel match versus mismatch on the response to the auditory test stimulus, the voltages from two electrode groups, one frontal (2, 3, 4, 7, 8, 11, 12, 14, 54, 55, 57, 58, 61, 62) and one posterior (25, 26, 27, 28, 31, 32, 33, 35, 36, 37, 38, 39, 40, 44) were averaged for each condition. These electrodes were chosen as they were located over the positive and negative maxima of the dipole

difference between VMM and VM at the peak of the auditory potential. The mean voltage was then averaged across the peak of the auditory response (200-300ms) and entered into an ANOVA with three factors: location of electrodes (frontal v. posterior); type of vowel (match v. mismatch); and gender (match v. mismatch).

#### *9.2.5.2 Gender match versus gender mismatch*

To examine the effect of gender match versus mismatch on the auditory response to the test stimulus, the voltages from two posterior electrode groups, one on the right (45, 46, 48, 49, 50, 51) and one the left (27, 28, 31, 32, 35, 36) were averaged for each condition. These electrodes were chosen as they were located over the positive and negative maxima of the dipole difference between GMM and GM at the peak of the auditory potential. The mean voltage was then averaged across the peak of the auditory response (230-330ms) (and across various other time intervals after stimulus onset) and entered into an ANOVA with two factors: location of electrodes (frontal v. posterior); gender (match v. mismatch); and vowel (match v. mismatch).

## 9.3 Results

### 9.3.1 Auditory response to all test stimuli

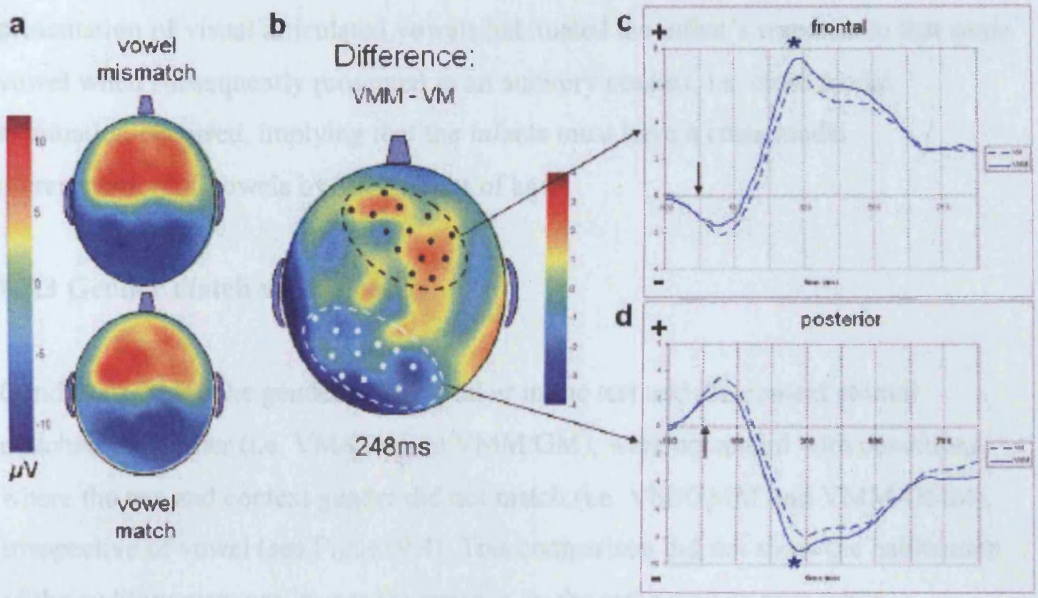
The main auditory potential, consisting of a strong frontal positivity and a posterior negativity, began around 130ms, peaked at around 270-80ms, and started declining gradually from around 450-500ms. Prior to this, from 0-100ms, there was a small frontal negativity/posterior positivity that peaked around 50ms after stimulus onset.

### 9.3.2 Vowel match vs. mismatch

Conditions where the vowel presented in the test and the context stimuli matched each other (i.e. VM/GM and VM/GMM), were compared with conditions where the test and context vowel did not match (i.e. VMM/GM and VMM/GMM) irrespective of gender. Examination of the topography revealed a difference between VMM and VM consisting of a dipole angled to the right across the head, with a right frontal positivity and a posterior negativity (see Figure 9.3b). This difference between VMM and VM started early and was greatest around 250ms, i.e. just before the peak of the auditory potential.

Analysis of the mean amplitude of the auditory response was performed over two packs of electrodes (See Figure 9.3b to see electrode locations), one frontal (electrodes 2, 3, 4, 7, 8, 11, 12, 14, 54, 55, 57, 58, 61, 62) and one posterior (electrodes 26, 27, 28, 31, 32, 33, 35, 36, 37, 38, 39, 40, 44) using an ANOVA with 3 factors: electrode location (frontal versus posterior); vowel (matched vowel versus mismatched vowel); and gender (gender match or gender mismatch). This revealed a significant interaction between the vowel (matched vowel versus mismatched vowel), and the location of the electrodes in the mean amplitude of the auditory potential from 200 to 300 ms after stimulus onset ($F_{(1,15)}=8.53$, $p=0.011$). Post hoc analyses showed that in the frontal hemisphere, the response to vowel mismatches was significantly more positive than the response to matches ($F_{(1,15)}=7.15$, $p=0.017$), (see Figure 9.3c). Meanwhile in the posterior hemisphere, the response to mismatches was significantly more negative than the response to matches ($F_{(1,15)}=6.34$, $p=0.024$), (see Figure 9.3d).

***Figure 9.3 – Vowel mismatch – vowel match***




*a)Topographies of the evoked potential in response to the auditory test stimulus at 248ms after stimulus onset, just before the peak of the auditory potential. b)topography of the maximum difference between the response to vowel mismatch and vowel match auditory test stimuli (VMM – VM) at 248ms after stimulus onset, just prior to the peak of the auditory potential. Two groups of electrodes were selected for statistical analysis: a frontal group shown in black, and a posterior group shown in white. c) The average wave form for the group of frontal electrodes located over the positive maxima of the difference (VMM – VM), showing a significantly greater response to vowel mismatches (VMM – solid line) than to vowel matches (VM – dashed line) from 200-300ms after stimulus onset. c) The average wave form for the group of posterior electrodes located over the negative maxima of the difference (VMM – VM), showing a significantly more negative response to vowel mismatches (VMM – solid line) than to vowel matches (VM – dashed line) from 200-300ms after stimulus onset. In c) and d) * indicates significance. Arrow indicated stimulus onset.*

In contrast the same 3 way ANOVA did not reveal a significant interaction between electrode location and gender match v mismatch ($F_{(1,15)} = 0.86$, $p = 0.37$) for these electrode groups. Nor was there a significant effect of gender match v mismatch in the frontal ($F_{(1,15)} = 0.036$, $p = 0.85$) or the posterior ($F_{(1,15)} = 3.04$, $p = 0.10$) electrode groups. Nor was there a significant interaction between gender and vowel.

The response to vowel matched test stimuli was weaker than the response to vowel mismatched stimuli, particularly in right frontal electrodes. This suggests that presentation of visual articulated vowels habituated the infant's response to that same vowel when subsequently presented in an auditory context, i.e. cross modal habituation occurred, implying that the infants must have a cross modal representation of vowels by 9-12 weeks of age.

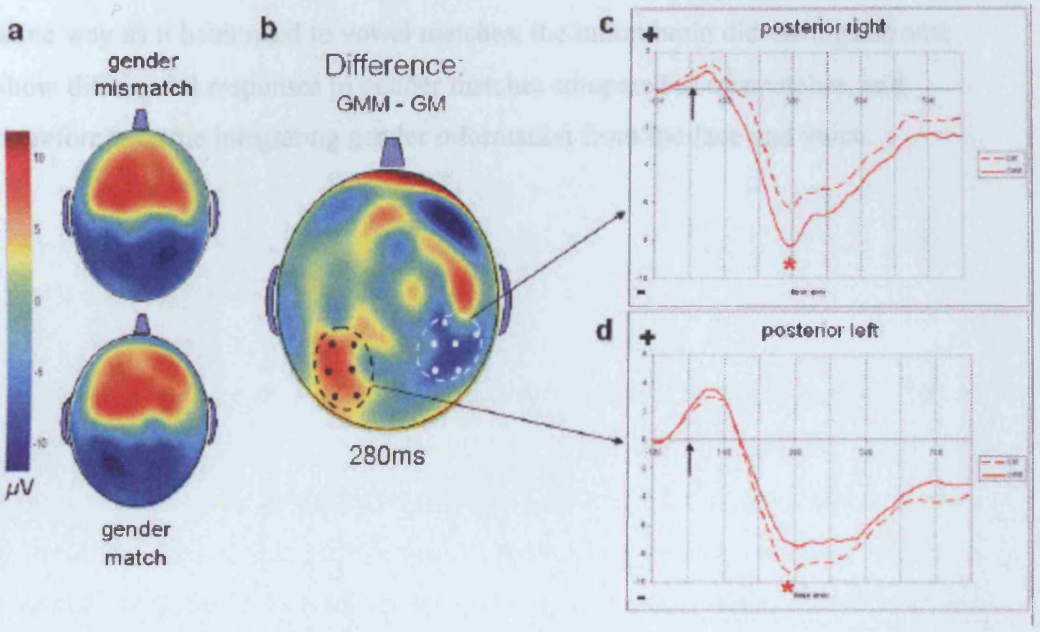
### 9.3.3 Gender match vs. mismatch

Conditions where the gender of the speaker in the test and the context stimuli matched each other (i.e. VM/GM and VMM/GM), were compared with conditions where the test and context gender did not match (i.e. VM/GMM and VMM/GMM), irrespective of vowel (see Figure 9.4). This comparison did not show the habituation of the auditory response by gender matches, in the same way as seen when comparing VM to VMM above. The comparison of GMM – GM did not result in the same difference topography as VMM – VM, namely a frontal positivity (lateralised to the right) and a posterior negativity (see Figure 9.3b). Instead there was a difference between the conditions across the posterior hemisphere, i.e. over the occipital electrodes (see Figure 9.4b). Over the posterior left electrodes the response to GMM was more positive than the response to GM (see Figure 9.4d), whereas over the posterior right electrodes the opposite was true, i.e. the response to GMM was more negative than the response to GM (see Figure 9.4c). So the difference formed a dipole across the posterior hemisphere that was positive on the left and negative on the right. This difference appeared from about 150 ms, peaked around 280ms and remained till around 400ms.

Analysis of the mean amplitude around the peak auditory response (230-330 ms) was performed over two posterior packs of electrodes, (see Figure 9.4b to see electrode locations), one on the right (45, 46, 48, 49, 50, 51,) and one on the left (27, 28, 31, 32, 35, 36) using an ANOVA with 3 factors: electrode location (posterior left versus posterior right); gender (gender match versus mismatch); and vowel (vowel match versus mismatch). This revealed a significant interaction between gender (gender match versus gender mismatch), and the location of the electrodes in the mean amplitude of the auditory potential ($F_{(1,15)} = 14.10$, $p = 0.002$). Post hoc analyses

showed that over the posterior left electrodes the response to gender mismatches was significantly more positive than the response to matches ($F_{(1,15)} = 12.81$, $p = 0.003$), whereas over the posterior right electrodes, the response to mismatches was significantly more negative than the response to matches ($F_{(1,15)} = 5.82$, $p = 0.029$), (see Figure 9.4c & d).

***Figure 9.4 – Gender mismatch – gender match***




*a) Topographies of the evoked potential in response to the auditory test stimulus at 280ms after stimulus onset, at the peak of the auditory potential. b) Topography of the maximum difference between the response to gender mismatch and gender match auditory test stimuli (GMM – GM) at 280ms after stimulus onset, at the peak of the auditory potential. Two groups of electrodes were selected for statistical analysis: a left posterior group shown in black, and a right posterior group shown in white. c) The average wave form for the group of right posterior electrodes located over the negative maxima of the difference (GMM – GM), showing a significantly more negative response to gender mismatches (GMM – solid line) than to gender matches (GM – dashed line) from 230-330ms after stimulus onset. c) The average wave form for the group of left posterior electrodes located over the postive maxima of the difference (GMM – GM), showing a significantly greater response to gender mismatches (GMM – solid line) than to gender matches (GM – dashed line) from 230-330ms after stimulus onset. In c) and d) * indicates significance. Arrow indicated stimulus onset.*

In contrast, the same 3 way ANOVA did not reveal a significant interaction between electrode location and vowel match v mismatch ($F_{(1,15)} = 0.94$, $p = 0.35$) for these electrode groups. Nor was there a significant effect of vowel match v mismatch in the left-hand ($F_{(1,15)} = 2.69$, $p = 0.12$) or the right-hand ($F_{(1,15)} = 0.002$, $p = 0.97$) electrode groups. There was no interaction between gender and vowel.

Thus, although the auditory response was not habituated by gender matches, in the same way as it habituated to vowel matches, the infant brain did distinguish and show differential responses to gender matches compared to mismatches, and therefore must be integrating gender information from the face and voice.

## 9.4 Discussion

I hypothesised that if infants have a neural network encoding a cross- or a-modal representation of phonemes, the response of such a network to auditory phonemes would be habituated by the prior presentation of that same phoneme visually. The response to vowel mismatched auditory test stimuli was significantly greater, than the response to vowel matched stimuli (see Figure 9.3). Thus the presentation of visually articulated vowels habituated the infant's response to that same vowel when subsequently presented in an auditory context. This suggests that infants must have a cross modal neural representation of vowels, i.e. a network of neurons that respond to specific phonetic information irrespective of the modality it is perceived in, by 9-12 weeks of age. This may explain infants' ability to recognise the speech sounds produced by observed articulations.

Preliminary analyses conducted by my colleagues (S.Baillet, G.Dehaene-Lambertz, J-F.Mangin and J.Mattout, personal communication) have localised the source of this cross-modal phonetic habituation to Broca's region and the left superior temporal gyrus/sulcus. This is consistent with the accumulating evidence in adults that both seen and heard speech activate regions involved in speech production (Calvert and Campbell, 2003;Fadiga et al., 2002;Skipper et al., 2005;Watkins et al., 2003;Wilson et al., 2004). In addition, there is evidence from studies of imitation of an early correspondence between heard speech and the appropriate motor representation in infants (Chen et al., 2004;Kuhl and Meltzoff, 1996). This preliminary result suggests that, like adults, infants represent seen and heard speech amodally in the motor regions involved in speech production. This is consistent with the motor theory of speech perception, which proposes that speech is primarily represented as articulatory gestures during both speech production and perception (Liberman and Mattingly, 1985;Liberman and Whalen, 2000). The involvement of the superior temporal gyrus, is consistent with activation in adults of the auditory cortex, including the superior temporal gyrus, by observation of someone silently articulating speech (Calvert et al., 1997;Pekkola et al., 2005). This suggests that infants, like adults, represent the predicted sensory consequences of the observed articulation in their own sensory cortices.

As expected, the response to the auditory test stimuli did not show cross-modal habituation to gender information as it did for phonemes. The frontal and posterior electrode bundles that were analysed to examine the difference between vowel matches and vowel mismatches, showed no significant effect of gender match versus gender mismatch. Nor did they show any significant interaction between gender and vowel. Instead, I found a large difference between the response to gender match and gender mismatch test stimuli, across the posterior electrodes (see Figure 9.4). This suggests that infants' brains do discriminate between gender matches and mismatches across modalities.

This finding is surprising in the light of previous behavioural findings in infants. Until 6-8 months of age, infants are unable to match gender information in faces and voices in preferential looking paradigms (Patterson and Werker, 2002;Walker-Andrews et al., 1991). But a lack of preferential looking does not necessarily mean that infants younger than 6 months cannot match gender information in faces and voices.

However, when gender and vowel matching are simultaneously put in full conflict with each other, such that infants can either look at a face that matches the vowel but not the gender of the voice heard, or vice versa, 4.5 month infants' ability to match phonetic information in face in voice is disrupted (Patterson and Werker, 2002). Thus is appears that conflicting gender information interferes with infants' ability to match face and voice on the basis of phonetic information, suggesting that infants, at some level, do detect equivalent gender information in face and voice, but are unable to use this information to guide visual exploration of facial cues when both gender and phonetic information are varied.

Our findings demonstrate a difference in neural response to gender matches and mismatches, and thus that infant's brains can detect equivalent cross/a-modal gender information in faces and voices at as young an age as 2.4 months, even if they do not use this information to match faces and voices in looking time paradigms until 6-8 months of age.

The topography of the difference between gender matches and gender mismatches was very different from the topography of the difference between vowel matches and mismatches (the electrodes showing significant of vowel match v. mismatch, did not show significant effects of gender match v. mismatch, and vice versa) suggesting that the neural sources involved in representing phonemes across modalities, are different from those involved in matching gender information across modalities. (See Figures 9.3b and 9.4b)

## 9.5 Conclusion

I have demonstrated phoneme specific cross modal habituation, suggesting that 2-3 month-old infants do indeed have a cross-modal neural representation of vowels. This could account for infants' ability to match phonetic information in faces and voices from as early as 2 months of age. I also demonstrated that 2-3 month -old infants' brains discriminate gender information in faces and voices, even though they do not yet use this information to guide their behaviour at this age. The topography of the differences between matches and mismatches was very different for gender and vowel suggesting that different neural networks are involved in detecting matching gender and phonetic information in face and voice.

# CHAPTER 10: COMPARISON OF CROSS-MODAL AND AUDITORY ONLY PHONETIC HABITUATION IN 2-3 MONTH OLD INFANTS

## 10.1 Introduction

In Chapter 9, I used high density electro-encephalography (EEG), to examine whether 2-3 month old infants have a cross-modal or a-modal neural representation of phonemes that is accessed by both auditory and visual speech. I designed a cross-modal habituation paradigm to see whether the response to auditory speech could be habituated by the prior presentation of visual speech in a phoneme specific manner. I hypothesised that if infants have a neural network encoding a cross-modal representation of phonemes, it should be possible to habituate the response of such a network to auditory phonetic stimuli by the prior presentation of that same phoneme visually. Any such habituation should be specific to the phoneme used for habituation, and that a change of phoneme, compared to presentation of the same phoneme, across modalities should elicit a greater neural response.

In that earlier chapter, I established that the response to vowel mismatched auditory test stimuli was significantly greater, than the response to vowel matched stimuli. Thus I demonstrated that presentation of visual articulated vowels habituated the infants' brain responses to that same vowel when subsequently presented in an auditory context. This implies that infants must have some sort of cross modal neural representation of vowels, i.e. a network of neurons that respond to specific phonetic information irrespective of the modality it is perceived in, by 9-12 weeks of age.

The topography of the difference between vowel match and vowel mismatch stimuli was extremely similar to that seen in purely auditory phonetic mismatch studies. In our study, the difference consisted of a more positive response for mismatches than matches over frontal areas and a more negative response for mismatches than matches over posterior temporo-occipital areas along a right frontal-left posterior axis (see Figure 9.3b). This is the same difference topography seen when comparing purely auditory phonetic standard and deviant stimuli in 2-month old infants (Dehaene-Lambertz and Dehaene, 1994) and neonates (Dehaene-Lambertz and Pena, 2001). Here I sought to directly compare purely auditory phonetic habituation and

the ensuing mismatch response, to cross-modal phonetic habituation and the ensuing mismatch response in the same group of 2-3 month old infants, in order to directly examine whether the same neural sources are involved and whether the timing of the two types of habituation is the same.

On each trial infants were presented with a short video clip of a person silently articulating a vowel, a French /a/ or a French /i/, (the visual habituation stimuli), or with an auditory vowel, a French /a/ or /i/, (the auditory habituation stimuli) presented twice in succession. This was followed by presentation of the test stimulus: an auditory only vowel, either a French /a/ or /i/. In half the trials the auditory test vowel was the same as the preceding visual or auditory vowels (vowel match trials), and in half the trials the alternative vowel was presented (vowel mismatch trials). I predicted that the response to vowel matched auditory test stimulus would be smaller than the response to the vowel mismatch auditory test stimuli, in both visual and auditory habituation conditions. I also predicted that the topography of the mismatch response would be the same for visual and auditory mismatch responses.

## 10.2 Materials and Methods

### 10.2.1 Subjects

21 full term infants (12 boys; 9 girls) were tested between 9 and 12 weeks after birth (mean age 10.2 weeks, SD = 0.7 weeks). 15 additional infants were tested but rejected for fussiness, excessive movement, or bad electrode recording.

### 10.2.2 Stimuli

To create the visual habituation stimuli, two adult male and two adult female actors were filmed articulating /a/ and /i/ against a white background to create the stimuli. Thus there were four possible visual habituation stimuli:

1) a female articulating /a/
2) a female articulating /i/
3) a male articulating /a/
4) a male articulating /i/.

One video clip of each vowel was selected for each actor. Four still images were extracted from each clip: i) mouth closed, ii) beginning of movement, iii) mouth semi-extended, iv) mouth fully extended. These 4 images were presented at fixed time intervals (calculated from the original videos) to recreate natural looking articulatory movements.

To create the auditory habituation stimuli two different male and two different female actors were recorded saying /a/ and /i/. Thus there were four possible auditory habituation stimuli:

1) a female spoken /a/
2) a female spoken /i/
3) a male spoken /a/
4) a male spoken /i/.

The auditory stimuli were recorded and edited using Audacity software. A single /a/ and /i/ lasting 190-200 ms were selected for the male and female speaker. To

minimise the difference between the auditory and visual habituation stimuli a visual background was created for the auditory habituation stimuli. A still image of each of the actors, used for the visual habituation stimuli, was extracted from their video clip, and the mouth region was hidden with a picture of a surgical mask using CorelDraw (Corel Corporation), so that the lack of mouth movement would not conflict with the sounds heard.

Similarly there were four possible auditory stimuli (the test stimuli):

1) a female spoken /a/
2) a female spoken /i/
3) a male spoken /a/
4) a male spoken /i/

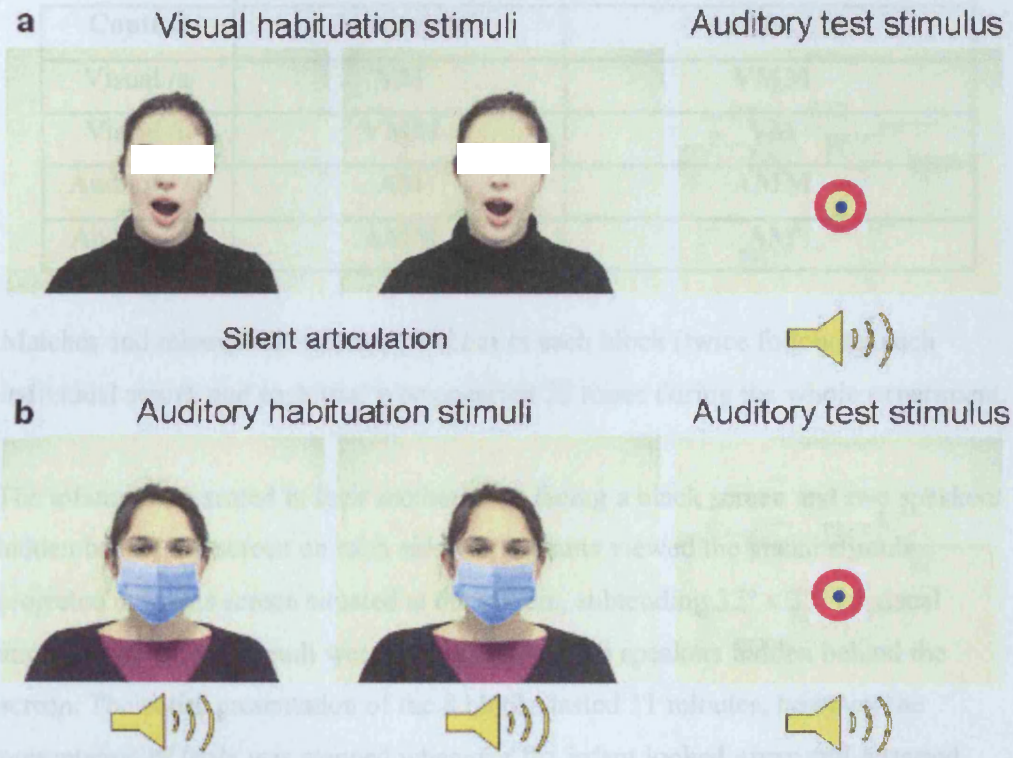
Whereas several different actors were used to create the visual and auditory habituation stimuli, the four test stimuli were always the same. Only one female and one male speaker were recorded and only one of each vowel was used for each speaker. The auditory stimuli were recorded and edited using Cool Edit Pro software. A single /a/ and /i/ lasting 190 ms were selected for the male and female speaker. The vowels were then matched for subjective intensity and volume.

### 10.2.3 Paradigm

Each trial consisted of 3 stimuli; 2 habituation stimuli, which were either visual or auditory vowels, presented in succession, followed by an auditory vowel (the test stimulus) (see Fig 10.1). Each visual habituation stimulus consisted of a short video clip of a person silently articulating a vowel. Each articulatory movement lasted 567ms, and was preceded and followed by 500ms of the mouth being fully closed. The auditory habituation stimulus consisted of a spoken vowel of duration 190-200ms, played while a photograph of a face with its mouth hidden behind a surgical mask was presented on screen for 1567ms. The auditory vowel occurred 634ms after the onset (the time at which the equivalent visual articulation stimuli would reach maximum opening). The auditory test stimulus consists of a spoken vowel of duration 190ms. The two visual context stimuli and the auditory test stimuli were presented with a 1567 ms interval between the onset of each stimulus (onset of the

two articulatory movements and onset of the sound) (see Figure 10.1 for trial structure). A brightly coloured bull's eye was presented after the offset of the habituation stimuli, and during the presentation of the auditory test stimulus, in the same location as the mouth and nose in the visual stimuli, to keep the infant's attention on that location in readiness for the appearance of the visual stimuli in the next trial.

***Figure 10.1 - Stimuli***




*a) A visual habituation trial, consisting of a video of a vowel silently articulated twice in succession followed by an auditory test stimulus. b) An auditory habituation trial, consisting of two auditory vowels presented against a background visual stimulus, matched for everything except the articulatory movement, followed by an auditory test vowel.*

Stimuli were presented using Eprime (Psychology Software Tools, Inc.). Trials were presented in 8 blocks of 16 trials (trial length = 5134 ms) of the same context (2 blocks for each possible context), e.g. a visual /a/ or an auditory /i/. Each of the 4 possible actors appeared 4 times in each block. In each trial the auditory test stimuli was either the same vowel (match) as in the habituation stimulus or the alternative

vowel (mismatch). The gender of the test stimulus was always the same as that of the habituation stimulus. Thus there were four possible trial types/conditions:

1) Visual match (VM)
2) Visual mismatch (VMM)
3) Auditory match (AM)
4) Auditory mismatch (AMM)

| | **Test Stimuli** | |
|---|---|---|
| **Context** | Auditory /a/ | Auditory /i/ |
| Visual /a/ | **VM** | **VMM** |
| Visual /i/ | **VMM** | **VM** |
| Auditory /a/ | **AM** | **AMM** |
| Audiotry /i/ | **AMM** | **AM** |

Matches and mismatches occurred 8 times in each block (twice following each individual actor), and each trial type occurred 32 times during the whole experiment.

The infants were seated in their mother's lap facing a black screen and two speakers hidden behind the screen on each side. Participants viewed the visual stimuli projected onto this screen situated at 60 ±10 cm, subtending 37° x 37° of visual angle. The auditory stimuli were played through the speakers hidden behind the screen. The entire presentation of the 8 blocks lasted 11 minutes, however the presentation of trials was stopped whenever the infant looked away and restarted once their attention returned to the screen. Pauses also occurred whenever the infant needed comforting. Once the infant's attention had returned to the screen, interrupted trials were restarted at their beginning.

### 10.2.4 ERP recording and data analysis

A continuous electro-encephalogram (EEG) was recorded with a Geodesic electrode net (EGI), with 128 electrodes, referenced to the vertex (electrode 129). The net was positioned in anatomical reference to the vertex and the cantho-meatal line. Scalp voltages were recorded amplified, digitized at 125 Hz and filtered between 0.5 and

20 Hz. Segmentation, artefact detection and averaging was then carried out on the EEG using EEGlab toolbox (Delorme and Makeig, 2004). The EEG was segmented into epochs starting 500 ms before the onset of each auditory test stimulus and ending 1000 ms after stimulus onset. The epochs were then automatically checked for artefacts. Channels contaminated by eye or motion artefacts were automatically rejected. All trials with more than 50% contaminated channels were rejected. Any electrodes contaminated in more than 70% of the retained trials were excluded from the analysis. The artefact free trials were averaged for each infant for each condition. Averages were then baseline corrected, with baseline from -200 to 0ms relative to stimulus onset, and an average reference transformation was applied to obtain absolute reference-independent potentials. Two-dimensional reconstructions of scalp voltage at each time step were computed using spherical spline interpolation.

### 10.2.5 Statistical analysis

To avoid any possibility of interference between subsequent blocks of different modality, for example information from an auditory habituation block interfering with a subsequent visual habituation block, I only analysed those blocks that were preceded by another block of the same modality, i.e. visual blocks preceded by a visual block (V), and auditory blocks preceded by an auditory block (A). Blocks that were preceded by a block of the opposite modality and thus at risk of interference i.e. visual blocks preceded by auditory blocks (aV) and auditory blocks preceded by visual blocks (vA) were not included in the analysis.

I then examined the effects of vowel match versus mismatch on the evoked response potential to the auditory test stimulus for both types of habituation – auditory and visual.

Scalp topographies of the difference between mismatches and matches in the visual habituation (VMM – VM), and auditory habituation conditions (AMM – AM) were generated. The difference topography was also calculated for all mismatches minus matches across habituation conditions (MM-M).

A bundle of electrodes showing the greatest difference between all matches and mismatches at the peak of the auditory response potential (272ms) was selected. The voltages from this right frontal electrode group, (electrodes: 105, 106, 107, 111, 112, 113, 118, 119) were averaged for each of the four conditions: VM, VMM, AM and AMM. The mean voltage was then averaged across the peak of the auditory response (240-304ms) and entered into an ANOVA with two factors: vowel (match v. mismatch); and type of habituation (auditory v. visual). Paired t-test were also carried out to compare the mean auditory response to VM and VMM, and to compare the mean auditory response to AM and AMM.

To see whether I was justified in excluding blocks preceded by a block of the opposite modality (which I did to avoid interference between adjacent blocks of opposite modalities) I also examined the effects of vowel match versus mismatch on the response to the auditory test stimulus, for those blocks that had been preceded by a block of the opposite modality (i.e. aV and vA) and thus excluded from my main analysis. I created scalp topographies of the difference between mismatches and matches, across habituation conditions (MM – M), and for the visual habituation (aVMM – aVM) and auditory habituation conditions (vAMM – vAMM) separately.

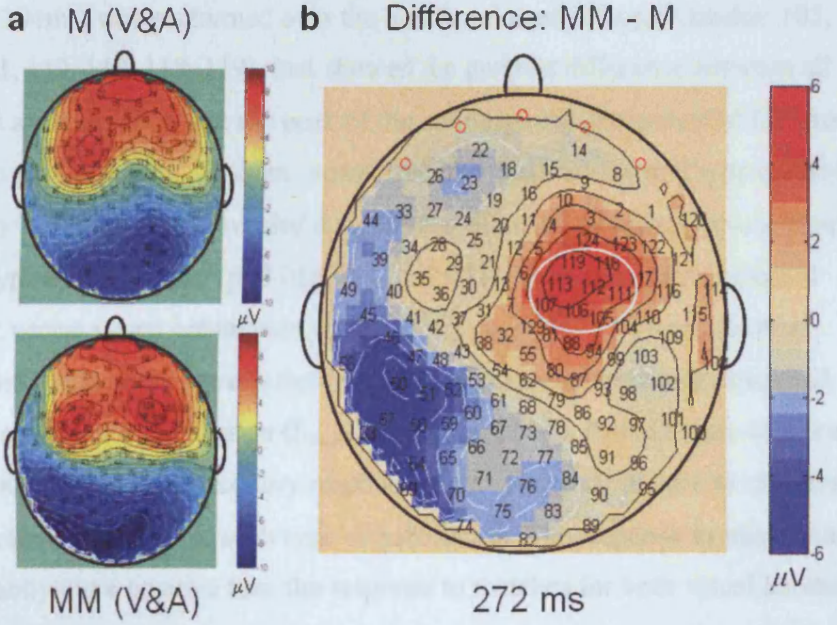
## 10.3 Results

### 10.3.1 Auditory response to all test stimuli

The main auditory potential, consisting of a strong frontal positivity and a posterior negativity, began around 120ms, peaked at around 270ms, and started declining gradually from around 480 ms.

### 10.3.2 Matches v. mismatches

***Figure 10.2 – Phonetic mismatch – match across habituation type***




***a)*** *Topographies of the evoked potential in response to the auditory test stimulus at the peak of the auditory potential 272ms after stimulus onset for phonetically matched (M) and mismatched (MM) test stimuli across auditory and visual habituation conditions.* ***b)*** *Topography of the difference between the response to phonetically matched and mismatched auditory test stimuli (MM – M), showing an increased response to mismatched test stimuli over the right frontal electrodes. A group of electrodes located over the maximum of this right frontal positivity was selected for statistical analysis (shown in white circle)*

Conditions where the vowel presented in the test and the context stimuli matched each other (i.e. VM and AM), were compared with conditions where the test and context vowel did not match (i.e. VMM and AMM) irrespective of habituation

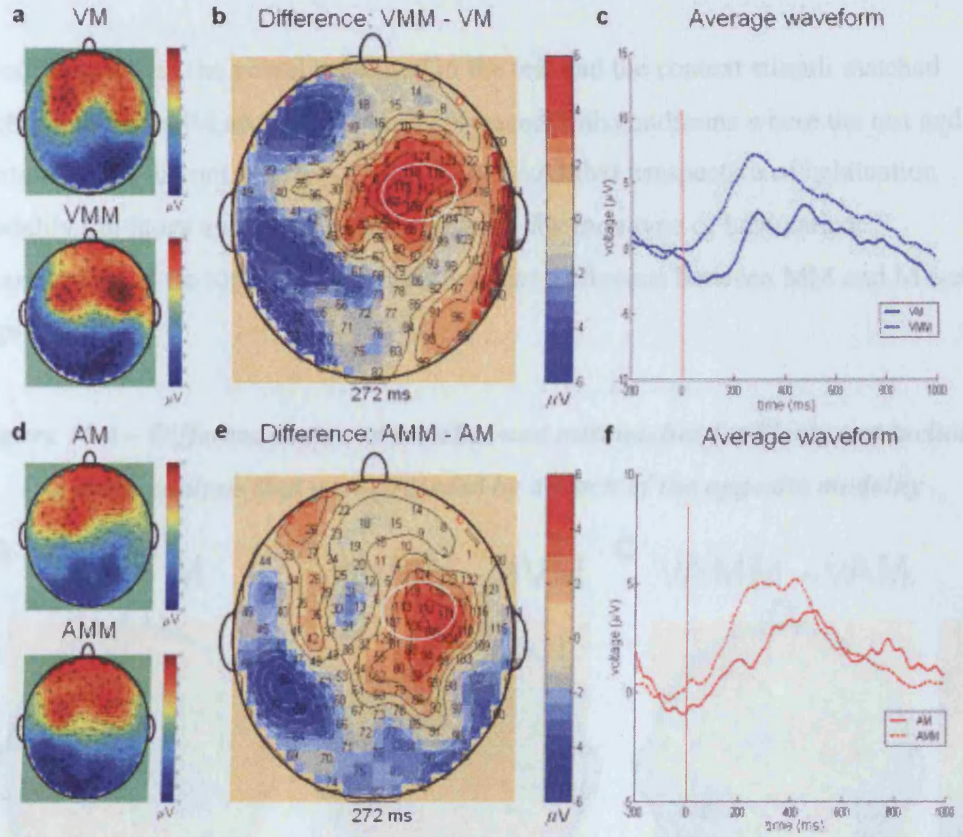
modality (auditory and visual), and separately for each type of habituation. Examination of the topography revealed a difference between MM and M consisting of an increased response to mismatched test stimuli in the right frontal electrodes (a right frontal positivity) (see Figure 10.2).

Examination of the topographies of VMM-VM and AMM-AM, also revealed very similar difference between matches and mismatches for each type of habituation, again consisting of an increased response to mismatched test stimuli in the right frontal electrodes (a right frontal positivity) (see Figure 10.3).

Analysis of the mean amplitude of auditory response across the peak of the response (240 to 304ms) was performed over the bundle of electrodes (electrodes: 105, 106, 107, 111, 112, 113, 118, 119), that showed the greatest difference between all matches and mismatches at the peak of the auditory response potential (272ms), using an ANOVA with 2 factors: vowel (match v. mismatch); and type of habituation (auditory v. visual). This revealed a significant effect of mismatch versus match, across type of habituation ($p=0.015$, $F_{(1,20)}=7.052$), but there was no effect of auditory versus visual habituation ($p=0.173$, $F_{(1,20)}=1.997$). Nor was there a significant interaction between the vowel (matched vowel versus mismatched vowel), and type of habituation ($F_{(1,20)}=0.434$, $p=0.517$). Paired t-tests were carried out to compare the mean auditory response of this electrode bundle to matches and mismatches separately for each type of habituation. The response to mismatches was significantly more positive than the response to matches for both visual habituation ($p=0.0483$) and auditory habituation conditions ($p=0.0256$).

The response to vowel matched test stimuli was weaker than the response to vowel mismatched stimuli, particularly in right frontal electrodes. This suggests that presentation of visual articulated vowels has habituated the infant's brain response to that same vowel when subsequently presented in an auditory context, i.e. cross modal habituation occurred, implying that the infants must have some sort of cross modal representation of vowels by 9-12 weeks of age.

***Figure 10.3 – Mismatch v. match for visual and auditory habituation conditions***

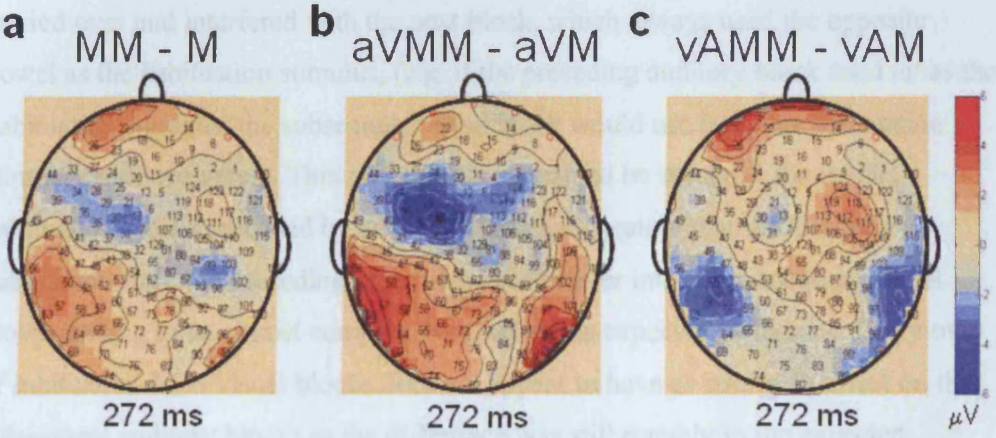



***a)*** *Topographies of the peak of the evoked response to the auditory test stimulus 272ms after stimulus onset for phonetically matched (VM) and mismatched (VMM) stimuli in the visual habituation condition.* ***b)*** *Topography of the difference between the responses to matched and mismatched test stimuli in the visual habituation condition (VMM – VM) at the peak of the auditory potential.* ***c)*** *The average waveform of the right frontal electrodes selected for statistical analysis (shown in white circle in b) located over the positive maxima of the difference (VMM – VM). The response to mismatches (VMM – dashed line) is significantly greater than the response to matches (VM – solid line) over the peak of the auditory potential (from 240 to 304ms after stimulus onset).* ***d)*** *Topographies of the peak of the evoked response to the auditory test stimulus 272ms after stimulus onset for phonetically matched (AM) and mismatched (AMM) stimuli in the auditory habituation condition.* ***e)*** *Topography of the difference between the responses to matched and mismatched test stimuli in the auditory habituation condition (AMM – AM) at the peak of the auditory potential 272ms after stimulus onset.* ***f)*** *The average waveform of the right frontal electrodes selected for statistical analysis (shown in white circle in e) located over the positive maxima of the difference (VMM – VM). The response to mismatches (AMM – dashed line) is significantly greater than the response to matches (VM – solid line) over the peak of the auditory potential (from 240 to 304ms after stimulus onset).*

### 10.3.3 Blocks preceded by the opposite type of block (vA and aV)

Conditions where the vowel presented in the test and the context stimuli matched each other (i.e. aVM and vAM), were compared with conditions where the test and context vowel did not match (i.e. aVMM and vAMM) irrespective of habituation modality (auditory and visual), and separately for each type of habituation. Examination of the topography reveals no clear difference between MM and M (see Figure 10.4a).

***Figure 10.4 – Difference between matches and mismatches for blocks not included in main analysis that were preceded by a block of the opposite modality***




***a)*** *Topography of the difference between the responses to phonetically matched (M) and mismatched (MM) test stimuli in visual and auditory habituation blocks that were preceded by a block of the opposite modality (i.e. visual blocks preceded by an auditory block and auditory blocks preceded by a visual block) at the peak of the auditory potential272ms after stimulus onset. There is no clear difference between matches and mismatches across habituation conditions, unlike for the blocks in the main analysis (see Figure 10.2).* ***b)*** *Topography of the difference between the responses to mismatched and matched stimuli (aVMM – aVM), at the peak of the auditory potential, in visual habituation blocks that were preceded by an auditory habituation block.* ***c)*** *Topography of the difference between the response to mismatched and matched stimuli (vAMM – vAM), at the peak of the auditory potential, in auditory habituation blocks that were preceded by a visual habituation block.*

Examination of the topographies of aVMM - aVM and vAMM - vAM, revealed differences but not those expected on the basis of previous auditory phonetic

habituation experiments or on the basis of my previous cross-modal habituation experiment (see Figure 10.4b & c).

The topography of aVMM – aVM revealed a difference almost completely opposite to that expected: more negative response to mismatches than matches over the frontal electrodes, and a more positive response to mismatches than matches over the posterior electrodes (see Figure 10.4b). The topography of vAMM – vAM revealed more positive response to mismatches than matches over the most frontal electrodes, and also revealed more negative response to mismatches than matches over the posterior right electrodes (see Figure 10.4c). These findings suggest that, as I suspected, the information from the previous block of the opposite modality, was carried over and interfered with the next block, which always used the opposite vowel as the habituation stimulus, (e.g. if the preceding auditory block used /a/ as the habituation stimulus, the subsequent visual block would use /i/ as the habituation stimulus and vice versa). This interference appears to be strongest for visual habituation blocks preceded by auditory blocks, suggesting that the auditory habituation from the preceding block was carried over into the subsequent visual block, leading to an almost complete reversal of the expected difference. Carry over of habituation from visual blocks does not appear to have as strong an effect on the subsequent auditory blocks as the difference was still roughly in the expected location (frontal positivity, posterior negativity). However, it was much weaker than in the auditory blocks not preceded by visual blocks suggesting that some interference still occurred. These data support the notion that I was correct to separate my analysis on this basis, and to exclude blocks preceded by a block of the opposite modality from my main analysis. I will thus only discuss the results of the main analyses.

## 10.4 Discussion

The mean amplitude of evoked response potential to vowel mismatched auditory test stimuli was significantly greater than the response to vowel matched stimuli across the peak of the response (240-304ms) for both auditory and visual habituation conditions (see Figure 10.3). Thus it appears that, as expected, both purely auditory and cross-modal habituation occurred. Repeated presentation of auditory vowels habituated the infants' brain response to that same vowel, i.e. auditory habituation occurred, and a change of phoneme elicited a mismatched response. This is consistent with previous studies of auditory phonetic habituation in 2 month old infants (Dehaene-Lambertz and Dehaene, 1994) and neonates (Dehaene-Lambertz and Pena, 2001). Likewise, as in my previous experiment, (see Chapter 9), visual presentation of silently articulated vowels habituated the infants' brain response to that same vowel when subsequently presented in an auditory context; and a change of phoneme across modality also elicited a mismatch response. This confirms my previous conclusion that infants have a cross modal neural representation of vowels, i.e. a network of neurons that respond to specific phonetic information irrespective of the modality it is perceived in, by 9-12 weeks of age.

The topography of the difference between the mismatches and matches seen for the visual habituation condition, is consistent to that seen in my previous cross-modal habituation experiment (see Chapter 9, Figure 9.3), and is extremely similar to that seen in the purely auditory phonetic habituation condition (see Figure 10.3). The same group of right frontal electrodes, selected on the basis of the location of the peak difference between all mismatches and matches across type of habituation (see Figure 10.2), showed a significantly greater response to mismatched compared to matched auditory test stimuli for both visual and auditory habituation across the peak of the auditory response potential, and there was no interaction between the effect of match versus mismatch and the type of habituation. This suggests that the same neural generators are involved in detecting a phonetic match or mismatch irrespective of the modality in which the mismatch occurs, and thus that the phonetic information is represented in the same brain areas, irrespective of whether it is presented in the auditory or visual modality. The timing of the mismatch response is similar in both conditions; with the effect being significant across the peak of the

auditory evoked potential in both conditions (if anything the cross-modal mismatch response appeared to start a little earlier), suggesting that visual and auditory phonetic information access this same phonetic neural representation in the infants' brains at approximately the same speed.

The results also suggest that the auditory phonetic information directly accesses the same cross modal neural representation as the visual phonetic information without passing through a uni-modal representation first, as if this was the case I would expect to see a difference in the topography or time course of the mismatch response between the auditory and visual habituation conditions, due to habituation of this putative uni-modal neural representation in the auditory condition only. This supports the notion put forward in the motor theory of speech, that phonetic information is primarily represented as articulatory gestures, rather than sounds (Liberman and Mattingly, 1985;Liberman and Whalen, 2000). If phonemes were represented as sounds first, one would expect the auditory mismatch response to appear earlier than the cross-modal mismatch response; however this was not the case. Thus it appears that auditory and visual phonetic information directly access the same cross modal representation.

## 10.5 Conclusion

I have again demonstrated phoneme specific cross-modal habituation, thus replicating my findings in Chapter 9, and confirming that 2-3 month-old infants do indeed have a cross-modal neural representation of vowels. I also demonstrated simple auditory phonetic habituation in the same group of infants. In addition I found that the timing and topography of the mismatch response to deviant phonemes was the same for both auditory only and cross-modal habituation. This suggests that visual and auditory phonetic information directly access the same amodal neural representation of phonemes in the infants' brains at approximately the same speed. This cross-modal representation may underlie infants' ability to match observed articulatory movements and their auditory consequences.

# CHAPTER 11: GENERAL DISCUSSION

This thesis has described a series of experiments investigating the neural mechanisms underlying our ability to monitor our own actions and predict their sensory consequences, and our ability to understand and predict the actions of others. It has been proposed that our ability to monitor our own actions and predict their consequences is based on the use of a forward model which uses an efference copy of the motor command to predict the sensory consequences of that action. Chapters 4 and 5 focused on the use of this sensory prediction to attenuate or cancel the sensory consequences of our actions. There is increasing evidence that our ability to understand and predict the actions of others and their consequences is based on the same neural mechanisms, that are involved in monitoring our own actions. In Chapters 6 and 7, I investigated the neural mechanisms involved in monitoring the actions of others and their sensory consequences. In Chapter 8, I examined the possibility that, in addition to using our own motor systems to understand the actions of others, we understand the sensations experienced by others by representing these sensations in our own sensory cortices. Chapters 9 and 10 focused on the development of our ability to monitor the actions of others. I investigated the neural basis of young infants' ability to recognise the sensory consequences of observed actions.

## 11.1 Sensorimotor attenuation of the consequences of our actions

It has been proposed that animals use an efference copy (von Holst, 1954) of their motor commands sent from the motor areas controlling the actions, in parallel with the motor signals, to predict the sensory consequences of their actions. On the basis of this efference copy, a prediction of the sensory consequences of the action is generated by an internal forward model (Wolpert and Miall, 1996). This sensory prediction is known as a corollary discharge (Sperry, 1950). This sensory prediction, or corollary discharge, can then be used to cancel self-produced sensory stimulation. There is substantial support for the existence of such a mechanism coming from a number of experiments demonstrating a reduced neural response to self-produced stimuli, compared to externally produced stimuli in the somatosensory (Blakemore et al., 1998b;Blakemore et al., 1999a;Blakemore et al., 1999b;Voss et al., 2006), and

auditory (Curio et al., 2000;Martikainen et al., 2005;Numminen et al., 1999;Schafer and Marcus, 1973) modalities.

Such a mechanism also appears to operate during blinking, as suggested by the fact that we rarely notice our blinks, despite their frequency and the pronounced interruption to visual input they cause. External darkenings of the visual field of a similar duration and magnitude as the interruptions to visual input caused by blinks, are readily apparent (Volkmann et al., 1980). Evidence for sensorimotor prediction and attenuation during blinks comes from several psychophysical studies demonstrating that visual sensitivity is reduced during blinks, an effect known as blink suppression (Manning et al., 1983;Riggs et al., 1982;Volkmann et al., 1980;Volkmann et al., 1982;Volkmann, 1986).This loss of visual sensitivity begins before the onset of the blink and thus is thought to result from a corollary discharge signal associated with the blink motor command (Manning et al., 1983;Volkmann, 1986). However, until now the neural mechanism underlying blink suppression remained unknown. In Chapters 4 and 5, I described two fMRI experiments investigating the neural mechanisms underlying the ability of blinks to pass unnoticed.

In Chapter 4, I compared the neural responses to self-produced darkenings (blinks) and externally generated darkenings. Two factors were independently manipulated in a blocked design; the presence/absence of voluntary blinking, and the presence/absence of visual stimulation. To control for the simple loss of visual input caused by eyelid closure I created a fifth condition where external darkenings were dynamically matched to each subjects' own blinks. Areas of lateral occipital cortex, including area V5/MT and V3a, showed a reduced response to visual stimulation during blinking. Matched external darkenings of the visual scene reduced activity in these regions to a lesser extent than blinks. Thus, I concluded that the reduced response to visual stimulation associated with blinking reflects an active suppression of these lateral visual areas, mediated by an oculomotor signal associated with the blink motor command. This suppression is consistent with the known loss in visual sensitivity that occurs during blinks, and therefore may be the neural mechanism underlying blink suppression.

In Chapter 5, by maintaining constant retinal illumination whether the eyes were open or shut, I was able to examine the top-down effects of blink-associated motor signals on cortical activity directly, without the need for an external darkening condition as a control for the confounding effect of the loss of visual input caused by eye-lid closure. Even though retinal illumination was kept constant during blinks, I found that blinking nevertheless suppressed activity in visual cortex, specifically area V3, and in areas of parietal and prefrontal cortex previously associated with awareness of environmental change. However, unlike in Chapter 4, no suppression of the response to visual stimulation in V5/MT was revealed in Chapter 5, because the trans-cranial retinal stimulation failed to activate V5/MT significantly. The reduced response to retinal stimulation during blinking observed in V3 in this experiment is consistent with the reduced response to visual stimulation observed in lateral occipital regions in Chapter 4. Likewise parts of the parietal cortex, showed a reduced response to visual input during blinking in both experiments. Thus the findings in Chapter 5 support the findings in Chapter 4. In addition, because retinal stimulation remained constant throughout the blink, the findings in Chapter 5 definitively demonstrate that the suppression of the neural response to visual stimulation observed during blinks, in both experiments, is an active top-down process associated with the blink motor command.

In addition, I observed a positive blink related signal in early visual areas in the total absence of retinal stimulation (as described in Chapter 5), which has been observed in previous studies of blinking but has not previously been remarked upon (Bodis-Wollner et al., 1999;Kato and Miyauchi, 2003a;Kato and Miyauchi, 2003b;Tsubota et al., 1999). A similar positive signal has also been observed in visual cortex during saccades (Sylvester et al., 2005). Since visual stimulation was entirely absent, this activation is likely to represent a motor signal associated with blinking in the visual cortex. However, the precise neural mechanisms relating the blink motor command to the neural suppression I have observed remains to be explored.

Together the studies described in Chapters 4 and 5, suggest a possible neural mechanism by which blinks go unnoticed, namely top down suppression of parts of the visual system, both early visual areas, and of areas involved in visual awareness, associated with the blink motor command. This parallels previous observations of

attenuation of the neural responses to self-produced stimuli in the somatosensory system (Blakemore et al., 1998b), in the auditory cortex (Curio et al., 2000;Martikainen et al., 2005;Numminen et al., 1999;Schafer and Marcus, 1973), and most recently in the visual cortex during saccades (Sylvester et al., 2005). Thus our findings provide further evidence that sensorimotor prediction and attenuation is a general mechanism in the human brain that operates in several, if not all, modalities.

### 11.2 Monitoring the actions of others

In Chapters 6 and 7 I investigated the neural mechanisms involved in monitoring the actions of others and their sensory consequences, in the light of accumulating evidence that this involves the same neural systems, including the internal forward model, as monitoring our own actions and predicting their sensory consequences.

Numerous studies have demonstrated activation of parts of our own motor system during the observation of actions (see General Introduction for a review). Simulation of observed actions by this mirror system is thought to underlie our ability to understand the actions of others (Rizzolatti et al, 2001;Rizzolatti and Craighero, 2004). It has recently been proposed that the mirror system acts in a predictive manner, predicting and simulating the actions of others, and then using the internal forward model, normally uses to predict the sensory consequences of our own actions, to verify its prediction (Kilner et al. in submission). According to the predictive model of the mirror system, the observer predicts the actions of others on the basis of the current context and the goals and intentions attributed to the other. The predicted action is then simulated in the observers own motor system and the internal forward model is used to predict the sensory consequences of the simulated action. This sensory prediction can then be compared to the action actually observed, giving rise to a prediction error, which can then be used to modify the original prediction of what the other person is doing. There is increasing evidence that the mirror system does indeed actively predict the actions of others rather than simply responding to sensory input (Flanagan and Johansson, 2003;Fogassi et al., 2005;Haueisen and Knosche, 2001;Kilner et al., 2004;Ramnani and Miall, 2004;Rotman et al., 2006;Umilta et al., 2001).

Two recent studies have shown that the superior temporal sulcus (STS), part of the mirror system, shows a greater response to unpredicted compared to predicted movements (Pelphrey et al., 2003;Pelphrey et al., 2004a). In these studies the observer's expectation of what the actor would do was experimentally controlled by the presence of a visible target, the inferred goal of the action. Eye and hand movements towards this target fulfilled the observer's expectation, while movements not directed towards the expected goal violated the observer's expectation. The increased STS activity is thought to reflect the reformulation of the observer's expectation or the prediction error, when the observed movement does not match the observer's original prediction.

In Chapter 6, I sought to investigate further the effect of the observer's expectation on the mirror system. In addition to inducing an expectation in the observer via the presence of a visible target, I also modified the observer's expectation by changing the social context of the gaze shift and thus the intention attributed to the person making the gaze shift. Two faces were presented, one gazing directly at the subject (the 'social' face) and one with averted gaze (the 'unsocial' face). One face then made a gaze shift that was either towards a visible target ('correct') or towards another location in space ('incorrect'). Direct gaze often signals the intention to communicate, and thus induced the expectation in the observer that the 'social' face (rather than the 'unsocial' face) would indicate the presence of the target by looking at it. When the 'unsocial' face made the gaze shift this expectation was violated. As in a previous experiment (Pelphrey et al., 2003), the presence of a visible target induced the expectation that the gaze shift would be directed towards the target. This expectation was violated in the 'incorrect' condition. I found significantly greater activation in the parieto-frontal oculomotor network, and in some parts of the posterior STS, in response to 'invalid' and 'unsocial', compared to 'invalid' and 'social', gaze shifts.

The increased activation of these areas during the 'unsocial' and 'incorrect' conditions is consistent with Kilner's predictive model of the mirror system, which includes the STS (Kilner et al. in submission), (see General Introduction for a review). I propose that the increased activity observed in the STS in the 'unsocial' and 'incorrect' conditions reflects the reformulation of the observer's expectations,

once their original prediction has been violated, or the prediction error between the observer's prediction of what the actor is going to do and the actual action observer. The increased activity in the fronto-parietal oculomotor network, which is thought to be part of an oculomotor mirror system (Grosbras et al., 2005), may also reflect the reformulation of the observer's prediction or the prediction error. However, the increased activation in these regions can also be explained in terms of additional attentional shifts during the 'unsocial' and 'incorrect' conditions. Therefore, unlike in the STS, I cannot definitively conclude that the observed increase in activity in the fronto-parietal network represents increased activation of the mirror system to unpredicted actions. However, the increased activity observed in the STS in response to unpredicted gaze shifts, provides support for Kilner's proposal that the mirror system is involved in actively predicting the actions of others rather than merely responding to sensory input.

Further support for the idea that the mirror system acts in a predictive manner comes from a number of studies demonstrating modulation of activity in our sensory cortices during action observation (see General Introduction for a review). This modulation may represent the prediction of the sensory consequences of the observed action, calculated on the basis of the simulation of the other's action by the mirror system. This would be in line with the proposal that the mirror system uses the same forward model used to predict the sensory consequences of our own actions to predict the sensory consequences of the actions of others.

In Chapter 7, I investigated whether the same neural systems are involved in monitoring the sensory consequences (a tone) of our own actions (a button press) and in monitoring the sensory consequences (a tone) of the actions of another person (a button press). I also sought to examine whether the neural response to sensory stimuli caused by the actions of others is modulated, compared to externally generated stimuli, and if so whether it is modulated in the same way as the response to self-produced stimuli.

Subjects performed a task in which they had to monitor the relationship between an action, namely a button press, and its sensory consequences, namely an auditory tone. The action was either performed by the subject or the experimenter, whose

hand was in the subject's field of view adjacent to the subject's own hand. In a control 'no agent' condition subjects monitored the relationship between an externally generated tone, and a computer generated event, the disappearance of a white dot.

Contrary to expectations, I did not identify a difference between the response to self-generated ('subject' condition) and externally generated ('no agent' condition) auditory stimuli in the auditory cortex. It may be that my auditory stimuli did not activate the auditory cortex sufficiently, relative to auditory activation caused by the background scanner noise, for a difference between the self- and externally-generated conditions to be detected. This may also explain the absence of a difference in the auditory cortex between the 'other' and 'no agent' conditions, and between the 'other' and 'subject' conditions. Thus I cannot conclude that agency does not affect the response to auditory stimuli, (a conclusion which in the case of self-produced stimuli would be contrary to many previous studies).

I found that a set of brain regions, previously implicated in action monitoring (Amodio and Frith, 2006;Frith, 2006;Saxe, 2006), namely the dorsal medial prefrontal cortex, precuneus, the posterior STS and temporal poles, were activated during both the 'subject' and the 'other' conditions, compared to the 'no agent' conditions. I conclude that these regions are involved in monitoring the relationship between actions and their consequences, irrespective of who is executing the action. This provides further support for the notion that the same neural systems are involved in monitoring the sensory consequences of our actions and the sensory consequences of the actions of others.

The cerebellum was also activated during both the 'subject' and 'other' conditions. The cerebellum has previously been implicated in the predicting the sensory consequences of our own actions, and it has been proposed that the cerebellum is the site of the internal forward model that predicts the sensory consequences of our actions (Blakemore et al., 1998a;Blakemore et al., 2001). Thus, my finding that the cerebellum is also involved in monitoring the consequences of other people's actions, provides support for the proposal that we use the same internal forward model, usually used to predict the sensory consequences of our own actions, to

predict the sensory consequences of the actions of others (Kilner et al. in submission).

In Chapter 8, I investigated whether in addition to representing actions of others in our own motor system, and representing the sensory consequences of these actions in our sensory cortices, we also represent the sensations experienced by others in a similar manner. Recently, a number of brain systems with 'mirror' properties have been described, for emotions (Carr et al., 2003;Wicker et al., 2003), pain (Singer et al., 2004), and most recently touch (Keysers et al., 2004). In the latter study, observing touch to someone else's legs activated similar regions in the secondary somatosensory cortex (SII) in the observer's brain as when the observer's own legs were touched. However, this SII activation was also found during the observation of touch to an object, and no primary somatosensory cortex activitywas found in either condition (Keysers et al., 2004). In Chapter 8, I investigated the potential existence of a touch mirror system by examining the neural response to the observation of touch to a human face relative to observation of touch to an object, and comparing this to the neural response to somatosensory stimulation.

In normal subjects the primary and secondary somatosensory cortices were somatotopically activated by somatosensory stimulation, and by the mere observation of touch to a human (relative to touch to an object). Thus it appears that we represent the sensory experiences of others by simulating the observed tactile sensations in our own somatosensory systems, similar to the way in which we represent the actions of others in our own motor system. This somatosensory stimulation may underlie our ability to understand the sensations experienced by others, in the same way that simulation of the actions of others is thought to underlie our ability to understand the actions of others (Rizzolatti et al., 2001). In one subject, C, which I describe in Chapter 8, this somatosensory mirror system was activated to a significantly greater extent than in all other subjects, with the result that rather than merely enabling C to understand the sensations others, C actually experiences the observed touch as somatosensory stimulation of her own body. Whether, like the action mirror system, this touch mirror system operates in a predictive manner remains to be seen.

## 11.3 Development of action monitoring

In this thesis I also investigated the development of our ability to monitor the actions of others and their consequences. There is strong behavioural evidence, mainly from studies of imitation, for the early development of a system for coupling the perception and production of actions (see General Introduction for a review). These studies suggest that infants, like adults, use their own motor system to simulate the observed actions of others. There is also behavioural evidence that infants can recognise the consequences of the actions of others from an early age. Two month old infants are able to match observed articulations with the appropriate speech sound (Kuhl et al., 1991;Kuhl and Meltzoff, 1982;Patterson and Werker, 1999;Patterson and Werker, 2003;Walton and Bower, 1993). In Chapters 9 and 10, I investigated the neural mechanism underlying infants' ability to recognise the auditory consequences of observed articulatory movements. Using EEG, I demonstrated phoneme specific habituation of the neural response to auditory phonetic stimuli by the prior presentation of visual speech, thereby demonstrating that 2-3 month old infants have a cross modal neural representation of phonemes. In Chapter 10, I directly compared this cross modal phonetic habituation to simple auditory only phonetic habituation. The topography of the difference between mismatches and matches was extremely similar for the two types of habituation, as was the timing of the mismatch response to deviant phonemes. These results suggest that visual and auditory phonetic information directly access the same amodal neural representation of phonemes in the infants' brains, at approximately the same speed.

In adults, both seen and heard speech activate brain areas involved in speech production (Calvert and Campbell, 2003;Fadiga et al., 2002;Skipper et al., 2005;Watkins et al., 2003;Wilson et al., 2004) (see General Introduction for a review). There is also evidence of a connection between heard speech and the corresponding motor representation in infants. When infants, aged 12-20 weeks, listened to an adult speaker produce different vowels, they produced more vocalisations resembling that particular vowel (Kuhl and Meltzoff, 1996). Likewise, new born infants, aged from 1 to 7 days, make the appropriate mouth movement in response to speech sounds (Chen et al., 2004). Given this evidence of an early correspondence between heard speech and motor production in infants, I

hypothesised that infants' ability to match observed articulations to the appropriate speech sound, might be based on a cross-modal neural representation of speech in the motor regions that would later be involved in speech production. Preliminary analyses conducted by my colleagues (S.Baillet, G.Dehaene-Lambertz, J-F.Mangin and J.Mattout, personal communication) have localised the source of the cross-modal phonetic habituation to Broca's area, suggesting that this is indeed the case. It appears that in infants, like adults, seen and heard speech activate a cross-modal motor representation of speech. The preliminary analyses also revealed a source in the left superior temporal gyrus. In adults the auditory cortex, including the superior temporal gyrus, is activated both by hearing speech and observation of silent articulations (Calvert et al., 1997;Pekkola et al., 2005). Thus the involvement of the superior temporal gyrus suggests that infants, like adults, represent the predicted sensory consequences of the observed articulation in their own auditory cortex.

Thus, the studies described in Chapters 9 and 10, provide evidence that from 2-3 months of age infants use their own motor and sensory cortices to represent the actions of others and the sensory consequences of these actions, at least in the context of speech. Further research is needed to elucidate whether this is also true of other types of actions.

## 11.4 Conclusion

The experiments in this thesis have added to our understanding of the neural mechanisms underlying our ability to monitor our own actions and predict their sensory consequences, and our ability to understand and predict the actions of others, and the sensory consequences of these actions. They provide evidence that our ability to understand and predict the actions of others and their consequences, is based on the same neural mechanisms that are involved in monitoring our own actions and predicting their sensory consequences, including the internal forward model. They also provide evidence that the mirror system acts in a predictive manner, anticipating and simulating the actions of others, and then using an internal forward model to verify its prediction, rather than merely responding to sensory input. In addition, the last two experiments begin to shed light on the development of our ability to understand other people's actions, providing evidence for the early development and involvement of the mirror system in action observation and in predicting the sensory consequences of actions. Future work should combine fMRI and EEG/MEG in order to look at the precise timing and the connectivity of the various regions implicated in the prediction system. Such studies would have the potential to reveal the neural mechanisms that underlie our ability to predict the consequences of actions.

## REFERENCES


Adler R.J. (1981). In The geometry of random fields, (New York: Wiley).

Allison,T., Puce,A., and McCarthy,G. (2000). Social perception from visual cues: role of the STS region. Trends Cogn Sci. *4*, 267-278.

Allison,T., Wood,C.C., and McCarthy,G. (1986). The central nervous system. In Psychophysiology; Systems, Processes and Application, M. G. H. Coles, S. W. Porges, and E. Donchin, eds. (New York: Guilford Press), pp. 5-25.

Amodio,D.M. and Frith,C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. Nat.Rev.Neurosci. *7*, 268-277.

Anisfeld,M. (1979). Interpreting "imitative" responses in early infancy. Science *205*, 214-215.

Anisfeld,M. (1991). Neonatal imitation. Developmental Review *11*, 60-97.

Anisfeld,M., Turkewitz,G., Rose,S.A., Rosenberg,F.R., Sheiber,F.J., Couturier-Fagan,D.A., Ger,J.S., and Sommer,I. (2001). No compelling evidence that newborns imitate oral gestures. Infancy *2* , 111-122.

Ashburner,J. and Friston,K.J. (1999). Nonlinear spatial normalization using basis functions. Hum.Brain Mapp. *7*, 254-266.

Ashburner,J., Neelin,P., Collins,D.L., Evans,A.C., and Friston,K.J. (1997). Incorporating prior knowledge into image registration. Neuroimage. *6*, 344-352.

Assmus,A., Marshall,J.C., Ritzl,A., Noth,J., Zilles,K., and Fink,G.R. (2003). Left inferior parietal cortex integrates time and space during collision judgments. Neuroimage. *20 Suppl 1*, S82-S88.

Astrup,J., Heuser,D., Lassen,N.A., Nilsson,B., Norberg,K., and Siesjo,B.K. (1978). Evidence against H+ and K+ as main factors for the control of cerebral blood flow: a microelectrode study. Ciba Found.Symp. 313-337.

Attwell,D. and Iadecola,C. (2002). The neural basis of functional brain imaging signals. Trends Neurosci. *25*, 621-625.

Attwell,D. and Laughlin,S.B. (2001). An energy budget for signaling in the grey matter of the brain. J.Cereb.Blood Flow Metab *21*, 1133-1145.

Avikainen,S., Forss,N., and Hari,R. (2002). Modulated activation of the human SI and SII cortices during observation of hand actions. Neuroimage. *15*, 640-646.

Aziz-Zadeh,L., Maeda,F., Zaidel,E., Mazziotta,J., and Iacoboni,M. (2002). Lateralization in motor facilitation during action observation: a TMS study. Exp.Brain Res. *144*, 127-131.

Bahrick,L.E. and Watson,J.S. (1985). Detection of intermodal proprioceptive-visual contingency as a potential basis of self-perception in infancy. Develomental Psychology *21*, 963-973.

Baillet,S., Mosher,J.C., and Leahy,R.M. (2001). Electromagnetic brain mapping. IEEE Signal Processing Magazine *18*, 14-30.

Bangert,M. and Altenmuller,E.O. (2003). Mapping perception to action in piano practice: a longitudinal DC-EEG study. BMC.Neurosci. *4*, 26.

Bates,A.T., Patel,T.P., and Liddle,P.F. (2005). External behaviour monitoring mirrors internal behaviour monitoring: error-related negativity for observed errors. J.Psychophysiology *19*, 281-288.

Baylis,G.C., Rolls,E.T., and Leonard,C.M. (1985). Selectivity between faces in the responses of a population of neurons in the cortex in the superior temporal sulcus of the monkey. Brain Res. *342*, 91-102.

Bays,P.M., Flanagan,J.R., and Wolpert,D.M. (2006). Attenuation of self-generated tactile sensations is predictive, not postdictive. PLoS.Biol. *4*, e28.

Bays,P.M., Wolpert,D.M., and Flanagan,J.R. (2005). Perception of the consequences of self-action is temporally tuned and event driven. Curr.Biol. *15*, 1125-1128.

Beck,D.M., Rees,G., Frith,C.D., and Lavie,N. (2001). Neural correlates of change detection and change blindness. Nat.Neurosci. *4*, 645-650.

Berger,H. (1929). Uber das Elektrekephalogram des Menschen. Archiv fur Psychiatrie und Nervenkrankheiten *87*, 527-570.

Blakemore,S.J. and Decety,J. (2001). From the perception of action to the understanding of intention. Nat.Rev.Neurosci. *2*, 561-567.

Blakemore,S.J., Frith,C.D., and Wolpert,D.M. (1999a). Spatio-temporal prediction modulates the perception of self-produced stimuli. J.Cogn Neurosci. *11*, 551-559.

Blakemore,S.J., Frith,C.D., and Wolpert,D.M. (2001). The cerebellum is involved in predicting the sensory consequences of action. Neuroreport *12*, 1879-1884.

Blakemore,S.J., Rees,G., and Frith,C.D. (1998a). How do we predict the consequences of our actions? A functional imaging study. Neuropsychologia *36*, 521-529.

Blakemore,S.J., Wolpert,D.M., and Frith,C.D. (1998b). Central cancellation of self-produced tickle sensation. Nat.Neurosci. *1*, 635-640.

Blakemore,S.J., Wolpert,D.M., and Frith,C.D. (1999b). The cerebellum contributes to somatosensory cortical activity during self-produced tactile stimulation. Neuroimage. *10*, 448-459.

Bodis-Wollner,I., Bucher,S.F., and Seelos,K.C. (1999). Cortical activation patterns during voluntary blinks and voluntary saccades. Neurology *53*, 1800-1805.

Bonda,E., Petrides,M., Ostry,D., and Evans,A. (1996). Specific involvement of human parietal systems and the amygdala in the perception of biological motion. J.Neurosci. *16*, 3737-3744.

Bour,L.J., Aramideh,M., and de Visser,B.W. (2000). Neurophysiological aspects of eye and eyelid movements during blinking in humans. J.Neurophysiol. *83*, 166-176.

Bremmer,F., Schlack,A., Shah,N.J., Zafiris,O., Kubischik,M., Hoffmann,K., Zilles,K., and Fink,G.R. (2001). Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. Neuron *29*, 287-296.

Buccino,G., Binkofski,F., Fink,G.R., Fadiga,L., Fogassi,L., Gallese,V., Seitz,R.J., Zilles,K., Rizzolatti,G., and Freund,H.J. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur.J.Neurosci. *13*, 400-404.

Burr,D.C., Morrone,M.C., and Ross,J. (1994). Selective suppression of the magnocellular visual pathway during saccadic eye movements. Nature *371*, 511-513.

Burton,H., Videen,T.O., and Raichle,M.E. (1993). Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans. Somatosens.Mot.Res. *10*, 297-308.

Calvert,G.A., Bullmore,E.T., Brammer,M.J., Campbell,R., Williams,S.C., McGuire,P.K., Woodruff,P.W., Iversen,S.D., and David,A.S. (1997). Activation of auditory cortex during silent lipreading. Science *276*, 593-596.

Calvert,G.A. and Campbell,R. (2003). Reading speech from still and moving faces: the neural substrates of visible speech. J.Cogn Neurosci. *15*, 57-70.

Carlsson,K., Petrovic,P., Skare,S., Petersson,K.M., and Ingvar,M. (2000). Tickling expectations: neural processing in anticipation of a sensory stimulus. J.Cogn Neurosci. *12*, 691-703.

Carr,L., Iacoboni,M., Dubeau,M.C., Mazziotta,J.C., and Lenzi,G.L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc.Natl.Acad.Sci.U.S.A *100*, 5497-5502.

Castelli,F., Happe,F., Frith,U., and Frith,C. (2000). Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. Neuroimage. *12*, 314-325.

Chen,X., Striano,T., and Rakoczy,H. (2004). Auditory-oral matching behavior in newborns. Dev.Sci. *7*, 42-47.

Cochin,S., Barthelemy,C., Roux,S., and Martineau,J. (1999). Observation and execution of movement: similarities demonstrated by quantified electroencephalography. Eur.J.Neurosci. *11*, 1839-1842.

Coles,M.G.H. and Rugg,M. (1995). Event-related potentials: an introduction. In Electrophysiology of the mind, M. G. H. Coles and M. Rugg, eds. (New York: Oxford University Press), pp. 1-23.

Corbetta,M., Akbudak,E., Conturo,T.E., Snyder,A.Z., Ollinger,J.M., Drury,H.A., Linenweber,M.R., Petersen,S.E., Raichle,M.E., Van Essen,D.C., and Shulman,G.L. (1998). A common network of functional areas for attention and eye movements. Neuron *21*, 761-773.

Coull,J.T., Vidal,F., Nazarian,B., and Macar,F. (2004). Functional anatomy of the attentional modulation of time estimation. Science *303*, 1506-1508.

Croft,R.J. and Barry,R.J. (2000). Removal of ocular artifact from the EEG: a review. Neurophysiol.Clin. *30*, 5-19.

Curio,G., Neuloh,G., Numminen,J., Jousmaki,V., and Hari,R. (2000). Speaking modifies voice-evoked activity in the human auditory cortex. Hum.Brain Mapp. *9*, 183-191.

Dale,A.M. and Sereno,M.I. (1993). Improved localisation of cortical activity by combining EEg and MEG with MRI cortical surface reconstruction: a linear approach. J.Cogn Neurosci. *5*, 162-176.

Dechent,P. and Frahm,J. (2003). Characterization of the human visual V6 complex by functional magnetic resonance imaging. Eur.J.Neurosci. *17*, 2201-2211.

Dehaene,S., Posner,M.I., and Tucker,D.M. (1994). Localization of a neural system for error detection and compensation. Psychological Science *5*, 303-305.

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

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

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

Del Gratta,C., Della,P.S., Tartaro,A., Ferretti,A., Torquati,K., Bonomo,L., Romani,G.L., and Rossini,P.M. (2000). Topographic organization of the human primary and secondary somatosensory areas: an fMRI study. Neuroreport *11*, 2035-2043.

Delorme,A. and Makeig,S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J.Neurosci.Methods *134*, 9-21.

Di Pellegrino,G., Fadiga,L., Fogassi,L., Gallese,V., and Rizzolatti,G. (1992). Understanding motor events: a neurophysiological study. Exp.Brain Res. *91*, 176-180.

Disbrow,E., Roberts,T., and Krubitzer,L. (2000). Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: evidence for SII and PV. J.Comp Neurol. *418*, 1-21.

Downing,P.E., Jiang,Y., Shuman,M., and Kanwisher,N. (2001). A cortical area selective for visual processing of the human body. Science *293*, 2470-2473.

Driver,J., Davis,G., Ricciardelli,P., Kidd,P., maxwell,E., and Baron-Cohen,S. (1999). Gaze perception triggers reflexive visuospatial orienting. Visual Cognition *6*, 509-540.

Dumoulin,S.O., Bittar,R.G., Kabani,N.J., Baker,C.L., Jr., Le Goualher,G., Bruce,P.G., and Evans,A.C. (2000). A new anatomical landmark for reliable identification of human area V5/MT: a quantitative analysis of sulcal patterning. Cereb.Cortex *10*, 454-463.

Elliott,R., Dolan,R.J., and Frith,C.D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb.Cortex *10*, 308-317.

Evinger,C., Shaw,M.D., Peck,C.K., Manning,K.A., and Baker,R. (1984). Blinking and associated eye movements in humans, guinea pigs, and rabbits. J.Neurophysiol. *52*, 323-339.

Fadiga,L., Craighero,L., Buccino,G., and Rizzolatti,G. (2002). Speech listening specifically modulates the excitability of tongue muscles: a TMS study. Eur.J.Neurosci. *15*, 399-402.

Fadiga,L., Fogassi,L., Pavesi,G., and Rizzolatti,G. (1995). Motor facilitation during action observation: a magnetic stimulation study. J.Neurophysiol. *73*, 2608-2611.

Falck-Ytter,T., Gredeback,G., and von Hofsten,C. (2006). Infants predict other people's action goals. Nat.Neurosci. *9*, 878-879.

Farrer,C., Franck,N., Georgieff,N., Frith,C.D., Decety,J., and Jeannerod,M. (2003). Modulating the experience of agency: a positron emission tomography study. Neuroimage. *18*, 324-333.

Farrer,C. and Frith,C.D. (2002). Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. Neuroimage. *15*, 596-603.

Felleman,D.J. and Van Essen,D.C. (1987). Receptive field properties of neurons in area V3 of macaque monkey extrastriate cortex. J.Neurophysiol. *57*, 889-920.

Ferrandez,A.M., Hugueville,L., Lehericy,S., Poline,J.B., Marsault,C., and Pouthas,V. (2003). Basal ganglia and supplementary motor area subtend duration perception: an fMRI study. Neuroimage. *19*, 1532-1544.

Field,T.M. (1979). Visual and cardiac responses to animate and inanimate faces by young term and preterm infants. Child Dev. *50*, 188-194.

Fink,G.R., Frackowiak,R.S., Pietrzyk,U., and Passingham,R.E. (1997). Multiple nonprimary motor areas in the human cortex. J.Neurophysiol. *77*, 2164-2174.

Fink,G.R., Markowitsch,H.J., Reinkemeier,M., Bruckbauer,T., Kessler,J., and Heiss,W.D. (1996). Cerebral representation of one's own past: neural networks involved in autobiographical memory. J.Neurosci. *16*, 4275-4282.

Flanagan,J.R. and Johansson,R.S. (2003). Action plans used in action observation. Nature *424*, 769-771.

Flanagan,J.R. and Wing,A.M. (1997). The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. J.Neurosci. *17*, 1519-1528.

Fletcher,P.C., Happe,F., Frith,U., Baker,S.C., Dolan,R.J., Frackowiak,R.S., and Frith,C.D. (1995). Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition *57*, 109-128.

Fogassi,L., Ferrari,P.F., Gesierich,B., Rozzi,S., Chersi,F., and Rizzolatti,G. (2005). Parietal lobe: from action organization to intention understanding. Science *308*, 662-667.

Fox,P.T. and Raichle,M.E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc.Natl.Acad.Sci.U.S.A *83*, 1140-1144.

Friston,K.J. (1997). Testing anatomical specified regional effects. Hum.Brain Mapp. *5*, 133-136.

Friston,K.J., Ashburner,J., Frith,C.D., Poline,J.B., Heather,J.D., and Frackowiak,R.S. (1995). Spatial registration and normalisation of images. Hum.Brain Mapp. *2*, 165-189.

Friston,K.J., Holmes,A.P., Worsley,K.J., Poline,J.P., Frith,C.D., and Frackowiak,R.S.J. (1994a). Statistical parametric maps in functional imaging: a general linear approach. Hum.Brain Mapp. *2*, 189-210.

Friston,K.J., Josephs,O., Rees,G., and Turner,R. (1998). Nonlinear event-related responses in fMRI. Magn Reson.Med. *39*, 41-52.

Friston,K.J., Williams,S., Howard,R., Frackowiak,R.S., and Turner,R. (1996). Movement-related effects in fMRI time-series. Magn Reson.Med. *35*, 346-355.

Friston,K.J., Worsley,K.J., Frackowiak,R.S., Mazziota,J.C., and Evans,A.C. (1994b). Assessing the significance of focal activations using their spatial extent. Hum.Brain Mapp. *1*, 214-220.

Frith,C. (2006). The social brain. Philos.Trans.R.Soc.Lond B Biol.Sci. *in press.*

Gallagher,H.L., Happe,F., Brunswick,N., Fletcher,P.C., Frith,U., and Frith,C.D. (2000). Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia *38*, 11-21.

Gallagher,H.L., Jack,A.I., Roepstorff,A., and Frith,C.D. (2002). Imaging the intentional stance in a competitive game. Neuroimage. *16*, 814-821.

Gallese,V., Fadiga,L., Fogassi,L., and Rizzolatti,G. (1996). Action recognition in the premotor cortex. Brain *119 ( Pt 2)*, 593-609.

Galletti,C., Battaglini,P.P., and Fattori,P. (1991). Functional Properties of Neurons in the Anterior Bank of the Parieto-occipital Sulcus of the Macaque Monkey. Eur.J.Neurosci. *3*, 452-461.

Galletti,C., Battaglini,P.P., and Fattori,P. (1995). Eye position influence on the parieto-occipital area PO (V6) of the macaque monkey. Eur.J.Neurosci. *7*, 2486-2501.

Galletti,C., Fattori,P., Battaglini,P.P., Shipp,S., and Zeki,S. (1996). Functional demarcation of a border between areas V6 and V6A in the superior parietal gyrus of the macaque monkey. Eur.J.Neurosci. *8*, 30-52.

Gawne,T.J. and Martin,J.M. (2000). Activity of primate V1 cortical neurons during blinks. J.Neurophysiol. *84*, 2691-2694.

Gawne,T.J. and Martin,J.M. (2002). Responses of primate visual cortical neurons to stimuli presented by flash, saccade, blink, and external darkening. J.Neurophysiol. *88*, 2178-2186.

Gazzola,V., Aziz-Zadeh,L., and Keysers,C. (2006). Empathy and the somatotopic auditory mirror system in humans. Curr.Biol. *16*, 1824-1829.

Gegenfurtner,K.R., Kiper,D.C., and Levitt,J.B. (1997). Functional properties of neurons in macaque area V3. J.Neurophysiol. *77*, 1906-1923.

Gehring,W.J., Goss,B., Coles,M.G.H., Meyer,D.E., and Donchin,E. (1993). A neural system for error detection and and compensation. Psychological Science *4*, 385-390.

Gibson,J.J. and Pick,A. (1963). Perception of another person's looking behavior. Am.J.Psychol. *76*, 386-394.

Glaser,E.M. and Ruchkin,D.S. (1976). Principles of neurobiological signal analysis. (New York: Academic Press).

Gloor,P. (1985). Neuronal generators and the problem of localization in electroencephalography: application of volume conductor theory to electroencephalography. J.Clin.Neurophysiol. *2*, 327-354.

Grafton,S.T., Arbib,M.A., Fadiga,L., and Rizzolatti,G. (1996). Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Exp.Brain Res. *112*, 103-111.

Grefkes,C., Weiss,P.H., Zilles,K., and Fink,G.R. (2002). Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. Neuron *35*, 173-184.

Grezes,J., Armony,J.L., Rowe,J., and Passingham,R.E. (2003). Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. Neuroimage. *18*, 928-937.

Grezes,J., Costes,N., and Decety,J. (1998). Top-down effect of strategy on the perception of human biological motion: a PET investigation. Cognitive Neuropsychology *15*, 553-582.

Grezes,J. and Decety,J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum.Brain Mapp. *12*, 1-19.

Grezes,J., Fonlupt,P., Bertenthal,B., Delon-Martin,C., Segebarth,C., and Decety,J. (2001). Does perception of biological motion rely on specific brain regions? Neuroimage. *13*, 775-785.

Grosbras,M.H., Laird,A.R., and Paus,T. (2005). Cortical regions involved in eye movements, shifts of attention, and gaze perception. Hum.Brain Mapp. *25*, 140-154.

Grossman,E., Donnelly,M., Price,R., Pickens,D., Morgan,V., Neighbor,G., and Blake,R. (2000). Brain areas involved in perception of biological motion. J.Cogn Neurosci. *12*, 711-720.

Hari,R., Forss,N., Avikainen,S., Kirveskari,E., Salenius,S., and Rizzolatti,G. (1998). Activation of human primary motor cortex during action observation: a neuromagnetic study. Proc.Natl.Acad.Sci.U.S.A *95*, 15061-15065.

Hari,R., Salmellin,R., Tissari,S.O., Kajola,M., and Virsu,V. (1994). Visual stability during eyeblinks. Nature *367*, 121-122.

Hasnain,M.K., Fox,P.T., and Woldorff,M.G. (1998). Intersubject variability of functional areas in the human visual cortex. Hum.Brain Mapp. *6*, 301-315.

Haueisen,J. and Knosche,T.R. (2001). Involuntary motor activity in pianists evoked by music perception. J.Cogn Neurosci. *13*, 786-792.

Haxby,J.V., Hoffman,E.A., and Gobbini,M.I. (2002). Human neural systems for face recognition and social communication. Biol.Psychiatry *51*, 59-67.

Haynes,J.D., Lotto,R.B., and Rees,G. (2004). Responses of human visual cortex to uniform surfaces. Proc.Natl.Acad.Sci.U.S.A *101*, 4286-4291.

Helmholtz,H. (1867). Handbuch der physiologischen optik. (Hamburg, Germany.

Hoffman,E.A. and Haxby,J.V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. Nat.Neurosci. *3*, 80-84.

Hooker,C.I., Paller,K.A., Gitelman,D.R., Parrish,T.B., Mesulam,M.M., and Reber,P.J. (2003). Brain networks for analyzing eye gaze. Brain Res.Cogn Brain Res. *17*, 406-418.

Hyder,F., Rothman,D.L., Mason,G.F., Rangarajan,A., Behar,K.L., and Shulman,R.G. (1997). Oxidative glucose metabolism in rat brain during single forepaw stimulation: a spatially localized 1H[13C] nuclear magnetic resonance study. J.Cereb.Blood Flow Metab *17*, 1040-1047.

Iacoboni,M., Molnar-Szakacs,I., Gallese,V., Buccino,G., Mazziotta,J.C., and Rizzolatti,G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS.Biol. *3*, e79.

Johansson,R.S., Hager,C., and Riso,R. (1992a). Somatosensory control of precision grip during unpredictable pulling loads. II. Changes in load force rate. Exp.Brain Res. *89*, 192-203.

Johansson,R.S., Riso,R., Hager,C., and Backstrom,L. (1992b). Somatosensory control of precision grip during unpredictable pulling loads. I. Changes in load force amplitude. Exp.Brain Res. *89*, 181-191.

Johansson,R.S. and Westling,G. (1984). Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. Exp.Brain Res. *56*, 550-564.

Jueptner,M. and Weiller,C. (1995). Review: Does measurement of regional cerebral bloof flow reflect synaptic activity? - Implications for PET and fMRI. Neuroimage. *2*, 148-156.

Kadekaro,M., Crane,A.M., and Sokoloff,L. (1985). Differential effects of electrical stimulation of sciatic nerve on metabolic activity in spinal cord and dorsal root ganglion in the rat. Proc.Natl.Acad.Sci.U.S.A *82*, 6010-6013.

Kadekaro,M., Vance,W.H., Terrell,M.L., Gary,H., Jr., Eisenberg,H.M., and Sokoloff,L. (1987). Effects of antidromic stimulation of the ventral root on glucose utilization in the ventral horn of the spinal cord in the rat. Proc.Natl.Acad.Sci.U.S.A *84*, 5492-5495.

Kageyama,G.H. and Wong-Riley,M. (1986). Laminar and cellular localization of cytochrome oxidase in the cat striate cortex. J.Comp Neurol. *245*, 137-159.

Kampe,K.K., Frith,C.D., and Frith,U. (2003). "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. J.Neurosci. *23*, 5258-5263.

Kanwisher,N., McDermott,J., and Chun,M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. J.Neurosci. *17*, 4302-4311.

Kastner,S., O'Connor,D.H., Fukui,M.M., Fehd,H.M., Herwig,U., and Pinsk,M.A. (2004). Functional imaging of the human lateral geniculate nucleus and pulvinar. J.Neurophysiol. *91*, 438-448.

Kato,C., Matsuo,K., Matsuzawa,M., Moriya,T., Glover,G.H., and Nakai,T. (2001). Activation during endogenous orienting of visual attention using symbolic pointers

in the human parietal and frontal cortices: a functional magnetic resonance imaging study. Neurosci.Lett. *314*, 5-8.

Kato,M. and Miyauchi,S. (2003a). Functional MRI of brain activation evoked by intentional eye blinking. Neuroimage. *18*, 749-759.

Kato,M. and Miyauchi,S. (2003b). Human precentral cortical activation patterns during saccade tasks: an fMRI comparison with activation during intentional eyeblink tasks. Neuroimage. *19*, 1260-1272.

Keysers,C., Wicker,B., Gazzola,V., Anton,J.L., Fogassi,L., and Gallese,V. (2004). A touching sight: SII/PV activation during the observation and experience of touch. Neuron *42*, 335-346.

Kilner,J.M., Friston,K.J., and Frith,C. (2006). The mirror system: a Bayesian perspective. Trends Cogn Sci. *in submission.*

Kilner,J.M., Vargas,C., Duval,S., Blakemore,S.J., and Sirigu,A. (2004). Motor activation prior to observation of a predicted movement. Nat.Neurosci. *7*, 1299-1301.

Kircher,T.T., Senior,C., Phillips,M.L., Rabe-Hesketh,S., Benson,P.J., Bullmore,E.T., Brammer,M., Simmons,A., Bartels,M., and David,A.S. (2001). Recognizing one's own face. Cognition *78*, B1-B15.

Kleinschmidt,A., Buchel,C., Zeki,S., and Frackowiak,R.S. (1998). Human brain activity during spontaneously reversing perception of ambiguous figures. Proc.R.Soc.Lond B Biol.Sci. *265*, 2427-2433.

Kohler,E., Keysers,C., Umilta,M.A., Fogassi,L., Gallese,V., and Rizzolatti,G. (2002). Hearing sounds, understanding actions: action representation in mirror neurons. Science *297*, 846-848.

Kornmuller,A.E. (1932). Eine experimentelle anesthesie der auseen augenmuskeln am menschen und ihre auswirkungen. Journal fur Psychologie und Neurologie *41*, 354-366.

Kuhl,P.K. and Meltzoff,A.N. (1982). The bimodal perception of speech in infancy. Science *218*, 1138-1141.

Kuhl,P.K. and Meltzoff,A.N. (1996). Infant vocalizations in response to speech: vocal imitation and developmental change. J.Acoust.Soc.Am. *100*, 2425-2438.

Kuhl,P.K., Williams,K.A., and Meltzoff,A.N. (1991). Cross-modal speech perception in adults and infants using nonspeech auditory stimuli. J.Exp.Psychol.Hum.Percept.Perform. *17*, 829-840.

Kutas,M. and Dale,A.M. (1997). Electrical and magnetic readings of mental functions. In Cognitive Neuroscience, M. Rugg, ed. (Cambridge, MA: MIT Press), pp. 197-242.

Kwong,K.K., Belliveau,J.W., Chesler,D.A., Goldberg,I.E., Weisskoff,R.M., Poncelet,B.P., Kennedy,D.N., Hoppel,B.E., Cohen,M.S., Turner,R., and . (1992).

Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc.Natl.Acad.Sci.U.S.A *89*, 5675-5679.

Langton,S.R. and Bruce,V. (1999). Reflexive visual orienting in response to the social attention of others. Visual Cognition *6*, 541-567.

Law,I., Svarer,C., Rostrup,E., and Paulson,O.B. (1998). Parieto-occipital cortex activation during self-generated eye movements in the dark. Brain *121 ( Pt 11)*, 2189-2200.

Lewis,P.A. and Miall,R.C. (2003). Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia *41*, 1583-1592.

Liberman,A.M. and Mattingly,I.G. (1985). The motor theory of speech perception revised. Cognition *21*, 1-36.

Liberman,A.M. and Whalen,D.H. (2000). On the relation of speech to language. Trends Cogn Sci. *4*, 187-196.

Livesey,A.C., Wall,M.B., and Smith,A.T. (2006). Time perception: Manipulation of task difficulty dissociates clock functions from other cognitive demands. Neuropsychologia.

Logothetis,N.K., Pauls,J., Augath,M., Trinath,T., and Oeltermann,A. (2001). Neurophysiological investigation of the basis of the fMRI signal. Nature *412*, 150-157.

Lumer,E.D., Friston,K.J., and Rees,G. (1998). Neural correlates of perceptual rivalry in the human brain. Science *280*, 1930-1934.

Macaluso,E., Driver,J., and Frith,C.D. (2003). Multimodal spatial representations engaged in human parietal cortex during both saccadic and manual spatial orienting. Curr.Biol. *13*, 990-999.

Magistretti,P.J. and Pellerin,L. (1997). Metabolic coupling during activation. A cellular view. Adv.Exp.Med.Biol. *413*, 161-166.

Magistretti,P.J. and Pellerin,L. (1999). Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. Philos.Trans.R.Soc.Lond B Biol.Sci. *354*, 1155-1163.

Magistretti,P.J., Pellerin,L., Rothman,D.L., and Shulman,R.G. (1999). Energy on demand. Science *283*, 496-497.

Manning,K.A., Riggs,L.A., and Komenda,J.K. (1983). Reflex eyeblinks and visual suppression. Percept.Psychophys. *34*, 250-256.

Mansfield,P. (1977). Multi-planar image formation using NMR spin echoes. J.Pysiology *10*, 349-352.

Martikainen,M.H., Kaneko,K., and Hari,R. (2005). Suppressed responses to self-triggered sounds in the human auditory cortex. Cereb.Cortex *15*, 299-302.

Mazziotta,J.C., Toga,A.W., Evans,A., Fox,P., and Lancaster,J. (1995). A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage. *2*, 89-101.

McCabe,K., Houser,D., Ryan,L., Smith,V., and Trouard,T. (2001). A functional imaging study of cooperation in two-person reciprocal exchange. Proc.Natl.Acad.Sci.U.S.A *98*, 11832-11835.

McGuire,P.K., Paulesu,E., Frackowiak,R.S., and Frith,C.D. (1996a). Brain activity during stimulus independent thought. Neuroreport *7*, 2095-2099.

McGuire,P.K., Silbersweig,D.A., and Frith,C.D. (1996b). Functional neuroanatomy of verbal self-monitoring. Brain *119 ( Pt 3)*, 907-917.

Meltzoff,A. and Moore,M.K. (1989). Imitation in newborn infants: exploring the range of gestures imitated and the underlying mechanisms. Develomental Psychology *25*, 954-962.

Meltzoff,A.N. and Moore,M.K. (1977). Imitation of facial and manual gestures by human neonates. Science *198*, 74-78.

Meltzoff,A.N. and Moore,M.K. (1983). Newborn infants imitate adult facial gestures. Child Dev. *54*, 702-709.

Miller,E.K., Li,L., and Desimone,R. (1991). A neural mechanism for working and recognition memory in inferior temporal cortex. Science *254*, 1377-1379.

Mintun,M.A., Lundstrom,B.N., Snyder,A.Z., Vlassenko,A.G., Shulman,G.L., and Raichle,M.E. (2001). Blood flow and oxygen delivery to human brain during functional activity: theoretical modeling and experimental data. Proc.Natl.Acad.Sci.U.S.A *98*, 6859-6864.

Mottonen,R., Jarvelainen,J., Sams,M., and Hari,R. (2005). Viewing speech modulates activity in the left SI mouth cortex. Neuroimage. *24*, 731-737.

Muller-Preuss,P. (1978). Single unit responses of the auditory cortex in the squirrel monkey to self-produced and loudspeaker transmitted vocalisations. Neurosci.Let.Supp. *1:S7*.

Muller-Preuss,P. and Ploog,D. (1981). Inhibition of auditory cortical neurons during phonation. Brain Res. *215*, 61-76.

Nobre,A.C., Sebestyen,G.N., Gitelman,D.R., Mesulam,M.M., Frackowiak,R.S., and Frith,C.D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. Brain *120 ( Pt 3)*, 515-533.

Nudo,R.J. and Masterton,R.B. (1986). Stimulation-induced [14C]2-deoxyglucose labeling of synaptic activity in the central auditory system. J.Comp Neurol. *245*, 553-565.

Numminen,J., Salmelin,R., and Hari,R. (1999). Subject's own speech reduces reactivity of the human auditory cortex. Neurosci.Lett. *265*, 119-122.

Nunez,P.L. (1981). Electric fields of the brain. (New York: Oxford University Press).

Nunez,P.L. and Silberstein,R.B. (2000). On the relationship of synaptic activity to macroscopic measurements: does co-registration of EEG with fMRI make sense? Brain Topogr. *13*, 79-96.

Ogawa,S., Lee,T.M., Nayak,A.S., and Glynn,P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. Magn Reson.Med. *14*, 68-78.

Ogawa,S., Tank,D.W., Menon,R., Ellerman,J.M., Kim,S.-G., Merkle,H., and Ugurbil,K. (1992). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc.Natl.Acad.Sci.U.S.A *89*, 5951-5955.

Olausson,H., Lamarre,Y., Backlund,H., Morin,C., Wallin,B.G., Starck,G., Ekholm,S., Strigo,I., Worsley,K., Vallbo,A.B., and Bushnell,M.C. (2002). Unmyelinated tactile afferents signal touch and project to insular cortex. Nat.Neurosci. *5*, 900-904.

Oostendorp,T.F. and van Oosterom,A. (1989). Source parameter estimation in inhomogenous volume conductors of arbitrary shape. IEEE Transactions on Biomedical Engineering *36*, 382-391.

Otten,L.J. and Rugg,M. (2004). Interpreting event-related brain potentials. In Event-Related Potentials: A Methods Handbook, T. C. Handy, ed. (Cambridge MA: MIT Press), pp. 3-16.

Patterson,M.L. and Werker,J.F. (1999). Matching phonetic information in lips and voice is robust in 4.5-month-old infants. Infant Behavior and Development *22*, 237-247.

Patterson,M.L. and Werker,J.F. (2002). Infants' ability to match dynamic phonetic and gender information in the face and voice. J.Exp.Child Psychol. *81*, 93-115.

Patterson,M.L. and Werker,J.F. (2003). Two-month-old infants match phonetic information in lips and voice. Developmental Science *6*, 191-196.

Pauling,L. and Coryell,C.D. (1936). The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. Proc.Natl.Acad.Sci.U.S.A *22*, 210-216.

Paus,T. (1996). Location and function of the human frontal eye-field: a selective review. Neuropsychologia *34*, 475-483.

Pekkola,J., Ojanen,V., Autti,T., Jaaskelainen,I.P., Mottonen,R., Tarkiainen,A., and Sams,M. (2005). Primary auditory cortex activation by visual speech: an fMRI study at 3 T. Neuroreport *16*, 125-128.

Pellerin,L. and Magistretti,P.J. (1997). Glutamate uptake stimulates Na+,K+-ATPase activity in astrocytes via activation of a distinct subunit highly sensitive to ouabain. J.Neurochem. *69*, 2132-2137.

Pelphrey,K.A., Morris,J.P., and McCarthy,G. (2004a). Grasping the intentions of others: the perceived intentionality of an action influences activity in the superior temporal sulcus during social perception. J.Cogn Neurosci. *16*, 1706-1716.

Pelphrey,K.A., Singerman,J.D., Allison,T., and McCarthy,G. (2003). Brain activation evoked by perception of gaze shifts: the influence of context. Neuropsychologia *41*, 156-170.

Pelphrey,K.A., Viola,R.J., and McCarthy,G. (2004b). When strangers pass: processing of mutual and averted social gaze in the superior temporal sulcus. Psychol.Sci. *15*, 598-603.

Perrett,D.I., Hietanen,J.K., Oram,M.W., and Benson,P.J. (1992). Organization and functions of cells responsive to faces in the temporal cortex. Philos.Trans.R.Soc.Lond B Biol.Sci. *335*, 23-30.

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

Picton,T.W., Lins,O.G., and Scherg,M. (1995). The recording and analysis of event-related potentials. In Handbook of Neuropsychology, F. Boller and J. Grafman, eds. (Amsterdam: Elsevier Science).

Pinard,E., Tremblay,E., Ben Ari,Y., and Seylaz,J. (1984). Blood flow compensates oxygen demand in the vulnerable CA3 region of the hippocampus during kainate-induced seizures. Neuroscience *13*, 1039-1049.

Portin,K., Salenius,S., Salmelin,R., and Hari,R. (1998). Activation of the human occipital and parietal cortex by pattern and luminance stimuli: neuromagnetic measurements. Cereb.Cortex *8*, 253-260.

Puce,A., Allison,T., Bentin,S., Gore,J.C., and McCarthy,G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. J.Neurosci. *18*, 2188-2199.

Rambold,H., Sprenger,A., and Helmchen,C. (2002). Effects of voluntary blinks on saccades, vergence eye movements, and saccade-vergence interactions in humans. J.Neurophysiol. *88*, 1220-1233.

Ramnani,N. and Miall,R.C. (2004). A system in the human brain for predicting the actions of others. Nat.Neurosci. *7*, 85-90.

Rees,G., Kreiman,G., and Koch,C. (2002). Neural correlates of consciousness in humans. Nat.Rev.Neurosci. *3*, 261-270.

Ridder,W.H. and Tomlinson,A. (1993). Suppression of contrast sensitivity during eyelid blinks. Vision Res. *33*, 1795-1802.

Ridder,W.H. and Tomlinson,A. (1995). Spectral characteristics of blink suppression in normal observers. Vision Res. *35*, 2569-2578.

Ridder,W.H. and Tomlinson,A. (1997). A comparison of saccadic and blink suppression in normal observers. Vision Res. *37*, 3171-3179.

Riggs,L.A., Kelly,J.P., Manning,K.A., and Moore,R.K. (1987). Blink-related eye movements. Invest Ophthalmol.Vis.Sci. *28*, 334-342.

Riggs,L.A., Volkmann,F.C., and Moore,R.K. (1981). Suppression of the blackout due to blinks. Vision Res. *21*, 1075-1079.

Riggs,L.A., Volkmann,F.C., Moore,R.K., and Ellicott,A.G. (1982). Perception of suprathreshold stimuli during saccadic eye movements. Vision Res. *22*, 423-428.

Rizzolatti,G. and Craighero,L. (2004). The mirror-neuron system. Annu.Rev.Neurosci. *27*, 169-192.

Rizzolatti,G., Fadiga,L., Gallese,V., and Fogassi,L. (1996a). Premotor cortex and the recognition of motor actions. Brain Res.Cogn Brain Res. *3*, 131-141.

Rizzolatti,G., Fadiga,L., Matelli,M., Bettinardi,V., Paulesu,E., Perani,D., and Fazio,F. (1996b). Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp.Brain Res. *111*, 246-252.

Rizzolatti,G., Fogassi,L., and Gallese,V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nat.Rev.Neurosci. *2*, 661-670.

Rochat,P. (1998). Self-perception and action in infancy. Exp.Brain Res. *123*, 102-109.

Rochat,P. and Hespos,S.J. (1997). Differential Rooting Response by Neonates: Evidence for an Early Sense of Self. Early Development and Parenting *6*, 105-112.

Rochat,P. and Morgan,R. (1995). Spatial Determinants in the Perception of Self-Produced Leg Movements by 3- to 5-Month-Old Infants. Develomental Psychology *31*, 626-636.

Rolls,E.T. (2004). The functions of the orbitofrontal cortex. Brain Cogn *55*, 11-29.

Rossi,S., Tecchio,F., Pasqualetti,P., Ulivelli,M., Pizzella,V., Romani,G.L., Passero,S., Battistini,N., and Rossini,P.M. (2002). Somatosensory processing during movement observation in humans. Clin.Neurophysiol. *113*, 16-24.

Rotman,G., Troje,N.F., Johansson,R.S., and Flanagan,J.R. (2006). Eye movements when observing predictable and unpredictable actions. J.Neurophysiol. *96*, 1358-1369.

Ruby,P. and Decety,J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nat.Neurosci. *4*, 546-550.

Saxe,R. (2006). Uniquely human social cognition. Curr.Opin.Neurobiol. *16*, 235-239.

Schafer,E.W., Amochaev,A., and Russell,M.J. (1981). Knowledge of stimulus timing attenuates human evoked cortical potentials. Electroencephalogr.Clin.Neurophysiol. *52*, 9-17.

Schafer,E.W.P. and Marcus,M. (1973). Self-Stimulation Alters Human Sensory Brain Responses. Science *181*, 175-177.

Schilbach,L., Wohlschlaeger,A.M., Kraemer,N.C., Newen,A., Shah,N.J., Fink,G.R., and Vogeley,K. (2005). Being with virtual others: Neural correlates of social interaction. Neuropsychologia.

Schmidt,K.E., Linden,D.E., Goebel,R., Zanella,F.E., Lanfermann,H., and Zubcov,A.A. (2003). Striatal activation during blepharospasm revealed by fMRI. Neurology *60*, 1738-1743.

Schmuckler,M.A. (1996). Visual-Proprioceptive intermodal perception in infancy. Infant Behavior and Development *19*, 221-232.

Schwartz,W.J., Smith,C.B., Davidsen,L., Savaki,H., Sokoloff,L., Mata,M., Fink,D.J., and Gainer,H. (1979). Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. Science *205*, 723-725.

Sereno,M.I., Dale,A.M., Reppas,J.B., Kwong,K.K., Belliveau,J.W., Brady,T.J., Rosen,B.R., and Tootell,R.B. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889-893.

Shergill,S.S., Bays,P.M., Frith,C.D., and Wolpert,D.M. (2003). Two eyes for an eye: the neuroscience of force escalation. Science *301*, 187.

Singer,T., Seymour,B., O'Doherty,J., Kaube,H., Dolan,R.J., and Frith,C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. Science *303*, 1157-1162.

Skipper,J.I., Nusbaum,H.C., and Small,S.L. (2005). Listening to talking faces: motor cortical activation during speech perception. Neuroimage. *25*, 76-89.

Smith,A., Taylor,E., Lidzba,K., and Rubia,K. (2003). A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds. Neuroimage. *20*, 344-350.

Smith,W.E., Dallas,W.J., Kullmann,W.H., and Schlitt,H.A. (1990). Linear estimation theory applied to the reconstruction of a 3-D vector current distribution. Applied Optics *29*, 658-667.

Sommer,M.A. and Wurtz,R.H. (2004a). What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. J.Neurophysiol. *91*, 1381-1402.

Sommer,M.A. and Wurtz,R.H. (2004b). What the brain stem tells the frontal cortex. II. Role of the SC-MD-FEF pathway in corollary discharge. J.Neurophysiol. *91*, 1403-1423.

Sperry,R.W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. J.Comp Physiol Psychol. *43*, 482-489.

Stiles,W.S. and Crawford,B.H. (1933). The luminous efficiency of rays entering the eye pupil at different points. Proc Roy Soc Lond B Biol Sci *112*, 428-450.

Sylvester,R., Haynes,J.D., and Rees,G. (2005). Saccades Differentially Modulate Human LGN and V1 Responses in the Presence and Absence of Visual Stimulation. Curr.Biol. *15*, 37-41.

Tai,Y.F., Scherfler,C., Brooks,D.J., Sawamoto,N., and Castiello,U. (2004). The human premotor cortex is 'mirror' only for biological actions. Curr.Biol. *14*, 117-120.

Teo,P.C., Sapiro,G., and Wandell,B.A. (1997). Creating connected representations of cortical gray matter for functional MRI visualization. IEEE Trans.Med.Imaging *16*, 852-863.

Todd,J.J. and Marois,R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. Nature *428*, 751-754.

Tregellas,J.R., Davalos,D.B., and Rojas,D.C. (2006). Effect of task difficulty on the functional anatomy of temporal processing. Neuroimage. *32*, 307-315.

Tsubota,K., Hata,S., Okusawa,Y., Egami,F., Ohtsuki,T., and Nakamori,K. (1996). Quantitative videographic analysis of blinking in normal subjects and patients with dry eye. Arch.Ophthalmol. *114*, 715-720.

Tsubota,K., Kwong,K.K., Lee,T.Y., Nakamura,J., and Cheng,H.M. (1999). Functional MRI of brain activation by eye blinking. Exp.Eye Res. *69*, 1-7.

Turner,R., Le Bihan,D., Moonen,C.T., Despres,D., and Frank,J. (1991). Echo-planar time course MRI of cat brain oxygenation changes. Magn Reson.Med. *22*, 159-166.

Ulanovsky,N., Las,L., and Nelken,I. (2003). Processing of low-probability sounds by cortical neurons. Nat.Neurosci. *6*, 391-398.

Umilta,M.A., Kohler,E., Gallese,V., Fogassi,L., Fadiga,L., Keysers,C., and Rizzolatti,G. (2001). I know what you are doing. a neurophysiological study. Neuron *31*, 155-165.

Ungerleider,L.G. and Desimone,R. (1986a). Cortical connections of visual area MT in the macaque. J.Comp Neurol. *248*, 190-222.

Ungerleider,L.G. and Desimone,R. (1986b). Projections to the superior temporal sulcus from the central and peripheral field representations of V1 and V2. J.Comp Neurol. *248*, 147-163.

van Schie,H.T., Mars,R.B., Coles,M.G., and Bekkering,H. (2004). Modulation of activity in medial frontal and motor cortices during error observation. Nat.Neurosci. *7*, 549-554.

VanderWerf,F., Brassinga,P., Reits,D., Aramideh,M., and Ongerboer,d., V (2003). Eyelid movements: behavioral studies of blinking in humans under different stimulus conditions. J.Neurophysiol. *89*, 2784-2796.

Vanzetta,I. and Grinvald,A. (1999). Increased cortical oxidative metabolism due to sensory stimulation: implications for functional brain imaging. Science *286*, 1555-1558.

Villringer,A. and Dirnagl,U. (1995). Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc.Brain Metab Rev. *7*, 240-276.

Vogel,E.K. and Machizawa,M.G. (2004). Neural activity predicts individual differences in visual working memory capacity. Nature *428*, 748-751.

Volkmann,F.C. (1986). Human visual suppression. Vision Res. *26*, 1401-1416.

Volkmann,F.C., Riggs,L.A., Ellicott,A.G., and Moore,R.K. (1982). Measurements of visual suppression during opening, closing and blinking of the eyes. Vision Res. *22*, 991-996.

Volkmann,F.C., Riggs,L.A., and Moore,R.K. (1980). Eyeblinks and visual suppression. Science *207*, 900-902.

Volkmann,F.C., Riggs,L.A., White,K.D., and Moore,R.K. (1978). Contrast sensitivity during saccadic eye movements. Vision Res. *18*, 1193-1199.

Von Grunau,M. and Anston,C. (1995). The detection of gaze direction: a stare-in-the-crowd effect. Perception *24*, 1297-1313.

von Holst,E. (1954). Relations between the central nervous system and the peripheral organs. British Journal of AnimalBehaviour *2*, 89-94.

Voss,M., Ingram,J.N., Haggard,P., and Wolpert,D.M. (2006). Sensorimotor attenuation by central motor command signals in the absence of movement. Nat.Neurosci. *9*, 26-27.

Walker-Andrews,A.S., Bahrick,L.E., Ragliono,S.S., and Diaz,I. (1991). Infants' bimodal perception of gender. Ecological Psychology *3*, 55-75.

Walton,G.E. and Bower,T.G.R. (1993). Amodal representation of speech in infants. Infant Behavior and Development *16*, 233-243.

Wandell,B.A., Chial,S., and Backus,B.T. (2000). Visualization and measurement of the cortical surface. J.Cogn Neurosci. *12*, 739-752.

Watkins,K.E., Strafella,A.P., and Paus,T. (2003). Seeing and hearing speech excites the motor system involved in speech production. Neuropsychologia *41*, 989-994.

Watson,J.D., Myers,R., Frackowiak,R.S., Hajnal,J.V., Woods,R.P., Mazziotta,J.C., Shipp,S., and Zeki,S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cereb.Cortex *3*, 79-94.

Weiskrantz,L., Elliot,J., and Darlington,C. (1971). Preliminary observations of tickling oneself. Nature *230*, 598-599.

Westling,G. and Johansson,R.S. (1984). Factors influencing the force control during precision grip. Exp.Brain Res. *53*, 277-284.

Wicker,B., Keysers,C., Plailly,J., Royet,J.P., Gallese,V., and Rizzolatti,G. (2003). Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron *40*, 655-664.

Wicker,B., Michel,F., Henaff,M.A., and Decety,J. (1998). Brain regions involved in the perception of gaze: a PET study. Neuroimage. *8*, 221-227.

Williams,J.H., Waiter,G.D., Perra,O., Perrett,D.I., and Whiten,A. (2005). An fMRI study of joint attention experience. Neuroimage. *25*, 133-140.

Wilson,S.M., Saygin,A.P., Sereno,M.I., and Iacoboni,M. (2004). Listening to speech activates motor areas involved in speech production. Nat.Neurosci. *7*, 701-702.

Wolpert,D.M., Ghahramani,Z., and Jordan,M.I. (1995). An internal model for sensorimotor integration. Science *269*, 1880-1882.

Wolpert,D.M. and Miall,R.C. (1996). Forward Models for Physiological Motor Control. Neural Netw. *9*, 1265-1279.

Wood,C.C. (1987). Generators of event-related potentials. In A textbook of clinical neurophysiology, A. M. Halliday, S. R. Butler, and R. Paul, eds. (New York: Wiley), pp. 535-567.

Woods,D.L. and Elmasian,R. (1986). The habituation of event-related potentials to speech sounds and tones. Electroencephalogr.Clin.Neurophysiol. *65*, 447-459.

Worsley,K.J., Evans,A., Marrett,S., and Neelin,P. (1992). A three-dimensional statistical analysis for rCBF activation studies in human brain. J.Cereb.Blood Flow Metab *12*, 900-918.

Worsley,K.J., Marrett,S., Neelin,P., Vandal,A.C., Friston,K.J., and Evans,A. (1996). A unified statistical approach or determining significance signals in images of cerebral activation. Hum.Brain Mapp. *4*, 58-73.

Wree,A. and Schleicher,A. (1988). The determination of the local cerebral glucose utilization with the 2-deoxyglucose method. Histochemistry *90*, 109-121.

Wurtz,R.H. and Sommer,M.A. (2004). Identifying corollary discharges for movement in the primate brain. Prog.Brain Res. *144*, 47-60.

Zeki,S., Watson,J.D., Lueck,C.J., Friston,K.J., Kennard,C., and Frackowiak,R.S. (1991). A direct demonstration of functional specialization in human visual cortex. J.Neurosci. *11*, 641-649.