RECOGNISING THE SENSORY CONSEQUENCES OF ONE'S OWN ACTIONS

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ABSTRACT

This thesis presents a series of studies that investigate how we recognise the sensory consequences of our own actions. The studies are based on an established 'forward model' of normal motor control. It is proposed that this type of internal model makes a prediction of the sensory consequences of self-generated movements, and this prediction is then compared with the actual sensory feedback from the movement. Self-produced sensations can be correctly predicted on the basis of motor commands, and there will therefore be little or no sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback. In contrast, externally generated sensations are not associated with any motor command and therefore cannot be predicted by the model and will produce a higher level of sensory discrepancy. Impairment of a component of the forward model might result in certain schizophrenic symptoms. It has been proposed that in people with schizophrenia self-produced sensations are interpreted as being generated by an external source, for example thoughts are interpreted as external voices (auditory hallucinations) and self-produced movements are interpreted as externally controlled (delusions of control or passivity phenomena) (Frith, 1992; Frith *et al.*, 1999).

Psychophysical and functional neuroimaging experiments that investigate the behavioural and physiological basis of forward models are described in this thesis. These studies support the notion that the forward model cancels the sensory consequences of self-produced actions in order to discriminate self-produced events from externally produced events and suggest that the cerebellum is involved in the predicting the sensory consequences of actions. Results of a psychophysical study involving psychotic patients with auditory hallucinations and passivity phenomena support the proposal that these symptoms are associated with an inability to distinguish self- and externally produced events. These symptoms are discussed in the context of an impairment of a component of the forward model.

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1 CHAPTER 1: INTRODUCTION

1.1 Detecting the consequences of our own actions

Our sensory systems are constantly bombarded with an enormous amount of sensory stimulation. It is crucial to be able to extract the few stimuli that correspond to important changes within the environment, which are in most circumstances of greater potential biological importance than sensory stimulation that arises as a necessary consequence of our own motor actions. Humans can readily detect whether sensory signals are the result of self-generated actions or other environmental events. We are able to distinguish self-generated (willed) movements from passive movements (those caused an external source), and we perceive the former, but not the latter, to be generated by our intentions to move. Similarly we are able to distinguish tactile stimulation caused by our own touch from that caused by an external source. In addition to actions and sensations, we are also able to recognise our own speech, thoughts and internal (sub-vocal) speech as our own, and distinguish it from someone else's voice. The mechanisms underlying the ability to distinguish the source of sensory signals are likely to have adaptive value because this ability permits the monitoring of ongoing actions and provides information about new environmental events.

It has been proposed that knowledge of our intentions is used to distinguish the sensory consequences of our own actions from externally produced sensory stimuli (Jeannerod, 1988; Frith, 1992; Wolpert *et al.*, 1995; Decety, 1996; Jeannerod, 1997; Wolpert, 1997). In order to achieve this, some kind of central monitor (Frith, 1992) or internal 'forward model' (Ito, 1970; Wolpert *et al.*, 1995) has been postulated. Forward models capture the forward or causal relationship between actions and their sensory outcome. It is proposed that efference copy signals are used to make a prediction of the sensory consequences of the motor act, and this prediction is then compared with the actual consequences of such an act. These mechanisms have been the subject of scientific investigation for over a century, mainly in the oculomotor domain.

In the mid-nineteenth century, Helmholtz (1867) noted that when making eye movements, the percept of the world remains stable, despite the movement of the retinal image. He suggested that the *effort of will* involved in making eye movements contains information about the sensory consequences of the eye movement, which is used by the visual areas in order for perceptual compensation to occur. Almost a century later, Von Holst & Mittelstaedt (1950; Von Holst, 1954) suggested that when sending motor commands to move the eyes the motor areas of the brain send a parallel *efference copy* to the visual areas. Based on this information a prediction of the sensory consequences (*corollary discharge*) of the movement is made. It was proposed that the visual system uses the corollary discharge to compensate for the retinal displacement caused by the eye movement, so that the percept of the world remains stable during eye movements (Sperry, 1950).

Evidence for this theory comes from two sources. Firstly, it was observed that when eye movement is caused indirectly, by pushing gently on the eye-lid with the finger, the percept of the world moves in the opposite direction of the movement of the eye. This was taken to show that perceptual compensation for retinal displacement does not occur unless the eye movement is caused by a direct intention to move the eyes generated by the eye movement centres (Von Holst & Mittelstaedt, 1950). Secondly, if the eye muscles are paralysed, and the subject attempts to move their eyes, the world appears to move in the direction of the attempted (intended) eye movement, despite there being no actual movement of the eyes. In this case, it was suggested, an efference copy of the intended eye movement would still be generated and used by the visual areas of the brain to compensate for the intended (but never accomplished) eye movement by shifting the percept of the world in the direction of the eye movement (Kornmuller, 1932; Von Holst & Mittelstaedt, 1950).

Although these mechanisms have mainly been studied with reference to eye movements, it appears that sensory predictions produced in conjunction with motor commands are not restricted to this one modality, but also provide perceptual stability in the context of all self-produced actions. Our ability to monitor, and recognise as our own, self-generated limb movements, touch, speech and thoughts suggests the existence of a more general mechanism (Frith, 1992). Hughlings Jackson suggested that thinking may be considered the highest and most complex form of motor activity (Hughlings Jackson, 1932). Feinberg later proposed that the corollary discharge mechanisms of control and integration of movements is also present in thinking (Feinberg, 1978). However, whether a single mechanism underlies our ability to recognise as our own all self-generated events including our own thoughts is the subject of philosophical debate (e.g. Gallagher, 1999; Zahavi, 1999). Frith's model assumes that thoughts, insofar as they are intended and self-generated, are kinds of actions and have to match the subject's intention to feel self-generated, as in the case of a motor action. It has been argued that the assumption that thoughts are comparable to motor action may not be not valid (see Zahavi, 1999). There is no direct evidence that thoughts are monitored by the same process as limb movements. However, there would be an evolutionary advantage of a single mechanism controlling all events in which a distinction between self- and externally is useful or necessary.

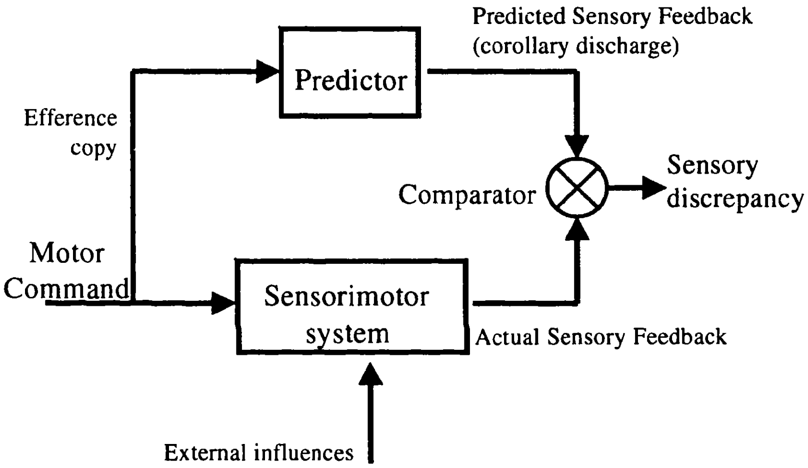
1.2 Internal representations of the motor system

It has recently been suggested that the self-monitoring mechanism involves an internal representation of the motor system (Frith *et al*, 1999; Frith *et al*, 2000). It is proposed that the central nervous system contains models or transformations that mimic aspects of one's own body and the external world. Such internal representations are known as *internal models* because they 'model' (or mirror) the motor system and the external world (Ito, 1970; Wolpert *et al*., 1995). There are two types of internal model, forward and inverse models. Whenever a movement is made, a motor command is generated by the CNS and a forward model (or predictor) estimates the sensory consequences of the motor command. An inverse model (or controller), on the other hand, captures the relationship between the desired state and the motor command required to achieve it. Such representations do not need to be detailed or accurate models of the external world. Often an internal model need only provide a rough approximation of some external transformation in order to play a useful role. This thesis is concerned with forward models.

1.2.1 Forward Models (predictors)

Forward models represent aspects of the external world and the motor system in order to capture the causal relationship between actions and their outcomes (Ito, 1970; Jordan, 1996; Wolpert *et al.*, 1995). An example of a simple forward model is shown in **Figure 1-1**. Every time a motor command is issued to make a movement, an efference copy of the motor command is produced in parallel with the motor command. Based on the efference copy, the forward model predicts the sensory consequences of the ensuing movement and this prediction can be used in several ways (Miall & Wolpert, 1996; Wolpert, 1997).

Figure 1-1



A model for determining the sensory consequences of a movement. An internal forward model makes predictions of the sensory feedback of movement based on the motor command. These predictions are then compared to the actual sensory feedback to produce the sensory discrepancy errors. The level of sensory discrepancy can be used to determine the course of the sensory signals: self-produced sensations can be correctly predicted on the basis of motor commands. This accurate prediction can be used to cancel, or attenuate, the ensuing sensation. In contrast, externally generated sensations are not associated with any efference copy and therefore cannot be predicted and will produce a higher level of sensory discrepancy.

There is a substantial body of evidence that the central nervous system makes use of such prediction:

1. A forward model is a key part of the system that uses an efference copy of the motor command to anticipate and cancel the sensory effects of movement (re-afference), as is the case during eye-movements (Helmholtz, 1867; Sperry, 1950; Von Holst, 1954). In order to determine the location of an object relative to the head, its retinal location and the gaze direction must be known. Helmholtz proposed that the gaze direction is determined by predicting the eye

location based on the efference copy of the motor command going to the eye muscles. Using this estimate of eye position together with the object's retinal location, its true position in space can be determined. When the eye is moved without using the eye muscles, the retinal location of objects changes, but the predicted eye position is not updated leading to the percept that the world is moving.

2. Prediction can be used to filter sensory information, attenuating the component that is due to self-movement (re-afference) from that due to changes in the outside world. When a sensation occurs its source can be determined by comparing the predicted sensory feedback with the actual sensory stimulation. Self-produced sensations can be correctly predicted on the basis of motor commands. As a result there will be little or no sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback. This accurate prediction can be used to cancel, or attenuate, the ensuing sensation. In contrast, externally generated sensations are not associated with any efference copy and therefore cannot be predicted and will produce a higher level of sensory discrepancy. As the discrepancy from the comparison increases so does the likelihood that the sensation is externally produced. By using such a system it is possible to cancel out or attenuate sensations induced by self-generated movement and thereby distinguish sensory events due to self-produced motion from sensory feedback caused by the environment, such as contact with objects. It is this system, which distinguishes between self- and externally produced events, that will be the focus of this thesis.
3. Forward models can also be used to maintain accurate performance in the presence of feedback delays. In most sensorimotor loops the feedback delays between the issuing of a motor command and the perception of its sensory consequences are large. This is due to both neural transduction and processing delays, which can be as large as 250 ms. These delays can result in inaccuracy if the motor system compares the desired outcome to the perceived outcome to determine the performance error. As the perceived outcome is delayed relative to the actual outcome the motor system will respond to a perceived error which may no longer exist, thereby generating a potentially inappropriate response. To avoid this, a forward model can be used to estimate the actual

outcome of the motor command without delay and compare this to the desired outcome. Such internal feedback of the estimated outcome of an action is available before the true sensory feedback and therefore changes to movements can be made without waiting for sensory feedback from the movement (Miall *et al.*, 1993).

4. A forward model plays a critical role in a system that integrates sensory and motor information in order to estimate the current state of the system. The state of the motor system is not directly observable by the CNS, which has access only to the outgoing motor commands and the subsequent sensory feedback. Instead, the state has to be estimated by observing these signals. To produce optimal estimates, two processes can be used. The first uses a forward model to estimate the next state of the system. The second process uses sensory feedback to modify this estimate (Wolpert *et al.*, 1995; Wolpert, 1997). By using both sources of information the uncertainty of the state estimate can be reduced.
5. Multiple forward models can be used to identify the context of a movement (Wolpert & Kawato, 1998). One problem the CNS must face is identifying the context in which a movement is occurring. For example, we need to know whether the object we are lifting is heavy or light when no clue is available from its visual appearance. Multiple forward models can be used to solve this problem. Each forward model learns to capture the relationship between motor commands and the sensory consequences of different sensori-motor contexts. At any instant each forward model generates a prediction based on the motor command and the sensorimotor context used by that model. The model that makes the best prediction is using the most likely sensorimotor context.

1.2.2 Inverse models (controllers)

Inverse models, or controllers, provide the motor commands that will achieve some desired outcome. Inverse models presuppose that the trajectory planning system is able to provide a desired outcome signal. For a simple reaching and grasping movement, the first step would be to plan the trajectory to be followed by the arm in order to reach the desired final position. The trajectory represents the desired configuration of the body at each point in time. The muscle activations necessary to achieve this trajectory depend on the dynamic parameters of the body such as the inertia and link lengths of the body segments. The inverse models must learn to generate the appropriate motor commands such that the muscle activations achieve the desired trajectory. The inverse models, therefore, receive a desired configuration of the body and produce motor commands, which should achieve this configuration.

In terms of internal models the performance of a simple action involves the following stages. Current wishes and plans are used to formulate the desired state (instantaneous goal) of the system. The inverse models generate appropriate motor commands on the basis of the difference between the actual state and the desired state. Computation by the inverse models is 'fine tuned' by the context in which the action is occurring. For example, if the action requires the grasping of an object, knowledge of the shape and position of the object provide 'affordances' which allow a more accurate computation of the appropriate motor commands (Greeno, 1994). Once the motor commands have been computed the forward models calculate the expected state of the system. Subsequently, or in parallel with this process, the action is performed. Once the movement has been made the new state of the system can be estimated on the basis of sensory feedback and knowledge of the motor commands that have been executed. If there are discrepancies between the new state and the desired and predicted states then modifications can be made to the forward models and inverse models and further actions can be performed to correct the situation.

1.3 Awareness of motor representations

The extent to which we are aware of the functioning of our motor control system is a major consideration and the subject of much research (Jeanerrod, 1994). This section briefly reviews evidence that certain components of the motor control system are available to consciousness while other components are not. The neural correlates of the components of internal models are also summarised in this section.

1.3.1 Motor imagery and motor preparation

Imagining making movements in the absence of any overt behaviour is possible and this mental activity can have detectable consequences. First, mental practice of various motor tasks can lead to a significant improvement in subsequent performance (see Feltz and Landers, 1983 for review). Mental training affects various outcomes of motor performance such as muscular strength (Yue and Cole, 1992), movement speed (Pascual-Leone *et al*, 1995) and temporal consistency (Vogt, 1995). Second, prolonged performance of tasks in the imagination can lead to significant physiological changes. Subjects who performed or mentally simulated leg exercise had increased heart rates and respiration rates in both conditions (Decety *et al*, 1991). Third, changes in brain activity associated with movements made in the imagination can readily be detected using brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Decety *et al.* (1994) asked subjects to imagine grasping 3D objects presented to them. Stephan *et al.* (1995) compared execution of a sequence of joystick movements with imagining making such a sequence. These studies showed that the brain regions activated during motor imagery are a subset of those activated during motor execution.

Jeannerod (1994) has argued that motor imagery is closely related to motor preparation. Preparing to make a movement and holding it in readiness while waiting for a signal to release the movement engages the same processes as those involved in imagining making that movement. Functional neuroimaging studies of motor preparation and motor imagery highlight activity in anterior cingulate cortex (ACC), anterior supplementary motor cortex (SMA), inferior lateral premotor cortex and inferior parietal lobe (Decety *et al.*, 1994; Stephan *et al.*, 1995; Krams *et al.*, 1998). Since these areas are engaged by motor preparation and motor imagery, it is proposed that they are involved with representations of intended and predicted movements.

1.3.2 Awareness of motor commands

There are a number of other observations that demonstrate that the motor control system can also function in the absence of awareness. Goodale *et al.* (1986; see also Bridgeman *et al.*, 1981) report a pointing experiment in which the target occasionally jumped several degrees while subjects made saccades – the target movement was thus unnoticed by the subjects. Nevertheless the subjects were able to adjust the trajectory of their moving hand to the target position. In this case the subjects were aware neither of the sensory information that elicited the movement correction nor of the change in the motor programme that was elicited. In another experiment involving reaching and grasping, Castiello *et al.* (1991) found that awareness (indicated verbally) of an unexpected target jump occurred more that 200 msec after the motor system had initiated an appropriate movement correction.

Furthermore, appropriate grasping movements can be made even when conscious perception of the object to be grasped is incorrect. In the Ebbinghaus (Tichener) Circles Illusion two identical circles appear to be of different sizes because of the context in which they occur: one circle is surrounded by a large number of small circles, while the other is surrounded by a small number of large circles. The strength of this illusion can be measured by asking subjects to adjust the size of the circles until they appear to be identical. However, the size of this illusion is greatly reduced if it is measured in terms of the distance between the finger and thumb when grasping the central circles (Aglioti *et al.*, 1995). The result from studies of this illusion and others (e.g. Gentilucci *et al.*, 1996) suggests that there is a dissociation between the perception of objects and the information that the sight of objects provides to fine tune our reaching and grasping movements. An extreme example of this lack of awareness is provided by the case of DF described by Milner & Goodale (1995). DF is unaware of the shapes of objects and is unable to describe them or to discriminate between them, but she can nevertheless produce appropriate grasping actions based on the shapes of which she is unaware. A similar pattern of behaviour has been observed in another patient by Perenin & Rossetti (1996).

These results suggest that we are not aware of the precise details of the motor commands that generate our actions, nor of the way in which immediate sensory information is used to fine tune these commands. Thus, it would appear that our awareness of our actions and of the sensory information on which these actions are based is derived from other sources.

The changes in representation that result from our own movements are entirely predictable on the basis of those movements and therefore do not require our attention. It seems plausible that, to be aware of representations that changed every time we moved our bodies, or even our eyes, would be a positive disadvantage. Indeed, the mechanisms that underlie our conscious perception seem designed to maintain stability and to emphasise the unexpected.

1.3.3 Awareness of the actual state of the motor system

In the outline of the motor control system presented above a major role is played by representations of the predicted state of the system that will result from intended acts. In most situations, especially those that are routine, the actual state of the motor system will correspond closely to the state predicted before the action was performed. If awareness puts an emphasis on the unexpected, then it would be predicted that there would be only limited awareness of the actual state of the motor system whenever this has been successfully predicted in advance. We may only be aware of the actual sensory consequences of our movements when they deviate from what we expect.

An extreme example of a lack of awareness of action resulting from predictability comes from over-learned tasks. With sufficient practice many tasks can become 'automatic' and can be performed without any need to think about the actions required to perform the task – they can be carried out at the same time as a second, attention demanding task without impairing performance (e.g. Passingham, 1996). While performing such tasks we are not aware of the actual state of our motor system, intended actions or their predicted consequences.

We can be unaware of even quite large deviations of actual movements from those expected as long as the desired state is successfully achieved. For example, Fourneret & Jeannerod (1998) gave false feedback about the trajectory of an arm movement so that subjects, who could not see their arm or hand, had to make considerable deviations from a straight movement in order to generate a straight line on a computer screen. The subjects could achieve the desired result of drawing a straight line by making deviant movements. However, verbal reports indicated that they were unaware that they were making deviant movements. It seems then that we are largely unaware of sensory feedback about the actual state of our motor system as long as our intentions have been achieved. In most cases successful achievement implies that sensory feedback has been correctly predicted, but in some circumstances we remain unaware even of unexpected sensory feedback.

1.3.4 The timing of awareness

In addition to examining which aspects of the motor control system are accessible to awareness, attempts have also been made to investigate the time at which awareness emerges during the generation of an action. Libet *et al.* (1983) and McCloskey *et al.* (1983) asked normal volunteers to estimate the time at which they initiated a finger movement. This reported time of awareness consistently anticipated the actual starting time of the movement by 50-80 ms. If transcranial magnetic stimulation (TMS) is applied to the motor cortex then there is a substantial delay in the initiation of a movement, but there is a much smaller delay in the perceived time of initiating the movement (Haggard & Magno, 1999). These observations imply that our awareness of initiating a movement is not derived from information from sensory signals arising in the moving limb, which is not available until after the limb has started moving. The most likely representation relating to awareness of movement initiation is the predicted state of the system. This information is available as soon as the forward models have estimated the expected sensory consequences of the intended movement.

Volunteers were also asked to indicate the time at which they aware of having the 'urge' to make a movement in the study by Libet (Libet *et al.*, 1983). It was found that this can precede the production of the movement by ~300 msec and might correspond to the formation of the representation of the intended position of the limb that precedes motor preparation. Haggard & Eimer (1999) asked subjects to indicate the time at which 'they first began to prepare the movement' and related this to various components of the motor readiness potential. In this study subjects moved either their left or their right index finger. Haggard & Eimer (1999) found that the onset of the lateralised readiness potential, rather than earlier components of the readiness potential, covaried with the perceived time at which preparation of the movement began. This observation suggests that the awareness of preparing to move is associated with the exact specification of the movement (i.e. which finger will be moved) rather than some more abstract representation of action. In terms of the framework of the motor system presented above, specification of the goal of the movement seems not to be sufficient for awareness of preparing to move. Awareness of preparing to move requires that the inverse models have completed the specification of the sequence of motor commands needed to make the movement. Awareness of initiating the movement has to wait for the forward models to predict the sensory consequences of the movement. It is these predicted consequences that form our awareness of initiating the movement.

1.4 Experimental evaluation of forward models used in this thesis

The experiments in this thesis were designed to specify further the behavioural and neural characteristics of forward models. There are numerous ways in which the components of internal models of the sensorimotor system can be empirically investigated. Components of internal models can be measured psychophysically. Two such psychophysical methods employed in the experiments in this thesis, are grip force modulation and sensory perception judgement. In addition, the neural correlates of internal models can be investigated. Studies in this thesis employed functional neuroimaging techniques - specifically PET and fMRI – to evaluate the neural correlates of forward models.

1.4.1 Psychophysical studies of forward models

1.4.1.1 Grip force modulation

Forward models are proposed to play a fundamental role in coordinative behaviour such as that used when manipulating objects. When subjects pick up an object using a precision grip, they exert sufficient grip force (normal to the surface of the object) to counteract the load force (tangential to the surface) exerted by the object to prevent the object from slipping, while avoiding excessive grip forces that may result in breakage of the object or fatigue (Johansson & Cole 1992; Johansson & Cole, 1994; Johansson *et al.* 1992; Johansson & Westling 1984). When the object is held at rest, the grip force depends both on the weight of the object, that is its load force, and the coefficient of friction of its surfaces. Grip force levels can be set without somatosensory feedback, anticipating the physical properties of the object, which include the object's weight, shape, and friction at its surface (Jenmalm and Johansson 1997; Johansson & Cole 1994; Johansson & Westling, 1984; Johansson & Westling, 1988a). Such object properties are learned through development, as indicated by children's increasing ability to adjust their grip force appropriately for the object being held (Eliasson *et al.* 1995; Forssberg *et al.* 1991, Forssberg *et al.*, 1992; Forssberg *et al.*, 1995; Serrien *et al*, 1999).

When an object is moved, the load force on the fingers changes because of the acceleration of the gripped object. Without a corresponding change in grip force, the object would slip. Despite sensory feedback delays associated with the detection of load force by the fingertips when movement of an object is self-generated grip force is modulated in parallel with load force (Johansson & Westling, 1984; Flanagan & Wing, 1993; Flanagan & Wing, 1995; Johansson *et al*, 1992). Zero lag between load and grip force suggest that an internal model of the object and the arm is able to anticipate the load force accurately (Flanagan & Wing, 1997). Conversely, when the motion of a gripped object is externally generated, grip force lags 60-100 ms behind load force and subjects make intermittent catch up responses in their levels of grip force (Johansson *et al*, 1992). This suggests a reactive response to the perturbation of the object, which cannot be predicted (Cole & Abbs, 1988).

So, the timing of grip force modulation can be used to quantify the accuracy of an internal model. Lags between grip and load suggest a reactive process in which the CNS is unable to predict the load force, whereas no lag indicates an internal model that accurately predicts the sensory (load force) consequences of movements. Experiments that measure grip force modulation can be employed to evaluate characteristics of the forward model. In chapter 4, the factors necessary for predictive grip force modulation are evaluated by employing a grip force modulation paradigm while manipulating aspects of the object's movement and the hand's motion.

1.4.1.2 Perception of self-produced actions

Evidence suggests that the sensory consequences of some self-generated movements are perceived differently from identical sensory input when it is externally generated. The attenuation of sensory feedback during movement is well documented in humans (Angel & Malenka, 1982; Chapman *et al.*, 1987; Milne *et al.*, 1988; Post *et al*, 1994; Collins *et al.*, 1998). For example, Chapman *et al.* (1987) demonstrated that the threshold for detecting tactile stimulation is increased during movement of the stimulated arm. Both active and passive movement of the stimulated limb increased detection thresholds, with active movement having a slightly greater and more consistent effect than passive movement. The authors therefore argued that both central and peripheral feedback factors appear to play a role in diminishing the ability to detect stimulation during movement. Findings such as these demonstrate that the perception of a sensory stimulus is attenuated if movement occurs simultaneously with the stimulus.

Another example of the perceptual attenuation during movement is the phenomenon that people cannot tickle themselves (e.g. Weiskrantz *et al.*, 1971; Claxton, 1975). It has been argued that efference copy produced in parallel with the motor command underlies this phenomenon. In Weiskrantz *et al.*'s (1971) psychophysical study, a tactile stimulus that transversed the sole of the subject's foot was administered by the experimenter, the subject or both. Subjects rated the self-administered tactile stimulus as less 'tickly' than the externally administered tactile stimulus. When the stimulation was caused by passive arm movements, the tickliness of the stimulus was reduced, but not to the level of the self-administered tactile stimulus. As the stimulus was highly similar in terms of force, amplitude and frequency in all conditions, the authors attributed the differences in response to the mode of delivery. Self-administered tactile stimulation produces both an efference copy of the motor command and re-afference produced by the arm movement; passive arm movement produces only re-afference and externally administered tactile stimulation produces neither efference copy nor re-afference. The authors therefore concluded that although re-afference plays a role, the attenuation signal is based mainly on the efference copy signal produced in concordance with a self-generated movement.

One explanation of these results is that there is a general 'gating' of all incoming sensory stimulation during self-generated movement. This explanation fits with the aforementioned studied demonstrating sensory gating during movement (Angel & Malenka, 1982; Chapman *et al.*, 1987; Milne *et al.*, 1988; Collins *et al.*, 1998). Such findings suggest that the perception of sensory stimulation might be attenuated simply if self-generated movement occurs simultaneously with the stimulus – the movement might not necessarily have to produce the sensory stimulus in order for it to be attenuated. This, however, is inconsistent with the theoretical approach of forward models outlined above, which posits that in order for sensory attenuation to occur, the specific sensory consequences of the movement must be accurately predicted. According to the above hypothesis, the sensory stimulation would have to correspond to the movement producing it in order for perceptual attenuation to occur. If this hypothesis is true, there are two further possibilities. Firstly the sensory stimulation might have to correspond *exactly* to the movement producing it for *any* perceptual attenuation to occur. Alternatively, the amount of perceptual attenuation might be proportional to the accuracy of the sensory prediction. Experiments that sought to investigate these possibilities will be described in chapter 5 of this thesis.

1.4.2 Neural correlates of forward models

There is considerable evidence that sensory stimuli are processed differently in the brain depending on whether they are self- or externally generated in several different modalities.

1.4.2.1 Vision and eye movements

The superior colliculus has been associated with generating a corollary discharge signal in several species of animal (Strasschill & Hoffman, 1974; Roucoux & Crommelinck, 1976; Richmond & Wurtz, 1980; Guthrie *et al.*, 1983; Peck, 1984; Bell & Grant, 1989). For example, neurons in the superior colliculus of the cat discharge with and during saccades, and it has been proposed by many researchers that they may be conveying a corollary discharge signal that allows visual neurons to distinguish real movement from self-induced movement (Peck, 1984).

The cerebellum has been associated with the control and timing of eye movements (Pastor *et al*, 1997; Quaia *et al*, 1999; Thier *et al*, 2000; O'Driscoll *et al*, 2000). Neurophysiological data suggesting that the cerebellar cortex is a storage site for internal models have been obtained for eye movements. Kawano and colleagues studied neural circuits involved in controlling ocular following responses (OFRs), which are reflex eye movements with a short latency. These circuits stabilise retinal images, and are driven by large visual field movements. They proposed that the error signals carried by the climbing fibre inputs to Purkinje cells during OFRs could be used by the cerebellum to stabilise the retinal image during eye movements (Kawano *et al*, 1996).

Perret and colleagues (1990) found that superior temporal sulcus (STS) neurons are not activated by the sight of the monkey's own hand movements. A proportion of STS cells that did not respond to the sight of the monkey's own limbs moving responded to the sight of other stimuli, for example the experimenter's hand, moving in the same trajectory. Perret argued that disregarding sensory events that arise from the animal's own actions enables the animal to be attuned to environmental sensory events such as those caused by the actions of other animals. He proposed that the STS is suited to defining sensory stimuli that have biological significance, such as those involved in social or predator/prey interactions. Hietanen and Perret (1993) also found that STS neurons that are inhibited to the movement of the monkey's own hand in view are activated by the sight of a novel object in the monkey's own moving hand. This suggests that external, unpredictable stimulation can be selectively detected by STS neurons, which effectively ignore predictable re-afferent visual stimulation, such as self-produced limb movements.

1.4.2.2 Audition

In the auditory domain, Muller-Preuss (1978) found cells in the superior temporal cortex of squirrel monkeys that respond to the vocalisations of other monkeys, but do not respond when the monkey itself vocalises. This lack of response to self-generated vocalisations could result from inhibitory signals arising from components of the volitional vocalisation system. Evidence in human subjects suggests that auditory stimuli are also processed differently depending on whether they are a consequence of self-generated actions (Shafer & Marcus, 1973). However in a subsequent paper Shafer and colleagues suggested that the attenuation of event-related potential (ERP) amplitude may be due to foreknowledge of stimulus timing in the self-stimulation case, rather than being a direct consequence of the willed actions. (Shafer *et al*, 1981). They argued that the difference between self-produced and externally produced tones was primarily a function of stimulus predictability. This is inconsistent with the theoretical approach to forward models outlined, which posits that self-generation of tones as well as their predictability should affect their processing. How the brain processes self-generated, as opposed to merely predictable, auditory stimulation in humans is investigated in chapter 3.

1.4.2.3 Somatosensory

Neurophysiological data demonstrate that neuronal responses in somatosensory cortex are attenuated by self-generated movement. Active touch is 'gated' in primary somatosensory cortex of rats (Chapin & Woodward, 1982) and monkeys (Chapman *et al.* 1988; Jiang *et al.*, 1991; Chapman & Ageranioti-Belanger, 1991; Chapman, 1994) compared to passive and external touch of an identical tactile stimulus. For example, neuronal activity in somatosensory areas 3b, 1 and 2 in monkeys was attenuated when monkeys moved their hand over a surface texture compared to when their hand was passively moved over the same surface, or when the surface moved underneath their hand (Chapman, 1994). Moreover, they found neurons that signalled changes in texture only during active tactile discrimination. This texture-related discharge disappeared when the cell was tested with passive movements. The authors argued that these neurons signal the behavioural significance of a stimulus: when an animal is actively exploring a tactile surface, changes in texture are likely to be behaviourally relevant. Several other researchers have found that somatosensory evoked cortical responses are attenuated during self-generated movement (e.g. Rossini *et al*, 1999; Brooke *et al*, 2000).

It is possible that such somatosensory 'gating' is responsible for the differential perception of self- and externally produced tactile stimuli in humans. The neural processes underlying movement-related somatosensory gating are undetermined. In order for somatosensory cortex activity to be attenuated, movements and their sensory consequences need to be predicted and this prediction used to cause the somatosensory gating in advance of the movement. Neural responses to self- and externally produced tactile stimulation issues are evaluated using fMRI in chapter 6 of this thesis.

1.4.2.4 The cerebellum and prediction

It has been argued that the cerebellum is a component of a forward model system that provides precise predictions of the sensory consequences of motor actions, which can be compared with the actual sensory consequences (Ito, 1970; Paulin, 1989; Miall, *et al.*, 1993; Wolpert *et al.*, 1998). Empirical research supports this account. The main input to the cerebellum, the climbing fibres from the inferior olive, has been proposed to act as a comparator between expected and achieved movement, signalling errors in motor performance (Oscarsson, 1980). Evidence for this comes from electrophysiological studies demonstrating that neurons in the inferior olive of cats respond to passively applied cutaneous stimuli but not to similar stimuli produced by a voluntary movement of the cat (except when stimuli were unexpectedly encountered during movement; Gellman *et al.*, 1985). Similarly, Andersson & Armstrong (1985; 1987) found that inferior olive neurons fire when a cat walking on a horizontal ladder encounters a rung that unexpectedly gives way. Therefore inferior olivary neurons have been proposed to act as somatic 'event detectors' responding particularly reliably to unexpected stimuli (Oscarsson, 1980; Simpson *et al.*, 1995). Miall *et al.* (1993) suggested that the cerebellum makes use of a forward model of the motor apparatus which provides rapid prediction of the sensory consequences of motor commands.

1.4.2.4.1 The cerebellum and predictive grip force modulation

It has been proposed that the cerebellum is involved in predictive grip force modulation. Evidence for this proposal comes from patient and neurophysiological studies. Muller and Dichgans (1994) found that patients with degenerative cerebellar lesions exhibit a lack of co-ordination of grip and load force when performing a lifting task and using a precision grip. In these patients grip and load force were decoupled - the two forces did not always change in parallel, in contrast to the performance of normal individuals (Johannson and Westling, 1984). Furthermore, the cerebellar patients did not adapt their grip force over trials to match the load forces - they failed to produce the normal anticipatory parametrisation of grip force. Similarly, Serrien & Wiesendanger (1999) demonstrated that patients with unilateral cerebellar lesions are less able to regulate the grip force in parallel with load force in their affected hand than in their unaffected hand.

Neurophysiological evidence that the cerebellum is involved in anticipatory grip force adjustments comes from work showing that the discharge of neurons in the cerebellum occurs before movement onset when monkeys reach and grasp objects (Espinosa and Smith, 1992; Smith *et al*, 1993). Recent functional neuroimaging studies in humans have revealed cerebellar activity during grip force – load force coupling (e.g. Tamada *et al*, 1999). In this experiment, hand movements while grasping an object in precision grip resulted in a larger activation of the lateral cerebellum than during a power grip. This suggests that the cerebellum is involved in predicting the sensory consequences of movement, a process necessary for grip force to be modulated in parallel with load force.

1.4.2.4.2 The cerebellum and forward model learning

Studies have shown that the cerebellar cortex can acquire internal models through motor learning (Mano *et al*, 1986; Mano *et al*, 1989; Bauswein *et al*, 1983; Wang *et al*, 1987; Ojakangas *et al*, 1992). Kawato and his colleagues have proposed that multiple internal models exist and that they compete to learn new environments and tools. Recently Imamizu *et al.* (2000) have proposed that the phylogenetically newer part of the cerebellum acquires internal models of objects in the external world. The model of a familiar object can then be activated through vision so that the object is instantly recognised and can be manipulated. Imamizu and colleagues performed a fMRI study in which subjects tracked a moving square target with a cursor on a screen using a 'normal' computer mouse during the baseline condition. During the test condition, the position of the cursor on the screen was rotated by 120° from the position of the computer mouse, so that the tool (the computer mouse) was novel to them. Two types of cerebellar activity were observed. At first, during the test period, large regions of the cerebellum were significantly activated compared with their activity during the baseline period. This activation decreased after repeated test trials in proportion to the reduction in tracking errors made by the subjects as they learned to use the novel tool. The authors propose that this activity corresponds to the acquisition of internal models during learning. In addition, certain restricted sub-regions of the cerebellum (near the posterior superior fissure) continued to be activated even after subject had learned to use the novel tool. The authors propose that this remaining activity represents an internal model that is acquired during the repeated test trials, and which defines the new relationship between movement of the cursor and of the mouse.

In summary, it has been proposed for over thirty years (Ito, 1970) that internal models of the motor system might be stored in the cerebellum. Studies involving patients, and electrophysiological and functional neuroimaging experiments support this suggestion. The hypothesis that the cerebellum is involved in predicting the sensory consequences of action is investigated in chapters 7 and 8 of this thesis.

1.4.2.5 Summary

The experiments in this thesis explore the behavioural and neural characteristics of the forward model using experimental paradigms described above.

1.5 Monitoring self-produced actions in schizophrenia

The final focus of study in this thesis is the possible consequences of a breakdown of components of the forward model. Misinterpreting self-produced events as originating from an external source characterises certain kinds of symptom associated with schizophrenia. It is possible then that these schizophrenic symptoms are caused by an impairment in the predictor or comparator mechanism of the forward model.

1.5.1 Background

Schizophrenia is a complex mental illness characterised by acute phases of delusions, hallucinations and thought disorder, and chronically by apathy, flat affect and social withdrawal. Schizophrenia affects 1% of the world's population, independent of country or culture and constitutes a severe public health issue (WHO, 1975). Schizophrenia was originally named 'dementia praecox' by Emil Kraepelin in 1896 (Kraepelin, 1919), emphasising its chronic and deteriorating course and separating it from psychoses with a good prognosis (which he called 'maniacal-depressive insanity') and dementia in the elderly. Later in 1911, Bleuler noted the fragmentation of personality and cognition that is fundamental to the illness and gave it its current label (schizo=split; phrenia=mind; Bleuler, 1987). This label encouraged the common misperception that schizophrenia is characterised by a split personality. In fact, schizophrenia is a complex illness comprising a combination of a number of different symptoms, for example auditory hallucinations, delusions and incoherent speech (Johnstone, 1991).

Auditory hallucinations normally consist of hearing spoken speech or voices (Hoffman, 1986; Johnstone, 1991). Certain types of auditory hallucinations are included as 'first rank' features in schizophrenia, features that have been regarded as pathognomic of the disorder in most circumstances (Schneider, 1959). These features have much in common with the 'nuclear syndrome of schizophrenia' described by the PSE / Catego system (Wing *et al.*, 1974). See Table 1-1 for examples of symptoms.

Table 1-1: Examples of auditory hallucinations and passivity symptoms (from Mellors, 1970).

Symptom	Example
Auditory hallucinations	• One female patient said she could hear God talking to her, saying things like "Shut up and get out of here." • Some patients hear voices talking about them, such as a man who said "I hear a voice saying 'He's an astronomy fanatic... He's getting up now. He's going to wash. It's about time'."
Thought insertion	• Thoughts are put into my mind like "Kill God." It's just like my mind working, but it isn't. They come from this chap, Chris. They're his thoughts.
Passivity experiences	• 'My fingers pick up the pen, but I don't control them. What they do is nothing to do with me... The force moved my lips. I began to speak. The words were made for me'.

Passivity experiences, or delusions of control, are a further 'first rank' features of schizophrenia (Schneider, 1959). The essence of this symptom is that the subject experiences his or her will as replaced by that of some other force or agency (Wing *et al.*, 1974). Patients describe their thoughts, speech and/or actions as having been influenced or even replaced by those of external agents rather than being produced by themselves. In most cases the actions made when the patient 'feels' that he or she is being controlled by alien forces are not discrepant with his or her intentions. Thus the patient may be correctly performing the task set by the experimenter (e.g. making random movements of a joystick; Spence, 1996) at the same time as having the experience of passivity. He/she does not try to correct these 'controlled' actions or prevent them from occurring.

1.5.2 Auditory hallucinations and passivity phenomena explained as a breakdown in the forward model

Frith (1992) suggested that these abnormal experiences arise through a lack of awareness of intended actions. He proposed that a defect in central 'self-monitoring' might underlie auditory hallucinations and passivity phenomena. Such an impairment might cause thoughts or actions to become isolated from the sense of will normally associated with them. This would result in the interpretation of internally generated voices or thoughts as external voices (auditory hallucinations and thought insertion), and of one's own movements and speech as externally caused (passivity or delusions of control). It has recently been suggested that the experience of passivity arises from a lack of awareness of the predicted limb position based on the forward model (Frith *et al.*, 1999). In the absence of such awareness the patient cannot correct errors prior to peripheral feedback and is not aware of the exact specification of the movement. Thus the patient is aware of the intention to move and of the movement having occurred, but is not aware of having initiated the movement. It is as if the movement, although intended, has been initiated by some external force. In a variation on this theme, Spence (1996) has suggested that the problem is to do with the timing of awareness. The awareness of the actual outcome of the movement precedes the awareness of the predicted outcome, which is contrary to the normal experience of our own agency. Normally we are aware of initiating a movement ~80 msec before the movement actually begins and therefore well before any sensory feedback resulting from the movement (Libet *et al.,* 1983; Haggard *et al.*, 1999). Spence suggests that, in the presence of delusions of control, the awareness of the sensory consequences of the movement precedes the awareness of initiating the movement – that is, in the opposite order to the normal experience of our own agency. This in contrast to Frith *et al.* (1999; 2000) who suggest that, in the presence of delusions of control, the patient is not aware of the predicted consequences of a movement and is therefore not aware of initiating the movement.

In terms of the forward model, it is possible that an impairment of either the prediction or the comparison process could cause auditory hallucinations and passivity experiences. For example, if the comparison process were impaired and always produced a high level of sensory discrepancy despite the accuracy of the sensory prediction, then self-produced sensations would be associated with high levels of sensory discrepancy despite being accurately predicted. In this way, self-produced stimulation could be interpreted as being externally produced. Self-produced events could also be confused with externally generated events if the former were not predicted accurately.

There is evidence that the auditory hallucinations experienced by people with schizophrenia are caused by their own inner speech. Originally Gould (1949) amplified the subvocal activity observed in a hallucinating schizophrenic patient with a microphone. He found that this activity represented whispered speech that was qualitatively different from the patient's own voluntary whispers. Moreover what the whispered voice said corresponded to the report given by the patient of her hallucinations. Green and Preston (1981) have more recently replicated this result. Further evidence suggesting that hallucinations are the consequence of subvocal speech came from studies showing that it is possible to suppress them (and hence reduce the number of auditory hallucinations significantly) by occupying the speech musculature by holding the mouth wide open (Bick and Kinsbourne, 1987). There is also evidence that hallucinating schizophrenics show defects in tasks that require self-monitoring. For example, they are more likely than normal controls to attribute to the experimenter items that they themselves generated a week earlier (Bentall *et al*, 1991a).

There is nothing obviously abnormal in the motor control of these patients. This suggests that accurate representations of predicted states are available and used by the motor system. However, these representations are not available to awareness. A number of experiments confirm that there are subtle problems consistent with a lack of awareness of predicted actions. These patients fail to make rapid error corrections based on awareness of discrepancies between intended and predicted limb positions, although they have no difficulty correcting errors based on visual feedback about actual limb positions (Malenka *et al.*, 1982; Frith & Done, 1989). Normal control subjects were adept at this monitoring task, suggesting that they monitor the response intended (via corollary discharge) and do not need to wait for external feedback about the response that actually occurred. In contrast, the patients failed to make rapid error corrections based on awareness of discrepancies between intended and predicted limb positions, although they had no difficulty correcting errors based on visual feedback about actual limb positions. In particular, failure to correct their errors in the absence of feedback was characteristic of schizophrenic patients with passivity symptoms in the study by Frith and Done (1989).

These patients have difficulty remembering the precise details of actions made in the absence of visual feedback (Mlakar *et al.* 1994; Stirling *et al.*, 1998) They also have difficulty distinguishing between correct visual feedback about the position of their hand and false feedback when the image of the hand they see is in fact that of another person attempting to make the same movements as the patient (Daprati *et al.*, 1997). Recent evidence demonstrates that patients with schizophrenia are more likely than normal control subjects to believe that they read aloud words they actually read silently (Franck *et al*, 2000). Patients who were hallucinating at the time of the experiment performed significantly worse – they confused reading silently and aloud more - than non-hallucinating patients. This was taken to support the suggestion that they are unable to discriminate correctly between inner and outer speech, and that this might play a role in the onset of their hallucinations. In the study presented in chapter 9, whether patients with auditory hallucinations and passivity experiences are able to differentiate perceptually between tactile stimuli that are self- and externally produced was evaluated.

1.5.3 Symptom-specific groups

Schizophrenia is a heterogeneous illness, comprising a variety of different symptoms. Using groups of patients defined by diagnosis (schizophrenia) may be problematic (and may explain the lack of consistent results from studies involving schizophrenic patients) since each symptom might be associated with a different aetiology or functional abnormality. One solution to this problem is to study symptom-defined groups.

Comparing patient groups to a group of normal control subjects is important in order to establish a baseline model of the processes or neural circuitry involved in an experimental task. However, there are clearly several problems with using non-psychiatric control subjects. These include the fact that normal control subjects are not medicated, hospitalised or affect-flattened, factors that might cause the patients to be more or less motivated, to attend or think more or less and might alter brain activity. Since psychiatric patients will be more matched on these factors, they may constitute be a preferable control group. However, there are also problems with using psychiatric patients as controls. There is the question of which psychiatric population should be used. Should they be taking the same medication, or is hospitalisation the most important factor? They might not be able to perform the experimental task for some reason that is different from that causing impairment in schizophrenic patients. Therefore, comparing schizophrenic to depressed patients, for example, may reveal activity specific to depression or to schizophrenia, rather than the task in question.

In chapter 9 of this thesis, an experiment is presented that investigates self-monitoring in symptom-defined groups of psychiatric patients. A clear advantage of using symptom-specific schizophrenic groups is that the control group can comprise people with a diagnosis of schizophrenia, who are thus matched in terms of medication and hospitalisation, but who do not have a particular symptom. Alternatively, the same group of schizophrenic patients can be used as their own control group if and when the symptom evaluated remits (see the study by Spence *et al.*, 1998). A clear shortcoming of using symptom-specific groups is that little can be discovered about schizophrenia as a syndrome.

1.5.4 Functional neuroimaging studies of schizophrenic symptoms

Functional neuroimaging has been used for several decades to evaluate abnormal neural processing in schizophrenia. This thesis focuses on specific symptoms associated with schizophrenia, that is those symptoms that may be caused by an impairment of the forward model (auditory hallucinations, thought insertion and passivity phenomena). Attempts have been made to correlate brain activity with specific symptoms. A brief review of those studies reveals that auditory hallucinations involve neural systems dedicated to auditory speech perception as well as a distributed network of other cortical and subcortical areas. Passivity phenomena have been associated with hyperactivation of the parietal lobe (see Blakemore & Frith, 2000 for review).

1.5.4.1 Auditory hallucinations

There are two distinct approaches to the study of the physiological basis of auditory hallucinations. The first, which is referred to as the state approach, asks what changes in brain activity can be observed at the time hallucinations are occurring. The second, which is referred to as the trait approach, asks whether there is permanent abnormality of brain function present in patients who are prone to experience auditory hallucinations when they are ill. This abnormality will be observable even in the absence of current symptoms.

1.5.4.1.1 State studies

Silbersweig *et al.* (1995) used PET to study brain activity associated with the occurrence of hallucinations in six schizophrenic patients. Five patients with classic auditory verbal hallucinations demonstrated activation in subcortical (thalamic and striatal) nuclei, limbic structures (especially hippocampus), and paralimbic regions (parahippocampal and cingulate gyri and orbitofrontal cortex). Temporoparietal auditory-linguistic association cortex activation was present in each subject. One drug-naive patient had visual as well as auditory verbal hallucinations, and showed activations in visual and auditory/linguistic association cortices. The authors proposed that activity in deep brain structures seen in all subjects may generate or modulate hallucinations, and the particular sensory cortical regions activated in individual patients may affect their specific perceptual content. Importantly this study pointed to the possibility that hallucinations coincide with activation of the sensory and association cortex specific to the modality of the experience, a notion that has received support from several further studies.

David *et al.* (1996) used fMRI to scan a schizophrenic patient while he was experiencing auditory hallucinations and again when hallucination-free. The subject was scanned during presentation of exogenous auditory and visual stimuli, while he was on and off antipsychotic drugs. The BOLD signal in the temporal cortex to exogenous auditory stimulation (speech) was significantly reduced when the patient was experiencing hallucinating voices, regardless of medication. Visual cortical activation to flashing lights remained the same over all four scans, whether the subject was experiencing auditory hallucinations or not.

A similar result was obtained by Woodruff *et al.* (1997b) who used fMRI to study seven schizophrenic patients while they were experiencing severe auditory verbal hallucinations and again after their hallucinations had subsided. On the former occasion, these patients had reduced responses in temporal cortex, especially the right middle temporal gyrus, to external speech, compared to when their hallucinations were mild. The authors thus proposed that auditory hallucinations are associated with reduced responsivity in temporal cortical regions that overlap with those that normally process external speech, possibly due to competition for common neurophysiological resources.

Dierks *et al.* (1999) used event-related fMRI to investigate three paranoid schizophrenics who were able to indicate the on-set and off-set of their hallucinations as in the study by Silbersweig *et al.*. Using this design they found that primary auditory cortex, including Heschl's gyrus, was associated with the presence of auditory hallucinations. Secondary auditory cortex, temporal lobe and frontal operculum (Broca's area) were also activated during auditory hallucinations, supporting the notion that auditory hallucinations are related to inner speech. Finally, hallucinations were also associated with increased activity in the hippocampus and amygdala. The authors suggested that these activations could be due to retrieval from memory of the hallucinated material and emotional reaction to the voices, respectively.

1.5.4.1.2 Trait studies

The finding that auditory hallucinations are associated with activation of auditory and language association areas is consistent with the proposal that auditory verbal hallucinations arise from a disorder in the experience of inner speech (Frith, 1992). This was investigated by McGuire *et al.* (1996). They used PET to evaluate the neural correlates of tasks that engaged inner speech and auditory verbal imagery in schizophrenic patients with a strong predisposition to auditory verbal hallucinations (hallucinators), schizophrenic patients with no history of hallucinations (nonhallucinators), and normal controls. There were no differences between hallucinators and controls in regional cerebral blood flow (rCBF) during thinking in sentences. However, when imagining sentences spoken in another person's voice, which entails both the generation and monitoring of inner speech, hallucinators showed reduced activation of the left middle temporal gyrus and the rostral supplementary motor area, regions activated by both normal subjects and nonhallucinators. Conversely, when nonhallucinators imagined speech, they differed from both hallucinators and controls in showing reduced activation in the right parietal operculum. McGuire and his colleagues suggest that the presence of verbal hallucinations is associated with a failure to activate areas concerned with the monitoring of inner speech.

In conclusion, functional neuroimaging studies suggest that hallucinations involve an interaction between the neural systems dedicated to the particular sensory modality in which the false perception occurs and a widely distributed cortico-subcortical system, including limbic, paralimbic and frontal areas. Intersubject variability in the specific location of the sensory activation associated with the hallucination could arise from differences between the patients in the sensory content and experience of their hallucinations.

1.5.4.2 Passivity phenomena

Spence *et al.* (1997) performed a PET study in which subjects had to make voluntary joystick movements in the experimental condition, and stereotyped movements in the baseline condition, and do nothing in the rest condition. They investigated a group of schizophrenic patients with delusions of control (and 4-6 six weeks later when they were in remission), a group of schizophrenic patients without delusions of control and a group of normal controls. Schizophrenic patients with passivity showed hyperactivation of inferior parietal lobe (BA 40), the cerebellum, and the cingulate cortex relative to schizophrenic patients without passivity. Similar results were found when schizophrenic patients with passivity were compared to normal controls. When patients were in remission, and no longer experienced passivity symptoms, a reversal of the hyperactivation of parietal lobe and cingulate was seen. Hyperactivity in parietal cortex may reflect the 'unexpected' nature of the experienced movement in patients, as though it were being caused by an external force. This is consistent with the idea that the sensory stimulation resulting from self-generated actions had not been cancelled. In consequence sensory stimulation resulting from movements would seem unexpected and an active movement would be experienced as if it were passive.

1.5.5 Summary

It has been suggested that several symptoms experienced in schizophrenia, including auditory hallucinations and passivity phenomena, are associated with an inability to monitor and recognise self-produced actions, speech and thoughts. This might be caused by a breakdown of the forward model. Functional neuroimaging studies have revealed that auditory hallucinations involve neural systems dedicated to auditory speech perception as well as a distributed network of other cortical and subcortical areas. Passivity experiences have been associated with over-activity in right inferior parietal cortex.

1.6 ***Questions explored in this thesis***

In this thesis a series of experiments will be described, in which behavioural and neural characteristics of forward models in humans are investigated. The central question in this series of experiments asks how we distinguish sensory stimulation that is externally produced from sensory stimulation that is produced by one's own actions. Forward model mechanisms have mainly been studied with reference to eye movements. The experiments presented in this thesis investigate forward model mechanisms in modalities other than the oculomotor domain, and in both normal control subjects and psychotic patients with auditory hallucinations and passivity phenomena.

CHAPTER 2: METHODS, ANALYSIS AND EXPERIMENTAL DESIGN IN FUNCTIONAL NEUROIMAGING

2.1 Functional neuroimaging methods

2.1.1 The relationship between neuronal activity and cerebral blood flow

The brain requires a constant supply of blood flowing to it to replenish its supply of oxygen and glucose, which it depends on for energy. The link between an increase in brain metabolism and a local increase in blood flow in the brain was originally suggested by Roy and Sherrington (1890). Their hypothesis that there is an increase of regional cerebral blood flow (rCBF) at the site of brain metabolism has been supported by many studies (e.g. Magistretti & Pellerin, 1999). The tight coupling between neuronal activity and the associated local cerebral glucose metabolism and therefore blood flow is the basic physiological principle behind functional neuroimaging. Functional neuroimaging techniques measure brain activity by detecting changes in blood flow or flow-related phenomena in human subjects.

The specific cellular and molecular mechanisms that underlie the signals detected by functional neuroimaging have not yet been unequivocally specified. Since over 85% of cerebral glucose is used by neurons, mainly presynaptic axon terminals, it has been proposed that the majority of cerebral energy (in the form of glucose) is needed for presynaptic neuronal activity, primarily for the maintenance of membrane potentials and restoration of ion gradients. The cerebral blood flow (CBF) monitored by functional neuroimaging is proposed by many researchers to correspond to this presynaptic neuronal activity (see Jueptner & Weiller, 1995, for review). However, this issue has been complicated by studies that have identified the neurotransmitter glutamate and astrocytes, a specific type of glial cell, as important in the coupling of synaptic activity with energy consumption (see Magistretti & Pellerin, 1999, for review). This and related issues concerning the specific neuronal mechanisms that underlie the signals detected by functional neuroimaging will be discussed later in this thesis. This thesis discusses functional neuroimaging studies that employ Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) to measure brain activity in human subjects during psychological and sensorimotor tasks.

2.1.2 Positron Emission Tomography

PET is a tracer imaging technique. Tracer imaging techniques were pioneered by Kety and Schmidt in 1940s (Kety and Schmidt, 1945). In PET cerebral blood flow can be imaged by following a tracer injected into the bloodstream as it flows through the brain. The tracer used in the PET studies in this thesis is radioactive water ($H_2{}^{15}O$), which is introduced into the blood stream via a bolus intravenous injection. The radioactive tracer can be observed because it emits a positron when it decays. The positron quickly combines with a nearby electron and the particles are annihilated, producing two gamma rays that travel in opposite directions. A circle of gamma ray detectors around the head registers simultaneous (coincidental) hits on scintillation crystal detectors on opposite sides of the head. These coincidence hits are used to pin-point the location of the radioactive sources. Typically, two photons are identified as coming from a single source if they arrive at detectors within about 15 ns of one another. In the PET studies described in this thesis, PET scans were performed with an ECAT EXACT HR+ scanning system [CTI Siemens, Knoxville, TN] in 3D mode with septa retracted (Townsend, 1991).

PET tracers have a relatively short half-life, so the time of radioactivity exposure to the subject is minimal. $H_2{}^{15}O$ has a half-life of two minutes. In the PET studies described in this thesis, approximately 350 MBq of $H_2{}^{15}O$ in 3ml of normal saline is loaded into intravenous tubing and flushed into the subject over 20 secs at a rate of 10ml/min by an automatic pump. After a delay of approximately 35 secs, a rise in counts can be detected in the head that peaks 30-40 secs later (depending on individual circulation time; Silbersweig *et al*, 1993). The interval between successive administrations is 8 mins.

Attenuation correction of the images prior to scanning is necessary because the annihilation photons originating from deep-seated tissues have a higher chance of being absorbed before leaving the body and therefore appear to contain less activity than more superficial tissues. Correction for attenuation is generally made using a transmission scan collected at the beginning of the study. Radiation is transmitted through the head from an external source, and the proportion of this radiation that is attenuated (absorbed) is calculated. This calculation is used to correct the counts in the subsequent emission data.

The data are acquired in one 90 sec frame, beginning during the rising phase of the head curve counts used as a measure of blood flow. Images are reconstructed by filtered back projection (Hanning filter, cut off frequency 0.5 cycles per pixel) into 63 image planes (separation 2.4mm) and into a 128x128 pixel image matrix (size 2.1 mm). The subject receives a dose of 9 mCi of radioactive substance per scan, and twelve scans are acquired per subject in each experiment.

2.1.3 Magnetic Resonance Imaging

In both PET and fMRI studies a high-resolution structural image of the brain is obtained for each subject for anatomical coregistration with the functional (activity) data. The structural image is acquired using Magnetic Resonance Imaging (MRI).

2.1.3.1 Sources of contrast in MRI

The MRI signal is based on the magnetic properties of atoms with an odd number of protons in their nucleus. These atoms possess a property called *spin.* When placed in a magnetic field, a spin has a magnetic moment. The net magnetic moment of all the spins in the magnetic field is the *magnetisation vector*, *M.* The majority of the spins in the magnetisation vector are aligned with the magnetic field. In order to observe a MRI signal the total magnetisation vector must be tipped away from the main field direction, to create a component of magnetisation precessing (rotating) about this axis, in the transverse plane. This is achieved by exciting the spins by applying a radiofrequency magnetic field (the *rf pulse*) perpendicular to the main magnetic field. This changes the alignment of the proton magnetic moments so the spins are tipped away from their equilibrium position. After excitation the spins produce a rf signal - this is the MRI signal. Although tissue and fat contribute to the MR signal, the largest contributions come from the protons in tissue water. The image intensity is dependent on the density of these protons, and can also be affected by the local environment of the water molecules and pulse sequence parameters.

2.1.3.2 Relaxation

After excitation with a rf pulse the protons will ultimately return to their equilibrium state. This *relaxation* process can take up to several seconds. During this time the magnetisation that has been created in the direction perpendicular to the magnetic field induces a signal voltage in an antenna (the coil) surrounding the object being scanned. The rate of recovery, called the *longitudinal relaxation time, T1*, depends on the type of tissue containing the relevant water molecules. For example, the relaxation time of protons in cerebrospinal fluid, which is close to pure water, is much slower (up to 5 seconds at 2 Tesla field strength) than that of protons in brain white matter (about 500 ms). By varying the repeat time between rf pulses, the contrast between tissue regions of long and short T1 can be changed dramatically.

There is a second type of relaxation that also allows different tissue types to be distinguished. The total magnetisation vector, M (the signal), is the sum of the individual spin magnetisation vectors. To produce maximum signal, the resonance frequencies of all the individual spins should be equal, allowing magnetisation to add up constructively from each proton. However, small differences (inhomogeneities) in the magnetic environment of each contributing spin will cause them to precess at slightly different resonance frequencies, resulting in a difference in the rotated phase angles. As M is the sum of the individual spin magnetisation vectors it will decrease with time as the spins disperse, and hence the MRI signal will decrease with time. The decay of M and therefore the signal is roughly exponential and can be characterised by a time constant *T2*, the *transverse relaxation time*. The difference in speed between T1 and T2 equilibrium can be deduced from their relaxation constants. Typical T1 values are in the order of a few hundred ms up to a second, whereas T2 constants are in the order of 50-100 ms. Magnetic field variations that can exist across the object can produce a further phase dispersion causing a more rapid decay of the signal. This additional relaxation time is called T2'. The total signal decaying time of T2 and T2' has a time constant T2* (where $1/T2^* = 1/T2+1/T2'$). Spins from solid structures like bone are not observable in the MR signal because their T1 and T2s are so short that they have relaxed back to equilibrium before any signal is detected. MRI therefore mainly detects protons present in biological liquid states.

2.1.3.3 Image formation

The resonance frequencies of spins are proportional to the magnetic field. By applying a linear magnetic field gradient it is possible to change the resonance frequencies of the spins. In this way the location and quantity of the spins along the gradient axis can be determined and used to form an image. Because there is not much variation in spin density over different tissues the contrast between them will not be very large. The differences in T1 and T2 relaxation can be used to increase image contrast. By choosing appropriate sequence parameters the scan can be tuned to T1, T2 or T2* differences between the imaged environments. In this way, an image can be T1-, T2- or T2*-weighted.

2.1.3.4 Functional MRI

MRI can also be used to trace blood flow in the brain. Initially researchers used an exogenous paramagnetic contrast agent, a non-toxic compound of gadolinium introduced into the bloodstream via a vein, to trace cerebral flow. A fraction of a millimole of contrast agent per kilogram of body weight is sufficient to give up to 40% loss of MR signal from the tissue surrounding the cerebral blood vessels that a bolus of contrast agent is passing through. This approach was applied to brain perfusion to obtain local cerebral blood flow as the ratio of blood volume to mean transit time. Echo Planar Imaging (EPI) is a fast imaging technique that can be used to acquire a complete image in less than 100 ms (Stehling *et al.*, 1991). This allows 'snapshots' of the contrast agent distribution as it passes rapidly through the brain.

In 1991 Belliveau and colleagues applied this technique to the human brain (Belliveau *et al*, 1991). Subjects were scanned using EPI fMRI while a bolus of contrast agent was injected into the leg vein. Single slice images of the brain in the plane of the calcarine fissure were obtained at 0.75 sec intervals to monitor the passage of the bolus. By integrating the time course of image intensity, estimates of relative blood volume were obtained while subjects received visual stimulation and compared (by image subtraction) with those obtained while subjects were at rest in darkness. The authors observed consistent increases, up to 30%, of blood volume in primary visual cortex.

2.1.3.4.1 BOLD fMRI

Oxygen transport in the blood is mediated by haemoglobin, contained within red blood cells. The binding of oxygen to haemoglobin is regulated by local oxygen pressure: when the pressure is high (e.g. in the lungs) oxygen is bound to haemoglobin; when the pressure is low (e.g. in the capillaries) oxygen is released. When haemoglobin has no oxygen bound to it, it has a net magnetic moment. As soon as oxygen becomes bound this net moment disappears. Haemoglobin's paramagnetic behaviour therefore depends on the amount of oxygen bound to it. The magnetic state of blood therefore reflects its level of oxygenation, with deoxyhaemaglobin being more paramagnetic than oxyhaemaglobin (Pauling & Coryell, 1936).

Because deoxyhaemaglobin is more paramagnetic than oxyhaemaglobin, a change in the MRI signal extending around the blood vessels can be caused by manipulating the oxygenation state of the blood. The more paramagnetic an agent the faster its relaxation time is, and the less signal it will produce. Therefore, deoxyhaemaglobin produces less MRI signal than oxyhaemaglobin. This was initially demonstrated by Ogawa *et al.* (1990), who observed blood oxygenation level dependent (BOLD) contrast in anaesthetised mice at high magnetic fields (7T and 8.4T). In T2* weighted gradient echo images they observed less signal (more dark lines) in brain scans when the mice were breathing 20% oxygen than when they were breathing 100% oxygen. These signal changes were reversible. The authors suggested that deoxyhaemoglobin was the source of the contrast, enhancing relaxation in and around the vasculature, resulting in the observed dark lines (corresponding to a loss of signal).

Using faster gradient echo EPI methods Turner *et al.* (1991) also showed how transient changes in oxygenation level could be monitored with BOLD contrast.

By temporarily withholding oxygen from a cat the researchers showed that a lowered oxygenation and blood flow level resulted in a signal drop in the well-perfused grey matter. Restoration of oxygen supply induced a signal increase again. An overshoot with respect to the initial value was observed, indicating that during the recovery time the blood flow supplied more oxygen than was being consumed. This demonstrates that BOLD contrast is determined by the balance of supply (blood flow, blood volume) and demand (extraction by tissue) of oxygen.

These results suggested that interventions on the state of the brain that create an imbalance between oxygen uptake and blood flow would cause a change of MRI signal around the cortical vessels. A change in MRI signal resulting from deoxyhaemoglobin in human visual cortex was first reported by Kwong *et al.* (1992) and Ogawa *et al.* (1992). Both groups scanned subjects using BOLD fMRI while viewing bright lights (the experimental task) or at rest (the baseline). By subtracting rest state images from activation images, Kwong and colleagues demonstrated activity-induced changes during the visual task. The signal from the visual cortical areas followed the on-off activation paradigm of the visual task, with a lag of several seconds between the visual stimulation and BOLD signal. This reflects the delay in vascular and metabolic responses and is known as the *haemodynamic response time.* Furthermore, the BOLD changes in the visual cortex occurred primarily in the grey matter, not in the white matter, as would be expected (Ogawa *et al*, 1992). Ogawa and colleagues also demonstrated that the BOLD signal changes were found to be larger the higher the magnetic field.

The rise in BOLD signal during visual stimulation indicates that there is a decrease in the concentration of paramagnetic deoxyhaemoglobin during stimulation relative to rest. Earlier research using PET demonstrated that there is a disproportionate increase in the amount of oxygenated blood flowing to an activated region, in that the rise in oxygen reuptake during somatosensory and visual stimuli is smaller than the rise in blood flow to activated brain regions (Fox & Raichle, 1986). Earlier observations during open skull surgery also demonstrated that blood leaving an active cortical regions is brighter red, i.e. more oxygenated, than when the region is not active, as a result of this mismatch between demand and supply (Penfield, 1933).

2.1.4 Resolution of PET and fMRI

PET measures blood flow on a spatio-temporal scale of about 6mm and 30 seconds. PET measures changes in blood flow or perfusion directly in terms of the amount of radiolabelled water that accumulates locally but this takes several tens of second to a minute or so. fMRI has a spatio-temporal scale of about 1-3mm and one or more seconds. The lower limits on the effective resolution of fMRI are physiological and imposed by the spatio-temporal organisation of evoked haemodynamic responses (2-5mm and 5-8 seconds). Local increases in neural activity cause both a relative deoxygenation of blood and an increase in perfusion, that quickly reverses the deoxygenation, leading to an increase in oxygenation that endures for several seconds.

2.2 Experimental Design in Functional neuroimaging

2.2.1 Background

The main aim of functional neuroimaging is to elucidate the neural correlates of a particular cognitive, sensory or motor process. There are several types of experimental design that can be employed to achieve this aim. Subtractive designs are the simplest sort of design, and have been employed since the onset of functional neuroimaging experiments. Recently more sophisticated designs, which have been shaped in the light of how the brain is organised and processes information and go beyond cognitive subtraction, have been implemented. These designs will be discussed in this section, are based on a functional specialisation view of the brain - the expression of patterns of neural activity in response to a specific stimulus or psychological process in specialised cortical areas.

2.2.2 Functional specialisation and functional integration

Patterns of brain activity elicited by sensory, motor or cognitive tasks are usually understood in terms of *functional specialisation* or the *functional integration* of specialised areas (Friston et al, 1997). The principle of functional specialisation has been the basis of the majority of functional neuroimaging studies to date. It is believed that the brain employs a strategy of functional segregation whereby cells with common properties are grouped together (Zeki, 1990). Zeki proposed that this architectural constraint requires cortical connections to converge into and diverge from any particular brain region. Connections between cortical regions are not continuous but occur in patches or clusters and in some areas, in particular the visual cortex, this patchiness has a clear relationship to functional segregation. If neurons in a given cortical area share the same responsiveness to some sensorimotor or cognitive process then their segregation is anatomical as well as functional.

So, scanning a subject while he or she is performing some sensorimotor or cognitive task should lead to activity changes in, and only in, the region of interest. The data analysis used in the studies in this thesis examines functional neuroimaging data for regionally specific effects based on this model of cortical functional and anatomical segregation. Recently functional neuroimaging has seen the emergence of experiments evaluating functional integration in the brain. These designs assess interactions among specialised cortical areas and how these interactions depend upon the sensorimotor or cognitive context.

From the perspective of functional neuroimaging, functional specialisation constitutes the identification of regionally specific effects that can be attributed to changing stimuli or task conditions. Functional integration, on the other hand, is usually assessed by examining the correlations among activity in different brain areas, or by trying to explain the activity in one area in relation to activities in other brain regions. These analyses are usually framed in the terms of *effective connectivity* (the influence that one neural system exerts over another; Buchel & Friston, 1997). This section describes functional specialisation and functional integration experimental designs that are employed in the functional neuroimaging experiments discussed in this thesis.

2.2.3 Subtraction designs

Categorical designs such as *cognitive subtraction* have been widely used in functional neuroimaging. Cognitive subtraction involves investigating the neural correlates of a particular cognitive (or sensorimotor) component of interest (CCI) by using two or more tasks that differ by one separable component. Differences in brain activity between the tasks are then attributed to this component. Generally in this types of design, subjects are scanned while performing an *experimental task* that engages the CCI. The same subject, in the same scanning session, would also be scanned while they are performing a *baseline task*. This task must engage all components of the experimental task, except the CCI. The two conditions should be identical in every way, except for the presence of the CCI in the experimental condition. Subtracting brain activity in the baseline task from that in the experimental task will, in principle, result in brain activity associated with the CCI.

A simple example of such a design might be that used in an investigation of the neural correlates of processing moving visual stimuli. In this case the subject might be scanned while he or she is performing an experimental task that engages visual motion processing, for example looking at moving dots. The baseline task would be looking at static dots. The two conditions are identical in every way, except for the presence of visual motion in the former condition. Subtracting brain activity in the baseline task from that in the experimental task will, in principle, result in brain activity associated with visual motion processing per se, independent of any other aspect of visual processing.

Although its simplicity is appealing this approach makes several strong assumptions about the way that the brain implements cognitive processes. A number of early functional neuroimaging studies violated these assumptions. Consider the following hypothetical example. Researchers interested in semantic processing, say, might have subjects read visually presented words in the experimental condition, and simply look at the same visually presented words in the baseline task. This subtraction would result in activity of many different brain areas, including motor, language and visual areas, and the (flawed) conclusion might be that these areas are implicated in semantic processing. This hypothetical study illustrates a number of the assumptions of simple subtraction designs:

1. The baseline and experimental task must be identical in every way except for the inclusion of the CCI in the former and the exclusion of the CCI in the latter.

The semantic processing experiment suggested above would violate this requirement because there are many processes in addition to the CCI in the experimental task that are not present in the baseline task, for example preparing to speak, motor execution, phonological processing and so on.

2. There must be no implicit processing of the CCI in the baseline task. In the semantic task example, it is probably difficult not to read (silently) a visually presented word, and if this is the case there will be semantic processing due to implicit reading of words in the baseline task.

3. 'Pure insertion' assumes that an extra cognitive component, in this case reading, can be introduced without affecting the expression of existing components, in this case visual processing. When a component is added to the task requirements, the new task comprises not only the previous components and the new component, but also the integration of the new and old components. This integration, or *interaction* effect can itself be considered as a new component. The difference between two tasks therefore includes the new component and the interactions between the new component and those of the original task. In other words, the whole can be greater than the sum of the parts (see Figure 2-1). Pure insertion requires that all these interaction terms are negligible, when in many instances they are not.

In the example, if visual cortex is activated more by reading words than by seeing words, it might be concluded that the visual cortex is involved in semantic processing. However, it cannot be assumed that adding the cognitive component of reading will not affect the processing or expression of the baseline component (seeing words). An equally likely explanation, and one that cannot be discerned from the analysis, is that there is a top-down effect of reading on the way words are processed visually.

2.2.4 Cognitive Conjunctions

One way of avoiding interaction effects is to use cognitive conjunction analysis. Cognitive conjunctions combine a series of subtractions with the aim of isolating a CCI that is common to two (or more) task pairs. In subtraction designs a hypothesis pertaining to the activation in one task relative to another is tested. In cognitive conjunctions several hypotheses are tested, asking whether all the activations, in a series of task pairs, are jointly significant. In this way, the assumption of pure insertion in subtractive designs can be avoided by extracting the presence of a main effect in the absence of an interaction.

This is a type of subtractive design that requires two (or more) task pairs: the activation task of each pair must engage the CCI, and each must have its own baseline task. There is little restriction on the baseline tasks: they can be as high level or low level as desired. The only restriction on the baseline tasks is that differences between the task pairs (the results of the subtraction of each baseline from each experimental task) both (or all) contain the CCI. The analysis results in any commonality in activation differences between the task pairs. The region that is activated by all the corresponding subtractions will be uniquely associated with the CCI in question. This is tenable even if interactions are present because the interactions will be specific to each pair. In this way cognitive conjunctions can be used to discount interactions and therefore do not violate the assumption of pure insertion. Instead the analysis retains areas that activate equally in all ‘contexts,’ so identifies robust, context-insensitive activations that can be attributed to the CCI per se, and not to some interactional effect.

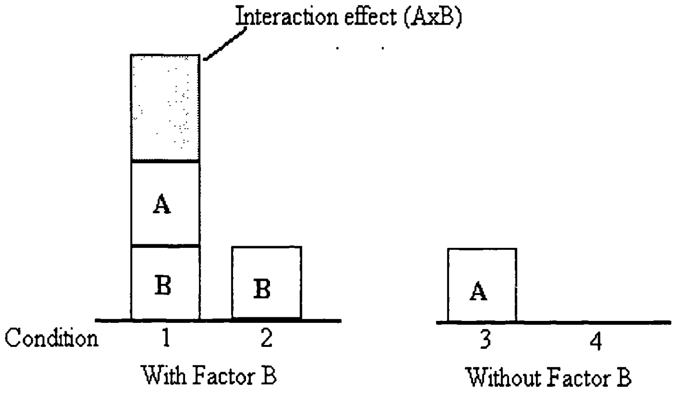
However, in some situations the interaction between factors may be of interest. Factorial designs allow this interaction effect to be assessed directly.

2.2.5 Factorial designs

Often an experimental question can be answered by investigating the *interaction* between two cognitive (or sensorimotor) processes. In this case a factorial design can be employed. In factorial designs there are two or more variables (factors), and the different levels of each factor must be equated. In functional neuroimaging, the main neural effects of each factor and the neural effects of the interaction between the factors can be calculated separately. The interaction identifies brain areas where the effect of one factor varies depending on the presence or absence of the other factor. This allows the effect of one factor on the expression of the other factor to be measured explicitly (**Figure 2-1**).

Figure 2-1

	With Factor A	Without Factor A
With Factor B	Condition 1	Condition 2
Without Factor B	Condition 3	Condition 4



In factorial designs there are two or more factors, in this case factors A and B. The main effects of each factor can be calculated by (1+2)-(3+4) and (1+3)-(2+4). In addition, the interaction between the factors can be calculated separately by (1-2)-(3-4) and conversely by (3-4)-(1-2). The interaction identifies areas where the effect of one factor varies depending on the presence or absence of the other factor.

For example, a factorial design could be employed to study the brain areas involved in the semantic processing. Two factors could be employed. One factor might be semantic processing (producing a semantic association or a non-semantic association of visually presented stimuli), and the other factor might be type of stimuli (words or pictures). So, there would be four conditions:

1. producing a semantic association of a word, e.g. door-window
2. producing a semantic association of a picture
3. producing a non-semantic association (e.g. size categorisation) of a word
4. producing a non-semantic association of a picture

The analysis would reveal brain activity associated with the main effects of semantic processing (irrespective of stimuli), and type of stimuli (irrespective of task). The analysis would also reveal brain areas associated with the interaction between semantic processing and seeing words, or semantic processing and seeing pictures. Such a factorial design using these factors was employed by Vandenberghe *et al.* (1996). They found that the left posterior inferior temporal sulcus was activated more by the semantic processing of words than by the semantic processing of pictures.

2.2.6 Parametric designs

In parametric designs the CCI is treated as a dimension as opposed to a category. Parametric designs are based on the principle that systematic changes in evoked neural responses will occur with the degree to which a CCI is expressed. Categorical designs, like those described above, use just two levels or rates of a parameter (e.g. semantic processing versus no semantic processing, as in the example above). Any non-linear relationship between brain activity and stimulus level will not be characterised by categorical designs. In some instances the relationship may be highly non-linear. For example, it is known that an inverted U behaviour in prefrontal cortex occurs with increasing stimulus presentation rates (Buechel *et al*, 1996). Linear and non-linear relationships between neural activity and stimulus level can be assessed by parametric designs.

The covariate of interest (or regressor) can be a factor whose level is manipulated externally by the experimenter (e.g. word presentation rate). Alternatively, subject responses (e.g. number of words correctly remembered in a memory experiment) can be used as the covariate of interest. The ensuing analysis reveals brain areas whose activity shows a significant regression (positive or negative) on the covariate of interest.

2.2.7 Psychophysiological Interactions

Psychophysiological interactions explain the physiological response in one part of the brain in terms of an interaction between a particular cognitive (or sensorimotor) process and activity in another part of the brain. They demonstrate functional integration in the brain. Psychophysiological interaction analysis uses regression analysis based on the following principles. If the activity in one region (area A) predicts the activity in another region (area B) then the strength of the prediction reflects the influence area A could be exerting on area B. If the strength of the prediction (measured by regression analysis) varies with the psychological context in which the physiological activity is measured then this is evidence for a psychophysiological interaction (Friston *et al.*, 1997). This has implications in terms of the top-down modulation of specialised cortical areas by higher brain regions.

This is an interesting analysis from two points of view. Firstly, the explanatory variables used to predict activity (i.e. the response variable) in any brain region comprises a standard predictor variable based on the experimental design (e.g. the presence or absence of a particular stimulus attribute) and a response variable from another part of the brain. Secondly, this analysis uses techniques usually used to make inferences about functional specialisation to infer something about functional integration, in this case, the effective connectivity between different brain areas. That is psychophysiological interaction analysis provides information about the contribution of one brain region over other regions in certain psychological contexts.

2.3 Data Processing

2.3.1 Spatial analysis

Before statistical analysis the functional neuroimaging data are realigned, normalised and smoothed.

2.3.1.1 Realignment

Artifacts in BOLD signal in fMRI and variance components in PET data can be caused by movement of the subject's head in the scanner. Movement is particularly a problem in fMRI because head motion can produce a BOLD signal that shows striking similarities to the BOLD signal produced by performance of a task in the functional images (Hajnal *et al*, 1994). This artifactual signal is especially a problem when the head motion is correlated with the stimulus. Stimulus-correlated motion can occur in paradigms that involve making limb, hand or even finger movements either as the task or as a response to the task (Hajnal et al, 1994).

Therefore PET and fMRI images are realigned to reduce movement-related artifacts. For PET this involves estimating movement relative to the first scan and realigning the scans *post hoc* using these estimations. Removing movement-related effects from fMRI time series is more complicated because movement in earlier scans can affect the signal in subsequent scans (due to differential spin-excitation histories). The head movements are first estimated (as they are in PET) and used to realign the images and then a mathematical adjustment is performed to remove the movement-related components that persist after simple realignment. The adjustment procedure is based on a moving average-auto-regression model of spin-excitation history effects. The latter components can be prominent and are specific to the way the fMRI signal is acquired.

2.3.1.2 Spatial normalisation

In order to implement voxel-based analysis of imaging data, data from different subjects and in different sessions must derive from homologous parts of the brain. Spatial transformations are therefore applied to PET and fMRI images that move and warp the images such that they conform approximately to some idealised or standard brain. This normalisation facilitates intersubject averaging and the reporting of results in a conventional way. Spatial normalisation involves the transformation of an image into a standard anatomical space. In the studies reported in this thesis the images are normalised to a template brain image from the Montreal Neurological Institute (Evans *et al*, 1994). The standard anatomical space used is that described in the atlas of Talairach and Tournoux (1988) as proposed by Fox *et al.* (1985). For PET the normalisation transformations can be computed on the basis of the PET data themselves, or on the basis of co-registered high-resolution anatomical MRI T1-weighted scans. If the T2*-weighted fMRI data are sufficiently good quality it is possible to normalise these directly. If not, the T1-weighted images are used.

2.3.1.3 Spatial smoothing

The images are then smoothed (convolved) with a Gaussian kernel. This is important for several reasons:

1. To increase signal to noise ratio. The neurophysiological effects of interest are produced by haemodynamic changes expressed over spatial scales of several millimetres, whereas noise generally has higher spatial frequencies. For PET the spatial frequency structure of noise is determined by the reconstruction process used to create the images. In fMRI the noise can (to a first approximation) be regarded as independent for each voxel and therefore has very high spatial frequency components.

2. Convolving with a Gaussian kernal conditions the data so they conform more closely to the Gaussian field model. This is necessary to make statistical inferences about the regionally specific effects.
3. For inter-subject averaging. Smoothing ensures that haemodynamic changes from subject to subject are assessed on a spatial scale at which homologies in functional anatomy are typically expressed. In other words, mapping of function on to anatomy may be meaningful at a resolution that is not confounded by microscopic and macroscopic organisational details that are specific to an individual brain.

2.3.2 Statistical analysis

2.3.2.1 The design matrix

The experimental design and the model used to test for specific neurophysiological responses are embodied in a mathematical structure called the *design matrix*. The design matrix is partitioned according to whether the effect is interesting (e.g. an activation) or not (e.g. a nuisance variable such as global activity). These effects can reflect factor levels (e.g. the presence or absence of a particular process) or can be continuous (a covariate such as reaction time).

The contribution of each effect to the observed physiological response is estimated. These estimated contributions, or *parameter estimates,* which are modelled by columns of the design matrix, can range from simple factors such as the mean activity associated with a particular condition to more complicated factors such as an interaction term in a multifactorial experiment. Regionally specific effects are framed in terms of differences among these parameter estimates (e.g. an activation effect) and are specified using linear compounds or *contrasts*. Different contrasts can be used to test a variety of effects, which generally fall into one of the design categories described above, namely subtraction, factorial or parametric designs.

2.3.2.2 Statistical parametric mapping and regionally specific effects

The significance of each contrast of the design matrix is assessed using statistical parametric mapping (SPM). SPM characterises regionally specific responses by computing a t statistic for each contrast (or difference in parameter estimates) in parallel for each and every voxel, to form a SPM(t). The SPM(t) is then converted to a Gaussian field or SPM(Z). The resulting statistical parameters are assembled into a statistical parametric map, in a standard anatomical space (Talairach & Tournoux, 1988). SPMs are brain images with voxel values that are, under the null hypothesis, distributed according to a known probability density function (usually Gaussian). 'Unlikely' excursions of the SPM are interpreted as regionally specific effects, attributable to the sensorimotor or cognitive process that has been manipulated experimentally. SPMs are the images of the statistical reliability or significance of an effect, and these regionally specific effects are shown as 'blobs' superimposed on the standard anatomical co-ordinate space.

2.3.2.3 Localisation of activations

Activation's are reported according to the location of the voxel of maximum intensity, which is given in Talairach & Tournoux co-ordinates, in which the origin (x,y,z = 0,0,0) is located at the anterior commissure, Co-ordinates are expressed in millimetres: x, distance to the right (+) or left (-) of the midsagittal plane; y, distance anterior (+) or posterior (-) to the vertical plane through the anterior commissure; z, distance above (+) or below (-) the intercommissural line.

2.3.2.4 *The General Linear Model*

The general linear model is an equation that relates the observed to the expected response variables in terms of a linear combination of expected components (explanatory variables) and some residual error. The general linear model is also referred to as 'analysis of covariance' or 'multiple regression analysis'.

The general linear model for a response variable xij, such as rCBF at voxel j=1....J is:

$Xij = G_{i1}B_{1j} + G_{i2}B_{2j} + \ldots\ldots + G_{iK}B_{Kj} + c + e_{ij}$

Where: X is the signal measured in a given voxel
i=1......n indexes the observation (e.g. scans acquired)
G is the value for each of the covariates used to fit the data
j is the total number of covariates
B are the parameter estimates of the regression for each covariate

c is a constant term

e is the error term.

X (the response/dependent variable) and G (the explanatory variable) are known. Multiple regression is used to estimate the values for B that minimise the error. The constant term c models the mean signal. The general linear model assumes the errors (e_{ij}) are independent and identically distributed normally. Linear compounds (or contrasts) can be used to assess regionally specific differences in the parameter of estimates.

The coefficients G_{ik} are explanatory variables relating to the conditions under which the observation (scan) i was made. These coefficients can be a covariate (e.g. global CBF, time etc) or dummy variables. Dummy variables take integer values to indicate the level of a factor under which the response variable (e.g. perfusion) is measured. For PET these include:

1. Conditions. The covariate is a simple vector that has value 1 for the scans acquired during one condition and 0 for all the other conditions. This is repeated for all the conditions.
2. Subject effects. This covariate is modelled in the form of a vector with ones for all scans from one subject, and zeros for scans for all other subjects.
3. Global signal (blood flow).
4. Other variables, such as reaction time, movement frequency etc. can be included in the model if they might contribute to the signal measured.

In fMRI the models are more complicated. The fMRI experiment in chapter 6 of this thesis employed a blocked design (in which a stimulus repeated for a block of say 30 seconds).

5. The covariate for a single condition is an on-off boxcar that has the value 1 for all the scans corresponding to one block when stimuli are presented and 0 everywhere else.
6. This boxcar function is temporally smoothed to take into account the autocorrelation of the fMRI signal. That is the signal measured in consecutive scans is not independent because the hemodynamic response is slow in respect to the data acquisition (10-15 secs versus 3-4 secs). This violates the assumption of independence of error in the general linear model to be violated.

To deal with this, the degrees of freedom in the t-statistic is recalculated to represent an uncorrelated set of observations.

7. Low frequencies in the signal measured can be modelled.

The data are then modelled in order to partition the observed neurophysiological responses into components of interest, confounds of no interest and an error term. This partitioning is achieved using the general linear model to estimate the components in terms of the parameter estimates associated with the design matrix. The analysis of regionally specific effects uses the general linear model to assess the contribution or differences among parameter estimates (specified by a contrast) in a univariate sense, by referring to the error variance. This assessment is in terms of a F or t value (a SPM(F) or SPM(t)) for each and every voxel. The SPM(t) is then transformed into a SPM(Z).

2.3.2.5 Statistical inference

A single P value obtains that compares the variance-covariance accounted for by effects of interest relative to error. If an anatomically constrained hypothesis about the effects in a particular brain region was made a priori, then the Z value in that region in the SPM(Z) can be used to test the hypothesis. With an anatomically open hypothesis (a null hypothesis that there is no effect anywhere in the brain), a correction for multiple non-independent comparisons is required. A straightforward correction procedure would be to divide each P value by the number of tests performed (a Bonferroni correction). However this would be much too conservative because the data are not independent due to having been smoothed. This is accounted for by treating the SPMs as realisations of Gaussian random fields. The general principle is that a 3-D image can be described as a field of elements of a given size (the voxel size) and an overall smoothness (smoothness of the residual error). The inferences that obtain are based on the probability of obtaining c or more clusters of volume k or more voxels above a threshold of u in the volume analysed (usually the whole brain). In some cases there is a regional specific hypothesis of where activation will occur. In this case it is not necessary to correct for the whole brain. Instead a *small volume correction* is used to assign corrected P values.

3 CHAPTER 3: HOW THE BRAIN DISTINGUISHES BETWEEN SELF- AND EXTERNALLY PRODUCED AUDITORY STIMULI

3.1 Introduction

In the introduction of this thesis it was proposed that the ability to distinguish the source of sensory signals permits the monitoring of ongoing actions and provides information about new environmental events. The experiments described in this and subsequent chapters explore how such a mechanism is implemented in the human brain. Sensory events that occur as a consequence of our own actions have the property of predictability in time, and usually in space. However the predictability of sensory stimuli is a more general phenomenon, as humans can reliably predict stimuli unrelated to their own actions if those stimuli occur in a regular spatiotemporal pattern. The sensory consequences of self-generated actions cannot therefore be recognised by their predictability alone, and additional information is required. In summary, sensory events can vary in at least two different ways: their predictability, and whether they occur as a consequence of self-generated actions. The latter class of sensory events are predictable events occurring *in the context of* self-generated actions.

It has been argued that self-monitoring mechanisms enable us to distinguish between sensory events produced by our own actions and sensory events caused by external agents. Most research on this issue has investigated corollary discharge during eye movements. The superior colliculus has been found to be involved in corollary discharge in several animal species (e.g. Guthrie *et al.*, 1983; Richmond & Wurtz, 1980; Roucoux & Crommelinck, 1976; Strasschill & Hoffman, 1974) and in humans (Paus *et al.*, 1995). However, whether the superior colliculus is also involved in the processing of self-produced auditory stimuli is unknown.

There have also been several studies investigating this type of phenomenon in the auditory domain. Neurons in the superior temporal cortex of squirrel monkeys respond to the vocalisations of other monkeys, but do not respond when the monkey itself vocalises (Muller-Preuss, 1978). Existing evidence in human subjects suggests that auditory stimuli are also processed differently depending on whether they are a consequence of self-generated actions (Shafer and Marcus,1973; Shafer *et al.,* 1981). Shafer & Marcus (1973) showed that cortical event-related potentials (ERPs) evoked by self-produced tones (produced by the subject pressing a button) have significantly smaller amplitudes and faster component latencies than those produced externally (occurring without any button presses made by the subject).

However in a subsequent study, Shafer and colleagues showed that the attenuation of ERP amplitude may be due to foreknowledge of stimulus timing in the self-stimulation case, rather than being a direct consequence of the willed action. Externally produced predictable (regular) tones modulated the ERPs in the same way as self-produced tones (Shafer *et al.,* 1981). The authors therefore argued that the difference between self-produced and externally produced tones was primarily a function of stimulus predictability. They claimed their results demonstrated that "knowledge of stimulus timing, however mediated," was the critical factor in the attenuation of brain activity associated with self-stimulation (Shafer *et al.,* 1981, p.9). This is inconsistent with the theoretical approach to self-monitoring outlined in the introduction of this thesis, which posits that being self-generated should affect the way in which the tones are processed quite independently of their predictability in time. In neither of their experiments did Shafer and colleagues explicitly test the hypothesis that stimulus predictability is modulated by self-generated action. In other words, the design of their experiment was not factorial - the authors did not explicitly investigate whether there was an interaction between stimulus predictability and self-generated action (see Methods chapter).

This experiment sought to address these issues by studying how stimulus predictability relates to self-generated actions using functional imaging with $H_2{}^{15}O$ PET. By employing a factorial design two independent manipulations were applied: the predictability of an auditory stimulus and whether or not a self-generated action occurred. There were four conditions: self-generated auditory stimulation; self-generated movement unrelated to auditory stimulation; externally generated predictable (regular) auditory stimulation; and externally generated unpredictable (irregular) auditory stimulation (**Figure 3-1**). These independent manipulations allow the separate characterisation of the effects of predictability and the effects of willed (self-generated) action, and a formal test of whether these two factors interact. The interaction term represents the way in which self-generated movement modulates the effects of stimulus predictability, independent of the activations produced by movement or hearing a predictable stimulus *per se.* Analysis of the imaging data resulted in the creation of statistical parametric maps reflecting the two main effects, self-generated movement and stimulus predictability, and the interaction between these two factors (see Methods section for details).

Many studies have investigated the neural effects of unpredictable, 'novel' stimuli. Several studies using functional imaging and electrophysiological techniques have implicated the temporal lobe in responses to stimuli that are novel in a spatial, object-related or semantic sense (Knight *et al.*, 1989; Ebmeier *et al.*, 1995; Holdstock & Rugg, 1995; Squire *et al.*, 1992; Tulving *et al.*, 1994; Tulving & Kroll, 1995; Tulving *et al.*, 1996). The stimuli used in the present study could be considered as 'temporally novel' i.e. familiar stimuli that occur at unpredictable intervals in time. One of the experimental main effects in the current study models brain responses to unpredictable relative to predictable tones. This main effect, therefore, characterises brain responses to 'temporal novelty'. Whether temporal novelty is associated with activity in similar brain regions to those associated with other types of novelty is unknown.

It was predicted that the comparison of conditions where the auditory stimuli differed in their predictability would characterise areas that give rise to the changes in evoked potentials observed by Shafer and colleagues. However it was additionally expected that there would be areas in which the activity related to stimulus predictability would be modulated by self-generated actions (i.e. when the tones were self-generated). Observation of such effects would suggest that attenuation of self-generated tones is not simply a consequence of predictability, contrary to the proposals of Shafer and colleagues. Areas showing such an effect may be involved in the self-monitoring process.

3.2 Method

3.2.1 Subjects

Six normal right-handed male volunteers (mean age 31.5 years) gave informed consent for the study, which was approved by the National Hospital for Neurology and Neurosurgery Ethics Committee. Permission to administer radioactive substances was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) U.K.

3.2.2 Experimental Design

There were four conditions using a within-subject factorial design (see **Figure 3-1**), with three repetitions of each condition per subject. Within each scan the subject listened to simple auditory tones played through earphones. Tones were identical in pitch and duration throughout the experiment. There were two experimentally manipulated variables: whether the tones were predictable, and whether the subjects were required to make self-generated movements. Movements, in the form of button presses, were always made with the thumb of the right hand. In all conditions, subjects were instructed to listen to the tones. Subjects were given clear instructions about the nature of each condition.

Figure 3-1

	Predictable auditory stimulation	**Unpredictable auditory stimulation**
Self-generated movement	A: Self-produced auditory stimuli	B: Self-produced movement, unrelated to auditory stimuli
No self-generated movement	C: Externally produced predictable auditory stimuli	D: Externally produced unpredictable auditory stimuli

2x2 factorial design used in the present study. There were four conditions – see text for details.

Condition A: self-generated tones

Subjects made irregular self-paced button presses, on average once every two seconds. A tone occurred in immediate response to each button press. No tones other than those produced by the subject occurred in this condition. Subjects were told that their button presses would immediately evoke a tone.

Condition B: self-generated movements; unpredictable tones

Subjects made irregular self-paced button presses, on average once every two seconds. Tones were presented randomly, on average once every two seconds, and the timing of tones was unrelated to the timing of the button press. Subjects were told that they would hear tones but these would bear no relation to their button pressing.

Condition C: externally produced predictable tones

No button presses were made by the subjects. Tones were played at regular 2-second intervals. Subjects were told that they would hear regular tones occurring exactly every two seconds.

Condition D: externally produced unpredictable tones

No button presses were made by the subjects. Subjects heard tones that were presented at random intervals (on average every two seconds). Subjects were told that they would hear irregular, unpredictable tones.

Subjects practised beforehand to ensure that they could reliably generate button presses irregularly and on average every two seconds. The total number of button presses was therefore not significantly different in conditions A & B. The total number of tones heard by the subject was comparable across all four conditions.

Each subject underwent 12 PET scans in a single session, comprising three repetitions of each condition, each run lasting 90 secs. There was an 8-minute interval between the start time of each run. The order of conditions was randomised and counterbalanced within and between subjects. Scanning took place in a darkened room and subjects were asked to keep their eyes closed during scanning.

3.2.3 Data acquisition

All subjects underwent both PET and structural MRI scanning on the same day. For the PET a venous cannula to administer the tracer was inserted in an antecubital fossa vein. Approximately 350 MBq of $H_2{}^{15}O$ in 3ml of normal saline were loaded into intravenous tubing and flushed into subjects over 20 secs at a rate of 10ml/min by an automatic pump. After a delay of approximately 35 secs, a rise in counts could be detected in the head that peaked 30-40 secs later (depending on individual circulation time). The interval between successive administrations was 8 mins. The data were acquired in one 90-sec frame, beginning 5 secs before the rising phase of the head curve. See Chapter 2 for details about PET scanning.

3.2.4 Statistical analysis

Functional neuroimaging analysis used the technique of statistical parametric mapping, implemented in SPM97 (Friston *et al*, 1997b). For each subject, the set of twelve PET scans was anatomically realigned and then stereotactically normalised (Friston *et al.*, 1995b) into the space of Tailarach & Tournoux (1988). The scans (72 in total) were then smoothed with a Gaussian kernel of 12mm full-width half maximum.

The analysis of functional imaging data entails the creation of statistical parametric maps that represent a statistical assessment of condition-specific effects hypothesised by the experimenter (Friston *et al.*, 1990; Friston *et al.*, 1995a). The effects of global changes in blood flow between conditions were modeled as a confound using a subject-specific ANCOVA (Friston *et al.*, 1990). Areas of significant change in brain activity were specified by appropriately weighted linear contrasts of the condition-specific effects and determined using the t-statistic on a voxel to voxel basis. The relevant SPM{t} was created for each comparison of conditions and then transformed into an SPM{Z} and thresholded at a Z-score of 3.09 ($P<0.001$ uncorrected). Clusters of activated voxels were characterised in terms of their peak height and spatial extent conjointly.

3.3 Results

Two factors were manipulated independently in this experiment: whether tones were predictable, and whether subjects made self-generated movements. Analysis of the imaging data resulted in the creation of statistical parametric maps reflecting these two main effects, and the interaction between these two factors.

3.3.1 *Main effect of self-generated movement* (**Table 3-1**)

Relative increases in rCBF (**Figures 3-2 & 3-3**)

Comparison of the two conditions in which the subjects made button presses with the two in which no movements were made [(A+B)-(C+D)] gives a measure of changes attributable to willed action. Activations (at a level of $P<0.05$ corrected) were seen in anterior supplementary motor area (SMA) bilaterally, right dorso-lateral pre-frontal cortex (DLPFC; BA 9 and 10), left anterior cingulate (BA 24), right inferior and anterior parietal cortex (BA 40), bilateral insular cortex, the right precuneus (BA 7), right superior temporo-parietal border (BA 22), the putamen and thalamus on the left, and the cerebellum bilaterally.

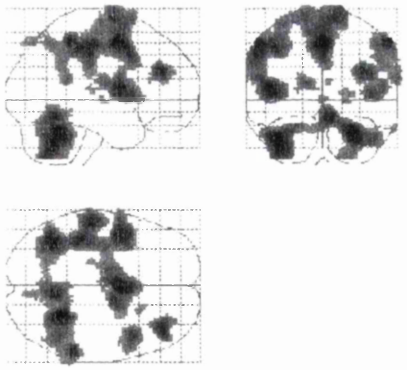
Relative decreases in rCBF (**Figure 3-4 & 3-5**)

Relative deactivations, where activity was greater in the conditions where no movement occurred [(C+D)-(A+B)] were seen in the inferior and superior temporal lobe bilaterally, and the medial pre-frontal cortex (BA 8, 9 and 10) bilaterally.

Table 3-1 Regions showing changes in activity in the comparison of the self-generated movement conditions and those without movement

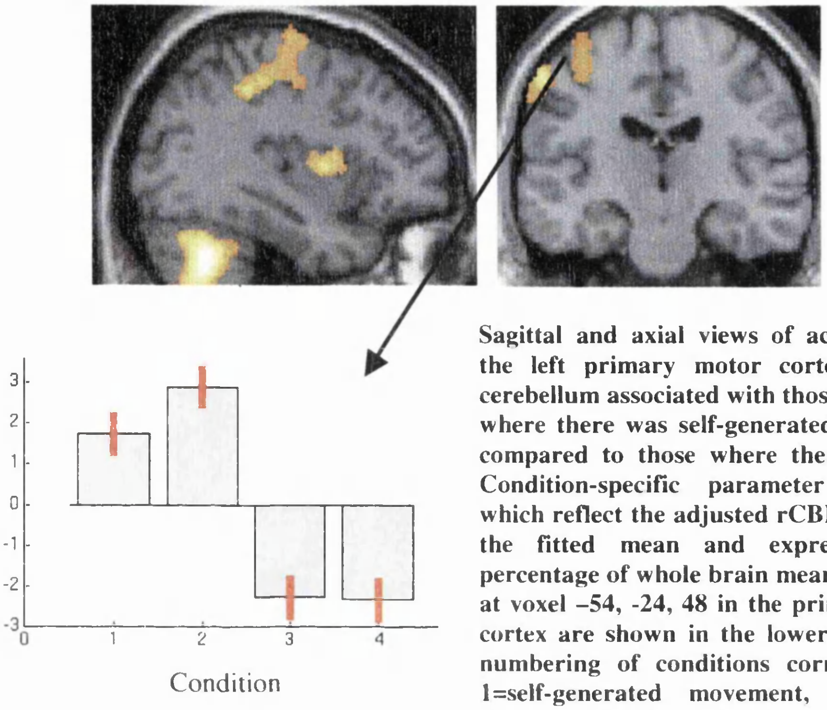
Area	Tailarach coordinates (x,y,z)	Z value
Relative increases (A+B)-(C+D)		
Cerebellum (R)	26 -52 -28	6.31
Cerebellum (L)	-40 -56 -32	5.51
SMA (BA 6)	2 0 52	5.69
Primary motor/SMC (L)	-54 -24 48	5.40
Lateral premotor (BA 6/44) (L)	-48 4 10	5.20
Insula (L)	-40 0 6	4.78
Anterior cingulate (BA 24)	2 8 42	4.75
DLPFC (BA 9/10) (R)	38 36 24	4.55
Thalamus (L)	-14 -8 14	4.32
Inferior Parietal (BA 40) (R)	58 -42 54	4.93
Precuneus (BA 7) (R)	6 -76 58	3.31
Relative Decreases (C+D)-(A+B)		
Superior Frontal (BA 10) (L)	-12 52 8	6.23
Dorsal Frontal (BA 10) (L)	-6 50 -10	6.03
Medial Frontal (BA 8) (R)	20 34 42	3.54
Superior Temporal (BA 22) (L)	-48 -62 26	6.61
Inferior Temporal (BA 21) (R)	66 -2 -18	5.05
Middle Temporal (BA 21) (R)	62 -10 -16	4.43
Fusiform gyrus (R)	40 -18 -30	4.10
Occipital gyrus (BA 19)	46 -72 20	4.94

Figure 3-2



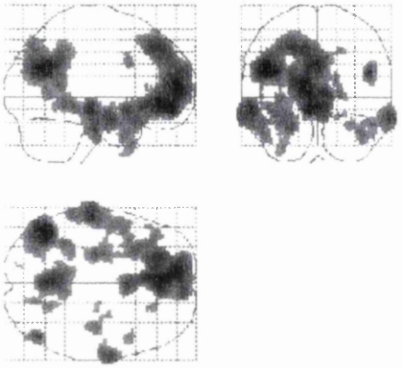
Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.001 corrected for multiple comparisons) activations from the group analysis associated with those conditions where there was self-generated movement compared to those where there was not: (A+B)--(C+D).

Figure 3-3



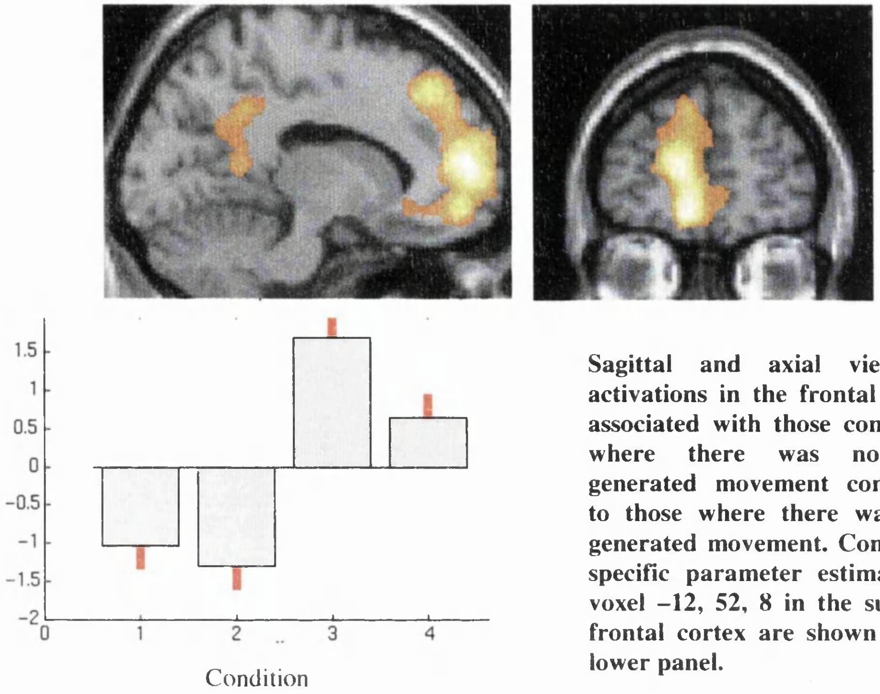
Sagittal and axial views of activations in the left primary motor cortex and the cerebellum associated with those conditions where there was self-generated movement compared to those where there was not. Condition-specific parameter estimates, which reflect the adjusted rCBF relative to the fitted mean and expressed as a percentage of whole brain mean blood flow at voxel –54, -24, 48 in the primary motor cortex are shown in the lower panel. The numbering of conditions corresponds to 1=self-generated movement, predictable tones; 2=self-generated movement, unpredictable tones; 3=no movement, predictable tones; 4=no movement, unpredictable tones.

Figure 3-4



Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.001 corrected) relative deactivations associated with those conditions where there was self-generated movement compared to those where there was not: (C+D)-(A+B).

Figure 3-5



Sagittal and axial views of activations in the frontal cortex associated with those conditions where there was no self-generated movement compared to those where there was self-generated movement. Condition-specific parameter estimates at voxel –12, 52, 8 in the superior frontal cortex are shown in the lower panel.

3.3.2 Main effect of stimulus predictability (**Table 3-2**)

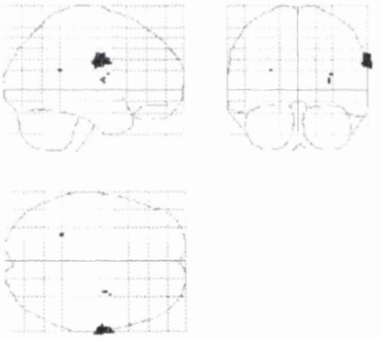
Relative increases in rCBF (**Figure 3-6**)

Comparison of the two conditions in which subjects heard predictable tones with the two conditions in which the tones were unpredictable gives a measure of changes attributable to stimulus predictability. Greater activity in the predictable compared to the unpredictable conditions [(A+C)-(B+D)] was seen in the right lateral premotor cortex (BA 6).

Table 3-2: Areas activated in the comparison of the conditions where predictable tones were heard with those where the tones were unpredictable

Area	Tailarach Coordinates (x, y, z)	Z value
Relative increases (A+C)-(B+D)		
Lateral premotor (BA 6) (R)	66 -6 34	3.46
Relative decreases (B+D)-(A+C)		
Middle Temporal (BA 21) (L)	-64 -40 -4	3.88
Superior Temporal (BA 21) (L)	-56 -38 6	3.72
Superior Temporal (BA 21) (R)	50 -56 22	3.63
Parahippocampal gyrus (R)	44 -26 -4	3.60
Parahippocampal gyrus (R)	28 -6 -32	3.52
Parietal cortex (BA 39) (R)	56 -62 12	3.48

Figure 3-6

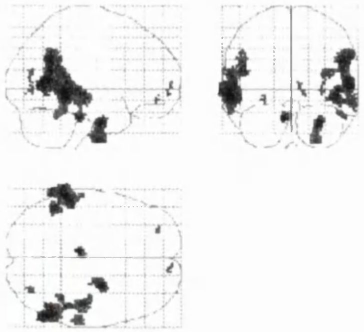


Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.001 corrected) activations associated with those conditions where predictable tones occurred compared to those where unpredictable tones occurred: (A+C)-(B+D).

Relative decreases in rCBF (**Figure 3-7 & 3-8**)

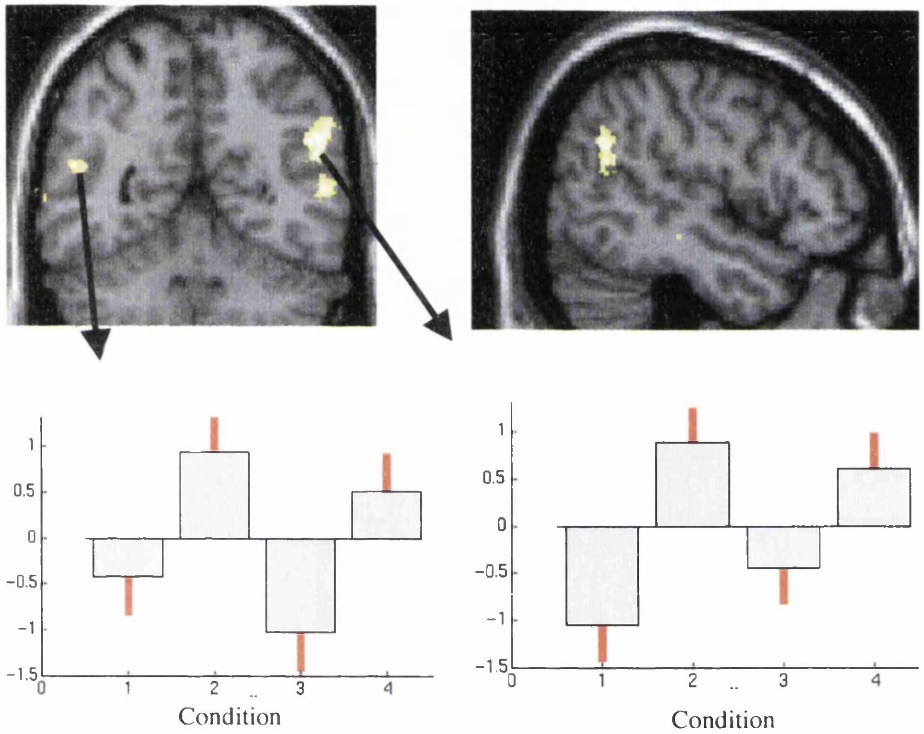
Relative deactivation - greater activity in the unpredictable compared to the predictable conditions [(B+D)-(A+C)] was seen in the inferior and superior temporal lobe (BA 21) bilaterally, the right parahippocampal gyrus and the right parietal cortex (BA 39).

Figure 3-7



Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.001 corrected) activations associated with those conditions where unpredictable tones occurred compared to those where predictable tones occurred: (B+D)-(A+C).

Figure 3-8



Sagittal and axial views of activations in the left middle temporal gyrus and the right superior temporal gyrus associated with those conditions where there unpredictable tones compared with those where only predictable tones occurred. Condition-specific parameter estimates at voxel -64,-40,-4 in the left middle temporal gyrus and 50 -56 22 in the right superior temporal gyrus are shown in the lower panel. The numbering of the conditions corresponds to 1=self-generated movement, predictable tones; 2=self-generated movement, unpredictable tones; 3=no movement, predictable tones; 4=no movement, unpredictable tones.

3.3.3 *Interaction between self-generated movements and stimulus predictability* (**Table 3-3**)

The interaction term in this factorial design represents the modulatory effect of self-generated action on the activity associated with stimulus predictability. This can be derived by the comparisons (A-B)-(C-D) and (C-D)-(A-B) using SPM.

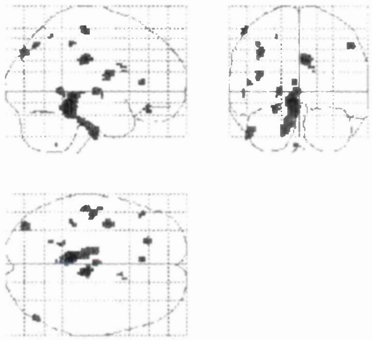
Table 3-3: Areas activated by the interaction between self-generated actions and stimulus predictability.

Area	Tailarach Coordinates (x, y, z)	Z value
Relative increases (A-B)-(C-D)		
Superior Colliculus (medial)	-4 -38 -8	3.57
Dorso-medial Thalamus (medial)	-2 -14 0	3.35
Insula (L)	-38 -2 18	3.49
Parahippocampal gyrus (L)	-18 -48 4	3.21
Posterior Cingulate (BA 31) (medial)	6 -24 30	3.18
Relative decreases (C-D)-(A-B)		
InferiorTemporal (R)	50 -32 -30	4.05

3.3.3.1 *Interaction between movement and predictability* (**Figures 3-9, 3-10 & 3-11**)

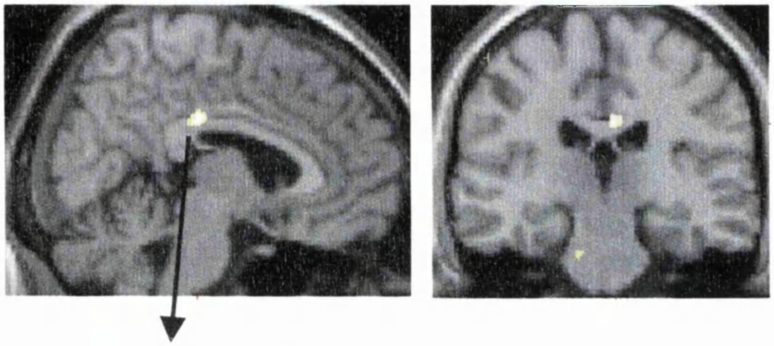
Significant activations were seen in the first of these comparisons in the superior colliculus, the dorsomedial thalamus, left insula, left parahippocampal gyrus, and medial posterior cingulate cortex (BA 31). Inspection of the adjusted rCBF values at each of these voxels confirmed that the effect of hearing tones was greater when they were self-generated than when they were externally generated but predictable, as shown in the parameter estimates in each figure.

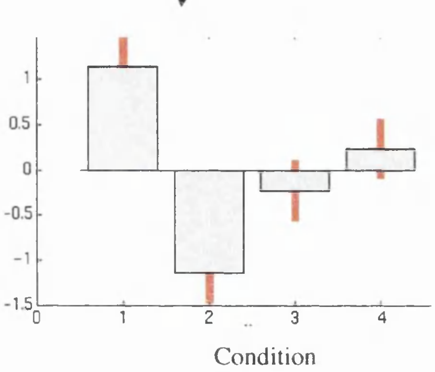
Figure 3-9



Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.001 corrected) activations associated with the interaction between the effects of self-generated movement and the predictability of tones: (A-B)-(C-D).

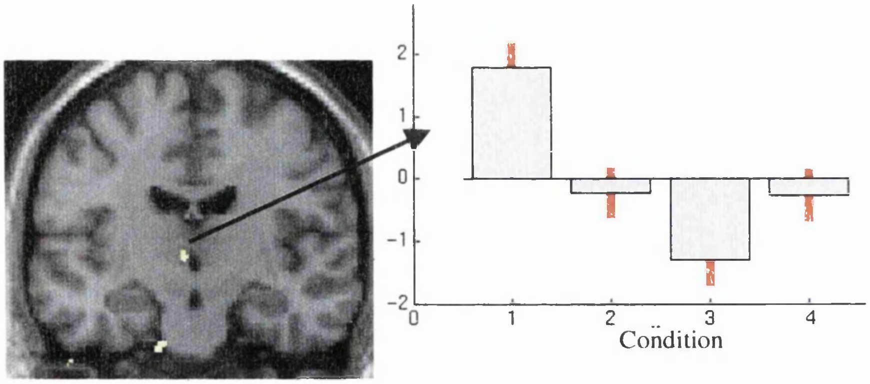
Figure 3-10





Significant activity in the posterior cingulate cortex, which was higher when tones were self-generated than when they were externally generated. Condition-specific parameter estimates at voxel 6, -24, 30 in the PCC are shown in the lower panel.

Figure 3-11

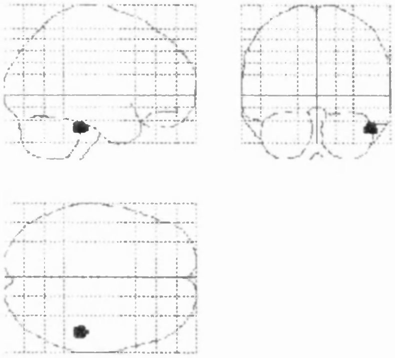


Significant ($p<0.001$) activity in the dorsomedial thalamus which was higher when tones were self-generated than when they were externally generated. Condition-specific parameter estimates at voxel -2 -14 0 in the dorsomedial thalamus are shown in the panel on the right.

3.3.3.2 Interaction between movement and unpredictability (**Figures 3-12 & 3-13**)

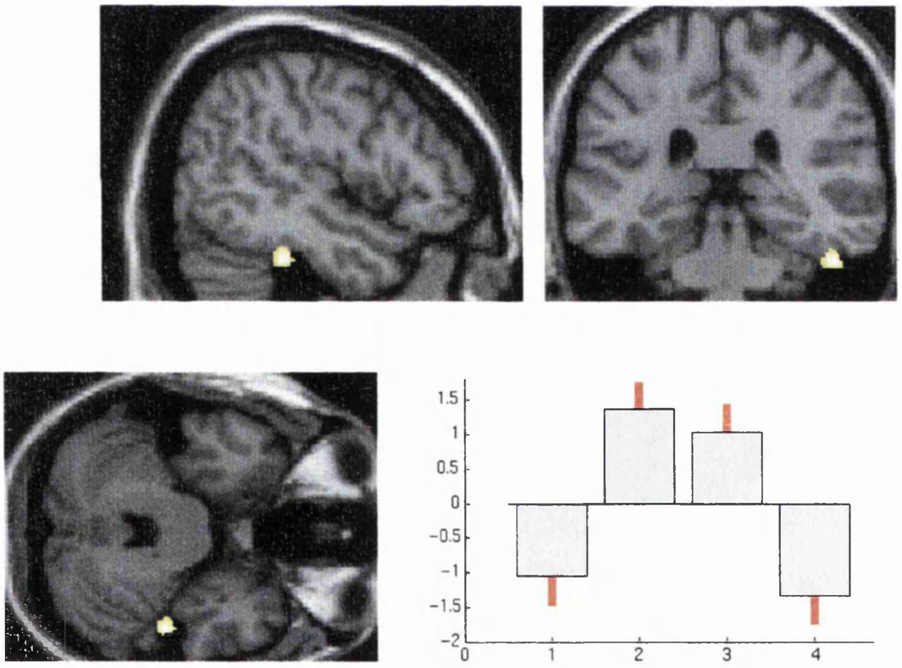
In the second comparison, significant activation was seen in the right inferior temporal lobe. Inspection of the adjusted rCBF values in this area confirms that the effect of predictable tones was smaller when self-generated movements were made.

Figure 3-12



Sagittal, axial and coronal views of statistical parametric maps showing significant (P<0.0001) activation which was higher when tones were externally generated than when they were self-generated: (C-D)-(A-B).

Figure 3-13



Significant (p<0.001) activity in the right inferior temporal lobe which was higher when tones were externally generated than when they were self-generated. Condition-specific parameter estimates at voxel 50 -32 –30 in the right inferior temporal lobe are shown in the lower panel.

3.4 Discussion

It has been argued that the recognition of the sensory consequences of our own actions involves the detection of predictable stimuli in the context of self-generated movements. This pattern of activity is identified in this experiment by those areas that show an interaction between willed action and stimulus predictability. Several areas were identified that showed such effects (**Table 3-3**), demonstrating that the effects of hearing an auditory stimulus depend not only on its predictability, but also whether that stimulus is produced by a self-generated movement. The two effects are not simply additive; there is an additional, modulatory effect of motor activity on stimulus predictability. The independent effects of self-generated action and stimulus predictability and the implications of their interaction will be discussed in relation to previous work in humans and other species.

3.4.1 Willed action

The current results show activity in a number of motor, premotor, prefrontal and cerebellar areas when subjects make self-generated finger movements. The range of activated areas is consistent with previous studies that have examined self-selection in terms of the nature of response (the volitional decision related to which of a set of possible responses to select; Deiber *et al.*, 1991; Deiber *et al.*, 1996; Frith *et al.*, 1991; Playford *et al.*, 1992). The distributed network of frontal activity observed during movements should be interpreted as being specifically associated with the internal process whereby subjects generate actions based on the will to do so. Specifically, the DLPFC has been proposed to control internally driven motor selection (Frith *et al.*, 1991; Jahanshahi *et al.*, 1995; Jahanshahi & Frith, 1998). Frith and colleagues scanned subjects while they made willed actions (either lifting a finger or speaking a word of their choice) compared with when they made routine actions (lifting a finger or speaking a word in response to an instruction). The only area that was activated more strongly by the willed actions (in both modalities) than by the externally triggered conditions was the DLPFC (Frith *et al.*, 1991). The current results replicate almost exactly those reported by Jahanshahi and colleagues in a study that examined self-selection of finger movements in which the volitional decision related to the precise timing of movements (Jahanshahi *et al.*, 1995). Jahanshahi and colleagues measured rCBF while Parkinson's patients and normal control subjects made self-initiated and externally triggered movements. For the normal control subjects, greater activation of the right DLPFC was the only area that showed a significantly higher level of rCBF during the self-initiated movements compared to the externally triggered movements. The authors concluded that "the DLPFC is activated in situations requiring non-routine decision making as in the self-initiated movements".

The relative deactivations observed in this comparison may represent either decreases of activity associated with self-generated movements, or increases in activity specifically concerned with attending to tones without making movements. One possibility is that there was a decrease in activity in the willed action conditions that represents suppression of stimulus analysis that would otherwise interfere with internal response generation. Frontal lobe activity may be suppressed when subjects are required to divide their attention between two tasks (producing self-paced movements and attending to tones).

3.4.2 Stimulus predictability

Bilateral activation of the inferior and superior temporal cortex, the right parahippocampal gyrus and right parietal cortex was associated with the presentation of unpredictable relative to predictable tones. The number of stimuli was constant across conditions, so the activity observed was specific to the predictability of the stimuli. The current findings are consistent with those of Shafer and colleagues who demonstrated that cortical potentials evoked by predictable tones have a significantly smaller amplitude than potentials evoked by unpredictable tones (Shafer & Marcus, 1973; Shafer *et al.*, 1981). It is possible that the areas activated by unpredictable auditory stimuli in this study are the source of the cortical potential differences observed by Shafer and colleagues.

The stimuli used in the present study could be considered as 'temporally novel' stimuli i.e. familiar stimuli that occur at unpredictable intervals in time. Several other studies using functional imaging and electrophysiological techniques have implicated the temporal lobe in responses to stimuli that are novel in a spatial, object-related or semantic sense (Knight *et al.*, 1989; Ebmeier *et al.*, 1995; Holdstock & Rugg, 1995; Schacter, 1990; Squire *et al.*, 1992; Tulving *et al.*, 1994; Tulving & Kroll, 1995; Tulving *et al.*, 1996). An intriguing aspect of the present findings is that 'temporal novelty' is associated with activity in similar (but not identical) brain regions to those associated with other types of novelty. These areas comprise the inferior and superior temporal lobe (BA 21) bilaterally, the right parahippocampus and right parietal cortex (BA 39). Involvement of the temporal lobe and hippocampus in novelty encoding has been found in several functional neuroimaging studies. Tulving and colleagues suggest that novelty detection (subserved by the right limbic system including the temporal lobes and hippocampus) plays a critical role in the long-term storage of information (the 'novelty/encoding hypothesis'; Tulving *et al.,* 1994; Tulving & Kroll, 1995; Tulving *et al.,* 1996).

Hearing temporally unpredictable tones in the present study activated regions close to those reported in the aforementioned novelty studies, but the activity observed in the current study was bilateral, and the activated regions were inferior to those reported by Tulving *et al.* (1996). This suggests that the change in activity observed is not in the same location as the 'novelty circuit' described by Tulving and colleagues, and hence likely to represent a distinct process. This difference in areas activated in studies by Tulving and colleagues and the present study might be due to the difference in stimuli used: the novel stimuli used by Tulving were generally semantic (words) or spatial (objects), whereas in the present study they were temporal (tones).

In ERP studies, the P300 is a positive deflection that occurs 200-600 msecs after novel, non-target (unpredictable) stimuli in oddball tasks. Oddball tasks involve the presentation of rare targets amongst more frequently occurring non-targets (Ebmeier *et al*, 1995; Holdstock & Rugg, 1995; Knight *et al*, 1989). The authors suggest that the P300 is a necessary but not sufficient requirement for the orienting response, the automatic response to an unexpected stimulus. In a single photon emission (SPET) study, oddball tasks were associated with activity in posterior brain regions similar to those reported here (Ebmeier *et al*, 1995). The authors suggested that novel stimuli activate a "posterior sound catalogue search to identify biologically significant noises". Such oddball tasks involve spatially or semantically unpredictable stimuli. A recent study by Strange *et al.*(1999) used event-related fMRI to measure neural responses to perceptual, semantic or emotional oddball nouns. All types of oddballs activated right inferior prefrontal and bilateral posterior fusiform cortices.

In the present study the tones did not differ in quality but were presented at unpredictable time intervals. It is possible that the temporal cortex activity associated with unpredictable tones in the present study may correspond to processes reflecting the P300 and also reflect the areas of activation found in the SPET study.

Temporally unpredictable sounds are likely to carry biological significance: it is important to be able to orient towards sounds that are unexpected. It is therefore possible that the role of the temporal lobes in processing unpredictable tones is related to the updating of information about the environment (as with the P300) rather than being associated with mnemonic functions (suggested in the novelty/encoding hypothesis). Such updating of an internal model has been termed 'context updating' and 'attention orienting' (Naatanen, 1992).

3.4.3 Interaction between stimulus predictability and willed action

Areas that show an interaction between the effects of stimulus predictability and self-generated action are those where the effects of stimulus predictability are modulated by the motor activity engaged in by the subject (**Table 3-3**). It is suggested that such areas are involved in the self-monitoring process of predicting the sensory con sequences of actions. In the current results these areas include the medial posterior cingulate cortex, left insula, dorsomedial thalamus, and superior colliculus. The proposed involvement of these areas in self-monitoring is consistent with previous studies demonstrating the involvement of each area in the monitoring of various classes of self-generated action. The areas activated by stimulus predictability per se (**Table 3-2**) are distinct from the areas that show an interaction between stimulus predictability and self-generated action. This suggests that the detection of expected stimuli and the detection of the sensory consequences of self-generated actions are functionally distinct processes, and are carried out in different cortical areas.

The posterior cingulate is a good candidate for involvement in the monitoring of intentions. There are strong connections between the posterior cingulate cortex (PCC) and the anterior cingulate cortex (ACC; Pandya *et al.*, 1993), which is involved in the intention to act (Vogt *et al.*, 1992), and it is quite likely that the functions of these two divisions are coordinated. It is possible that the output of the ACC is directed and monitored by the PCC.

An important role of the ACC is in the generation of motor output: it is proposed that it provides the attention and motivation necessary to perform motor acts (Vogt *et al*, 1992). In particular the caudal regions of the ACC, below the supplementary motor area, are believed to specialise in the control of manual responses (Turken & Swick, 1999). Since the PCC was activated by predictable stimuli only in the context of self-generated actions and the ACC was activated by self-generated movements (**Table 3-1**), the PCC might monitor intentions and actions, functions associated with the ACC. In support of this speculation, neuronal activity in the PCC is associated with assessing the environment and assigning mnemonic associations to sensory input rather than the initiation of action. For example, neurons in the PCC appear to monitor the execution of eye movements (Olson & Musil, 1992). Its functions may be considered 'evaluative' rather than executive. The PCC seems to be devoid of functions related to motivation and affect that characterise the ACC. It is possible that the PCC together with the ACC act as a monitoring system, the PCC monitoring intentions and actions, functions that are associated with the ACC. This pattern of connectivity has been referred to as a feed-forward system by Van Hoesen *et al.* (1993). The results of the present study support such a suggestion: the PCC was activated by predictable stimuli in the context of self-generated actions, while the ACC was active in the movement conditions and not modulated by stimulus predictability.

Subjects had to integrate signals arising from sensorimotor areas and auditory areas when they produced tones. The insular cortex and the dorsomedial thalamus have multiple connections with several brain areas (Augustine, 1985; Vogt & Gabrial, 1993) and their functions include providing low level integration between signals from different modalities (Mesulam & Mufson, 1985; Vogt & Gabrial, 1993), a function that would be essential for their possible contribution to self-monitoring. Activation of the insular cortex was restricted to the left hemisphere. A possible explanation for this laterality is the fact that movements were always made with the right hand.

The finding that the superior colliculus was active when subjects heard self-produced tones supports and expands previous findings demonstrating its involvement in corollary discharge in several animal species (e.g. Guthrie *et al.*, 1983; Richmond & Wurtz, 1980; Roucoux & Crommelinck, 1976; Strasschill & Hoffman, 1974) and in humans (Paus *et al.*, 1995). However, while previous studies have mainly implicated the superior colliculus in processing self-produced visual stimuli, the present findings demonstrate that the superior colliculus is also involved in the processing of self-produced auditory stimuli. This is consistent with its proposed involvement in multisensory and sensorimotor integration (Sparks & Groh, 1995): the superior colliculus plays an important role in the localisation of and orienting towards visual, auditory and somatosensory targets (Jay & Sparks, 1984; Stein *et al.*, 1995). Stein *et al.* (1995) argue that information from peripherally separated senses converges in the superior colliculus, where it is synthesised in order to achieve cross-modal integration. Cross-modal integration occurs in the present study when subjects heard tones produced by motor actions. However, it is interesting that the superior colliculus was active when subjects produced tones relative to when they pressed buttons and heard unrelated tones, which would also require sensorimotor integration. This suggests that the superior colliculus is particularly involved in egocentric sensorimotor integration: the synthesis of self-generated action and sensory stimulation in sensorimotor contingencies.

The increase in right inferior temporal lobe activity associated with the processing of externally produced predictable tones relative to self-produced tones is interesting in light of a study by Muller-Preuss (1978). He found cells in the superior temporal cortex of squirrel monkeys that respond to the vocalisations of other monkeys, but do not respond when the monkey itself vocalises. This lack of response to self-generated vocalisations could result from inhibitory signals arising from components of the volitional vocalisation system. In the current study, perhaps the volitional system (which was activated by self-generated movement) inhibited inferior temporal cortex when subjects produced tones.

3.5 Conclusion

PET was used to study brain responses to predictable sensory events and to similar unpredictable sensory events. The study was designed to show how the processing of predictable sensory events is modified by the context of a causative self-generated action. Increases in activity when the tones were unpredictable were seen in the temporal lobes, the right parahippocampal gyrus and right parietal cortex, and it is suggested that these areas might be involved with processing unexpected, 'novel' stimuli. A modulation of activity associated with self-generated auditory stimuli was observed in the medial posterior cingulate cortex, left insula, dorsomedial thalamus, and superior colliculus. It is proposed that areas where activity is greater during self-produced than during externally produced tones may be involved in self-monitoring processes.

A potential criticism of this study is its lack of ecological validity. Pairing auditory stimuli with button presses is an indirect way of investigating the sensory predictions made by a forward model and such contingencies rarely occur in everyday life. The next chapter discusses an empirical investigation of a much more direct sensorimotor contingency, that is the grip-force modulation used when manipulating objects. A grip-force modulation paradigm is employed to investigate the circumstances under which accurate sensory predictions are made by the forward model.

4 CHAPTER 4: PREDICTING THE CONSEQUENCES OF OUR OWN ACTIONS: THE ROLE OF SENSORIMOTOR CONTEXT ESTIMATION

4.1 Introduction

The previous chapter described a study that investigated how the processing of predictable sensory events is modified by the context of a causative self-generated action. However, paring auditory stimuli with button presses is an indirect way of investigating the sensory predictions made by a forward model. Such indirect contingencies rarely occur in everyday life. This chapter discusses an empirical investigation of a much more direct and common sensorimotor contingency, that is the manipulation of objects with the hands.

Forward models are believed to play a fundamental role in coordination behaviour such as that used when manipulating objects. When subjects pick up an object using a precision grip, they exert sufficient grip force (normal to the surface of the object) to counteract the load force (tangential to the surface) exerted by the object to prevent the object from slipping. At the same time, subjects must avoid excessive grip forces that might result in breakage of the object or fatigue (Johansson & Cole 1992; Johansson & Cole, 1994; Johansson *et al.* 1992; Johansson & Westling 1984). When the object is held at rest, the grip force depends both on the weight of the object, that is the load force, and the coefficient of friction of its surfaces. Grip force levels can be set without somatosensory feedback, anticipating the physical properties of the object, which include the object's weight, shape, and friction at its surface (Jenmalm & Johansson 1997; Johansson & Cole 1994; Johansson & Westling 1984, 1988). Such object properties are learned during development, as indicated by children's increasing ability to adjust the grip force according to the object being manipulated (Eliasson *et al.* 1995; Forssberg *et al.* 1991, Forssberg *et al.*, 1992; Forssberg *et al.*, 1995).

When an object is moved, the load force on the fingers changes according to the acceleration of the gripped object. Without a corresponding change in grip force, the object would slip. Despite sensory feedback delays associated with the detection of the load force by the fingertips grip force is modulated simultaneously (in parallel) with load force under discrete (Johansson & Westling, 1984; Flanagan & Wing, 1993) and continuous (Flanagan & Wing, 1993; Flanagan & Wing, 1995) self-generated movement and when pulling on fixed objects (Johansson *et al*, 1992). For example, Flanagan & Wing (1993) examined grip forces and load forces during point-to-point arm movements made by subjects holding an object with a precision grip. They demonstrated that grip force is finely modulated with load force in vertical and horizontal movements performed at various rates. Despite the relatively rapid response of cutaneous afferents, the parallel scaling of the grip force to the load force cannot be explained as a reaction to peripheral feedback (Flanagan & Wing 1995; Johansson & Westling 1984) due to unavoidable feedback delays (Forssberg *et al.* 1992; Johansson & Westling 1984). A system based solely on feedback control would be ineffective for manipulative actions with frequencies above ~1 Hz, which would exclude many complex skills (Johansson & Cole 1994; Kunesch *et al.* 1989). This suggests that for self-produced movements the CNS may use the motor command, in conjunction with internal models of both the arm and the object, to anticipate the resulting load force and thereby adjust grip force appropriately (Flanagan & Wing, 1997; Wing *et al.* 1997). Such anticipatory behaviour has been attributed to the ability to predict the consequences of one's own actions (Johansson & Cole 1994; Lacquaniti *et al.* 1992; Massion 1992), a process that requires internal models of both one's own body and the external world.

Conversely, when the motion of the object is externally generated, grip force lags 60-100 ms behind load force and subjects make intermittent catch up responses in their levels of grip force (Johansson *et al*, 1992) suggesting a reactive response to the perturbation of the object (Cole & Abbs, 1988). Therefore, the timing of grip force modulation can be used to quantify the accuracy of an internal model. Lags between load and grip suggest a reactive process in which the CNS is unable to predict the load force, whereas no lag indicates an accurate internal model.

Both hands are often used together when manipulating objects. Several studies have investigated anticipatory coordination during bilateral tasks. For example, the position of a subject's arm was measured during an unloading task (Dufosse *et al.* 1985; Paulignan *et al.* 1989). When the load held by the subjects on their hand was removed with the contralateral hand, there was associated anticipatory control of the position of the load-bearing forearm that acted to minimise the effects of the perturbation. However, no corresponding anticipatory action was found when unloading was performed externally, even if it was preceded by a warning tone, or triggered by the subject themselves. Duffose *et al.* concluded that temporal cues regarding the precise time that the unloading occurred is, by itself, inadequate information for anticipation. Similarly, Johansson & Westling (1988) examined grip force responses when a small ball was dropped into a cup that was gripped by the subject. When the ball was dropped by the experimenter, a reactive grip response occurred 70-80 ms after impact. Conversely, anticipatory grip force responses occurred when the load force was self-generated (when subjects dropped the ball themselves) independent of the length of the drop. This suggests that anticipatory grip force modulation can be appropriately timed for different delay (length of drop).

To assess the generality of the predictive mechanism during self-generated movement the relationship between grip and load force when a sinusoidal load is applied to an object held in a fixed location by the right hand was examined. The first experiment was designed to test the hypothesis that provided the load force is self-generated, predictive grip force modulation will be observed. Conditions were examined in which the load force was generated by motion of either the right or left hand. When the left hand generated the motion it did so either directly on the object or indirectly by causing a robot, under joystick control, to exert the force on the object. A condition was also examined in which the sinusoidal load force was externally generated by a robot. It was predicted that grip force would lag behind load force when load force was externally produced. In contrast, it was predicted that precise predictive grip force modulation would be seen when the load force was self-produced by either hand, either directly or indirectly, via the joystick.

4.2 Experiment 1

4.2.1 Method

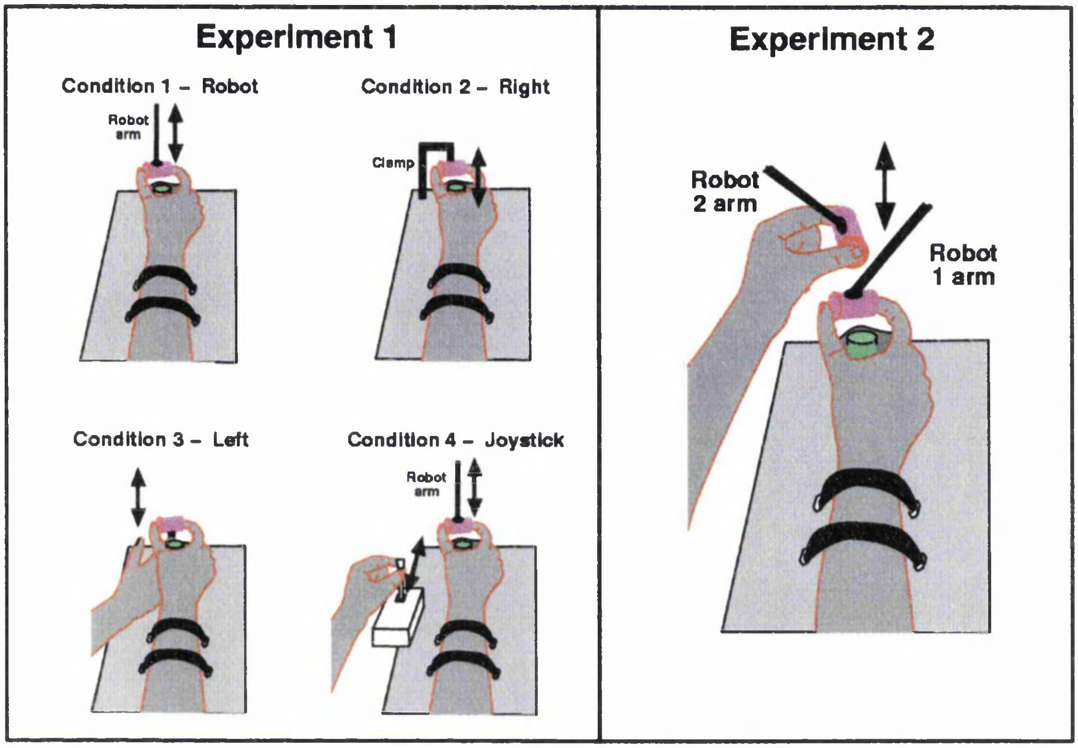
4.2.1.1 Subjects

A total of 14 right-handed subjects (mean age 24 years), who were naive to the issues involved in the research, gave their informed consent and participated in the study. Nine subjects (6 male, 3 female) participated in the first experiment. This study was approved by the National Hospital Ethics Committee.

4.2.1.2 Apparatus

Subjects sat at a table and gripped a cylindrical object (radius 1 cm and width 4 cm) with the tips of their right thumb and index finger (**Figure 4-1**). The forearm was supported on the table and stabilised using velcro straps. The hand was further stabilised by requiring subjects to grasp a vertically oriented aluminium rod (diameter 2 cm) with their three ulnar fingers. The mass of the gripped object (50 g) was centred midway between the two grip surfaces, which were covered with sandpaper (Grade No. 240). A 6-axis force transducer (Nano ATI Inc.) embedded within the object allowed the translational forces (and torques) to be recorded with an accuracy of 0.05 N including cross-talk. The forces and torques were sampled at 250 Hz by a CED 1401plus data acquisition system. The data were stored for later analysis as well as being used on-line during the experiments. Grip force was measured perpendicular to the plane of the grip surface and the load force tangential to this plane.

Figure 4-1



Schematic diagram of the apparatus used in each condition of experiment 1. In all conditions subjects held a cylindrical object in their right hand. In condition A (Robot), the object was attached to the robot, which produced the load force on the object. In condition B (self-produced; right hand), subjects were required to pull down on the object, which was fixed in a clamp, to track the target load waveform. In condition C (self-produced; left hand), subjects were required to push the object upward from underneath with their left index finger to match the target load waveform. In condition D (self-produced; joystick), the object was attached to the robot and the forces produced by the robot were determined by the position of a joystick moved by the left hand. Experiment 2: An object attached to a second robotic device was held in the left hand. The motion of the left hand determined the load force on the object in the right hand. The relationship between the force acting on the left and right objects was parametrically varied between trials. See text for details.

4.2.1.3 Procedure

In all experiments the target and actual load force acting on the right hand were displayed to the subject as a continuous scrolling trace on an oscilloscope. The target load force acted as a guide to the subject's movements. The subject was instructed to produce a load force that corresponded to the frequency and amplitude of the sinusoidal target waveform. For clarity, the load force produced by the subject was displayed on the oscilloscope below the target waveform - two horizontal lines indicated the desired load amplitude.

In conditions A and D of experiment 1 the object was attached at its midpoint to the end of a lightweight, robotic manipulator (Phantom Haptic Interface, Sensable Devices, Cambridge, MA). The robot could generate vertical forces up to 10 N.

Subjects performed trials of 14 seconds in which they were required to produce a load force that matched the target load force. The target load force was a sinusoid with offset of 3.5 N and amplitude 3 N. The target load force, therefore, varied between 0.5 N and 6.5 N, and always acted in an upwards direction on the subjects' right hand. In all conditions subjects were instructed to hold on to the object with their right hand and maintain it in a constant position. For each trial the target frequency was fixed. Six different target frequencies equally spaced between 0.5 and 3.5 Hz were each repeated 5 times in a pseudorandom order. To prevent the analysis of initial transients, 10 seconds of data were recorded after the first 4 seconds of each trial. Subjects practised each condition until they could perform the task adequately - this took between 30 and 60 seconds.

Condition A: externally produced; robot (**Figure 4-1-1**)

The object was attached to the robot, which was programmed to produce the target waveform. Subjects gripped the object with their right hand and were required to restrain the object, and the target and actual load force were displayed on the oscilloscope. In this condition the subject did not need to track the load force as this was generated automatically by the robot.

Condition B: self-produced; right hand (**Figure 4-1-2**)

Subjects gripped the object, which was fixed in a clamp, with their right hand. They were required to pull down on the object to track the target load waveform, so that the force acting on their right hand was in an upwards direction.

Condition C: self-produced; left hand (**Figure 4-1-3**)

Subjects were required to push the object upwards from underneath with their left index finger to match the target load waveform. Subjects were specifically instructed to use their right hand to restrain the object only, and to avoid using it to push down on the object to match the target waveform.

Condition 4: self-produced; joystick **(Figure 4-1-4)**

The object was attached to the robot and the forces produced by the robot were determined by the position of a low-friction joystick held in the left hand. The force generated by the robot was linearly related to the angular position of the joystick with a movement of 4 mm producing 1 N. Subjects were required to move the joystick in the sagittal plane to match the target waveform and were informed that movements of the joystick cause the force exerted on their right hand.

4.2.1.4 Data analysis

Load and grip force were filtered using a Butterworth 5th order, zero phase lag, low pass filter with a 10 Hz cut-off. To analyse the relationship between these two time series, cross-spectral analysis was performed using Welch's averaged periodogram method (window width 512 points with a 50% overlap; Matlab signal analysis toolbox).

As the time series were predominantly sinusoidal five measures at the dominant load frequency were calculated. To quantify amplitude relationships between the two signals, independent of th phase relationship, two measures were used. The *baseline gain* was taken as the ratio of the mean grip and load force (mean grip / mean load). The relative degree of modulation was quantified by the *amplitude gain* taken as the ratio between the amplitude of the grip and load force modulation.

To quantify the relative temporal relationships between the grip and load force series three measures were made. The first two, *phase* and *lag*, quantify the temporal shift required to align the two series. *Phase* is expressed in degrees and was taken to lie between -270^{O} and 90^{O} with negative values corresponding to grip lagging behind load. This split was chosen at a point where there were very few data points, based on all the data only 0.9% lay within a 45^{O} band of $+90^{O}$. The *lag* represents the same shift in ms (and should not be confused with phase lag, which is used to measure phase delays in degrees), and again a negative value indicates grip lagging behind load.

Finally, the *coherence* of the two signals was used as a measure of the variability of the phase relationship between grip and load force. Coherence values always lie between 0 and 1. If the phase difference is constant over the entire trial coherence is 1, whereas fluctuations in the phase difference results in coherence values lower than 1.

For each condition in experiment 1, the five measures were averaged across all trials and subjects, binned by frequency and plotted with standard error bars. Actual rather than target frequency of tracking was used when calculating statistics and plotting graphs.

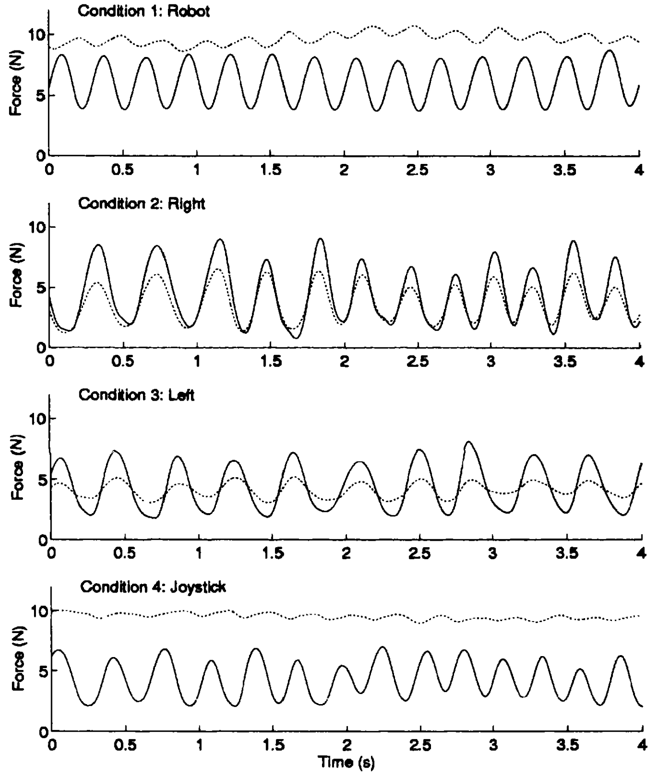
Average values across frequencies and linear regression as a function of load force frequency were used to test the influence of frequency and condition on the five measures. To test the influence of frequency on a particular measure and condition, separate linear regressions were performed for each of the nine subjects and paired t-tests performed across the slope estimates. To compare the parameters between conditions paired t-tests, by subject, were performed on these parameters. To test the mean levels across all frequencies paired t-tests were performed for each subject mean within a condition and paired t-tests between conditions.

4.2.1.5 Results of Experiment 1

After practice each subject was able to track the desired load waveform with reasonable accuracy and produced load forces that were predominately sinusoidal with narrow power spectra around their dominant frequency. The grip forces were also predominantly sinusoidal. In particular the modulation was smooth and showed little evidence of catch-up responses, which have been reported to occur to unpredictable onsets of load force (Johansson *et al*, 1992).

Typical raw data for the four conditions are shown in **Figure 4-2**. These traces show that when the load force was externally generated by the robot, the mean grip force level was high, showed low modulation and lagged behind the load force (**Figure 4-2-1**). In contrast, when the load force was self-generated by the right hand the mean grip force level was lower, showed a large degree of modulation and appeared in phase with the load force (**Figure 4-2-2**). When the left hand was used to generate the load a similar predictive modulation was seen to that of the right hand condition, but with a smaller amplitude of modulation (**Figure 4-2-3**). However, when the left hand generated the load force indirectly through the joystick, the pattern of grip force modulation was similar to that of the externally generated condition (**Figure 4-2-4**).

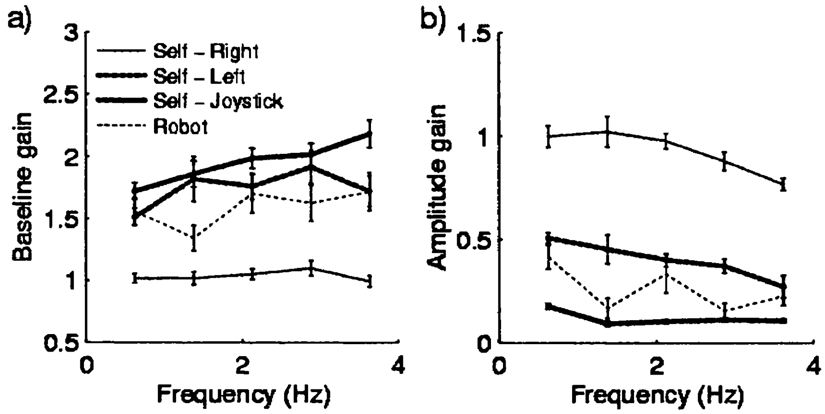
Figure 4-2



Typical example of grip force (dashed line) and load force (solid line) traces for the four conditions of Experiment 1 taken from a single subject tracking a frequency of 3.5 Hz. The data are taken from the same four-second time period in each trial and have been low pass filtered.

Analysis of the group data is shown in **Figure 4-3 & 4-4**. In all conditions subjects showed a grip force that was modulated, to some extent, with load force. As expected, when the subjects generated the load force with their right hand they showed a large degree of grip force modulation (**Figure 4-3**) and this modulation showed a small, significant ($P<0.01$) average phase advance of +10.6 ms across the frequencies tested (**Figure 4-4**). However, when the same load force was externally produced by the robot the modulation was significantly smaller ($P<0.01$) and showed a significant ($P<0.001$) average phase lag of -100.4 ms.

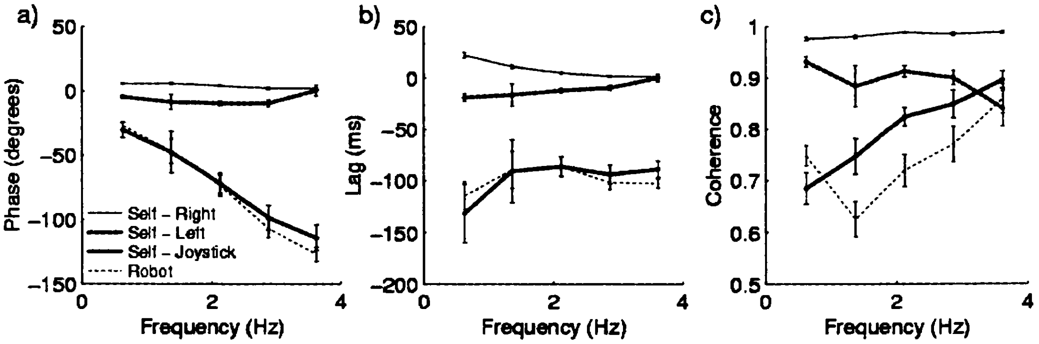
Figure 4-3



A) average baseline and b) amplitude gain of grip force modulation plotted against frequency for the four conditions of Experiment 1.

When subjects used their left hand to generate the load force directly there was a small average phase lag of -12 ms which was not significantly different from 0 (**Figure 4-4-B**). However when the left hand generated the same load force through the joystick-controlled robot, and subjects were explicitly informed of this relationship, performance was markedly different. In this condition the baseline gain, amplitude gain, phase and lag were not significantly different from these values in the externally generated condition (**Figure 4-3 & 4-4**). In particular, in the joystick condition the grip force modulation had a significant (P<0.01) phase lag of -104.2 ms with respect to load.

Figure 4-4



a) average *phase* b) *lag* and c) *coherence* between load force and grip force plotted against frequency for the four conditions of Experiment 1.

Analysis of coherence (**Figure 4-4-C**) showed that it was significantly (P<0.01) higher when the movements were self-generated by the right hand compared to the other three conditions.

4.2.1.6 Discussion of Experiment 1

The first experiment was designed to test the hypothesis that provided the load force is self-generated, predictive grip force modulation will be observed. This was not found to be true. Precise predictive grip force modulation was seen in the conditions in which the load force was generated directly by motion of either the right or left hand. In contrast, when the left hand produced the load force indirectly, via the joystick, there was no prediction: grip force significant lagged behind load force. This was similar to the condition in which the load was externally generated by the robot.

Two possible reasons were hypothesised to account for the lack of precise prediction in the *indirect (joystick)* condition when compared to the direct action of the left hand on the object. The first was that the coordinate transformation between joystick action, which was both remote to the right hand and in the sagittal direction, prevented precise prediction. Alternatively the difference in sensory feedback received by the left hand in the two conditions produced the differential results. In the *direct* condition the left hand received force feedback that was equal and opposite to that experienced by the right hand whereas in the *joystick* case the left hand received minimal force feedback.

To examine these hypotheses, grip force modulation was examined when the force feedback to the left hand was parametrically varied. This was achieved by simulating a virtual object, simulated by two robots, whose properties did not necessarily conform to normal physical laws. The left hand generated the load force on the right hand by acting through the virtual object, and using this robotic set-up the forces acting on each hand could be dissociated. The force acting on the active left hand relative to the right hand was parametrically varied. At one level of the force feedback parameter, the force feedback to each hand was equal and opposite thereby simulating a normal physical object between the hands. The hypothesis was that in order to use the motion of the left hand to generate precise predictive grip force modulation in the right hand, the hands must act through a physically realisable object.

4.3 Experiment 2 - virtual objects

4.3.1 Method

4.3.1.1 Subjects

Nine subjects (6 male, 3 female) participated in the second experiment, including four of the subjects who participated in the first experiment. The experiments were carried out one month apart.

4.3.1.2 Apparatus

The general apparatus was as in Experiment 1. As in conditions A and D of experiment 1 the object was attached at its midpoint to the end of a lightweight, robotic manipulator (Phantom Haptic Interface, Sensable Devices, Cambridge, MA). Subjects held a second object in a precision grip with the thumb and index finger of their left hand. This object was held directly above the first and was attached to a second robotic device (**Figure 4-1-Experiment 2**).

4.4

4.4.1.1 Procedure

Subjects were required to move the object held in their left hand vertically so as to produce the load force on the object held in their right hand. The load force acting on the right hand was the same for all trials.

Vertical forces at time t into the trial, were generated independently on both the right hand F^r_t and the left hand F^l_t. For all trials the relationship between movement of left hand and the force generated on the right object was simulated, by the robot, as a stiff spring between the objects. The force was given by $F^r_t = K (L_t - R_t - D)$ where L_t and R_t were the vertical positions of the left and right object respectively at time t, K was a fixed spring constant of 20 N cm^{-1} and D was the initial vertical distance between the objects at the start of the trial. Hence, at the start of each trial there was no force acting on the right hand (as $L_0 - R_0 - D=0$) and an upward movement of the left hand caused an upward force on the object in the right hand. The force acting on the left hand depended on a feedback gain parameter g which could be varied between trials such that $F^{l}_{t} = -gK(L_t - R_t - D)$. When g=0 the left hand received no force feedback, whereas when g=1 the force feedback to the left hand was equal and opposite to that exerted on the right. These conditions are similar, in terms of haptic feedback to the left hand, to conditions D (*self-produced; joystick*) and C (*self-produced; left hand*) of Experiment 1, respectively.

For each block of trials the value of the feedback gain parameter g was fixed at one of 7 values equally spaced between 0 and 1.5. Within each block for gains of 0 and 1 six different target frequencies equally spaced between 0.5 and 3.5 Hz were used as in experiment 1. For each of the other gain values (0.25, 0.5, 0.75, 1.25 and 1.5) three different target frequencies (1.1, 2.3 and 3.5 Hz) were used. Each frequency was presented for 10 seconds and repeated 5 times in a pseudorandom order, and data were recorded after 2 seconds in each trial. Subjects were told that the load on the object held in their right hand was produced by the movements of their left hand. They were instructed to move the object in their left hand so as to match the target waveform whose amplitude was 2 N with offset 2.3 N. The load force therefore varied between 0.3 N and 4.3 N, and was always in an upwards direction. Subjects practised the task until they could perform it adequately - this took between 1 and 2 minutes.

4.4.1.2 Data analysis

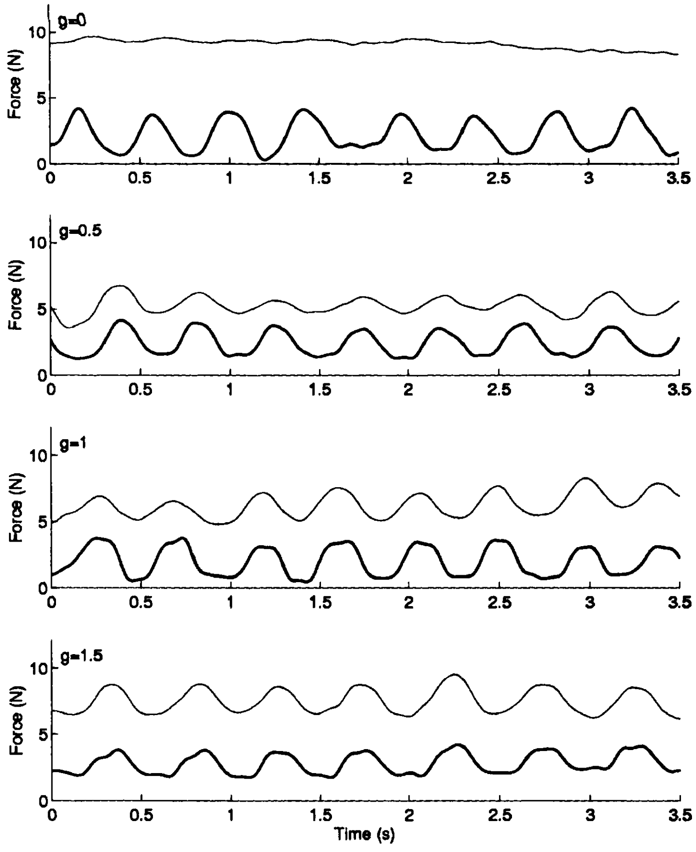
The data analysis was the same as that used in Experiment 1. The same five sinusoidal measures (baseline gain, amplitude gain, phase, lag and coherence) were calculated. For the g=0 and g=1 conditions, the five measures were averaged across all trials and subjects, binned by frequency and plotted with standard error bars. Actual rather than target frequency of tracking was used when calculating statistics and plotting graphs

A repeated measures ANOVA was performed on each measure as a function of the gain, *g* (as categorical variables). A polynomial contrast was used to determine whether there were significant linear, quadratic or higher order trends across the gains, *g*. The highest order polynomial for which this was true was used to fit the ensemble data for individual and combined frequencies. For all plots for which a quadratic regression significantly fitted the data the *g* value at which the quadratic peaked was calculated and t-tests were performed to test whether this point differed significantly from 1 across the subjects. The value of the peak of the quadratic was also calculated.

4.4.1.3 Results of Experiment 2

Typical raw data for the four of the levels of feedback gains, *g* to the left hand, are shown in **Figure 4-5.** This shows that modulation of grip force grip was small for *g*=0 and increased as the feedback gain to the left hand increased.

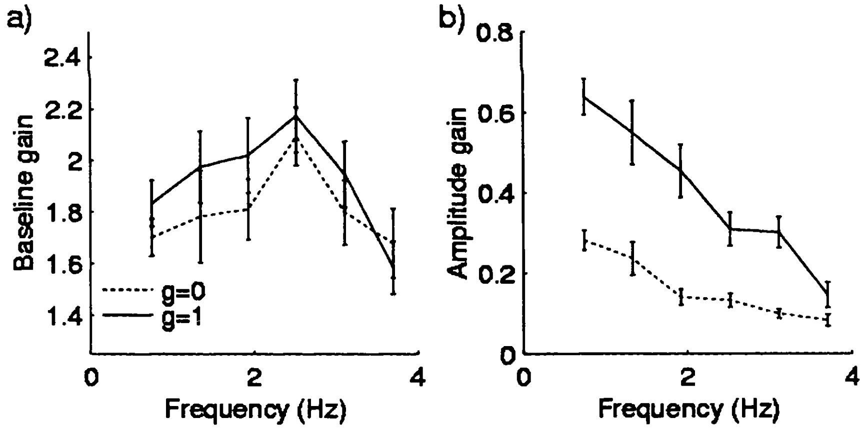
Figure 4-5



Typical example of grip force (thin line) and load force (thick line) traces for four feedback gains, *g*, of Experiment 2 taken from a single subject tracking a frequency of 2.3 Hz. The data are taken from the same time period in each trial and have been low pass filtered.

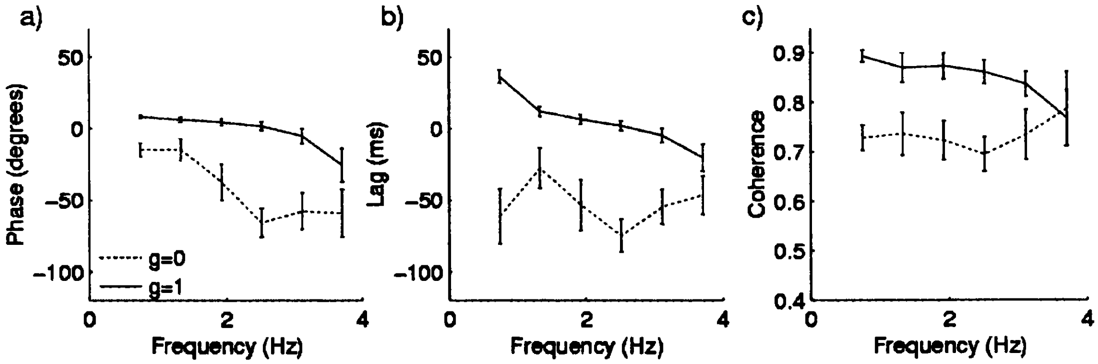
Analysis of the group data for feedback parameter *g*=1 (solid lines) and *g*=0 (dashed line) are shown in **Figure 4-6 & 4-7**. At a value *g*=1 the effect should be qualitatively similar to the *self-produced left hand direct* condition of experiment 1 as the robots simulate a single object between the two hands. Correspondingly, when *g*=0 the effect should be similar to left hand operating indirectly through the joystick. When the feedback gain parameter *g* was 1 the average phase advance was significantly higher (P<0.01) at +11.4 ms compared to a lag of -57.7 ms when *g*=0. The grip force modulation amplitude was significantly greater for *g*=1 compared to *g*=0 (P<0.05; see **Figure 4-7-b**). Modulation of grip decreased in amplitude with increasing frequencies in both conditions (P<0.05). Coherence (**Figure 4-7**-c) was significantly higher when *g*=1 compared to *g*=0 (P<0.01). The differences between the *g*=0 and *g*=1 conditions are therefore qualitatively similar to the joystick and left-hand conditions of experiment 1.

Figure 4-6



a) baseline gain and b) amplitude gain of grip force modulation against frequency at feedback gains *g*=1 (solid lines) and *g*=0 (dashed lines).

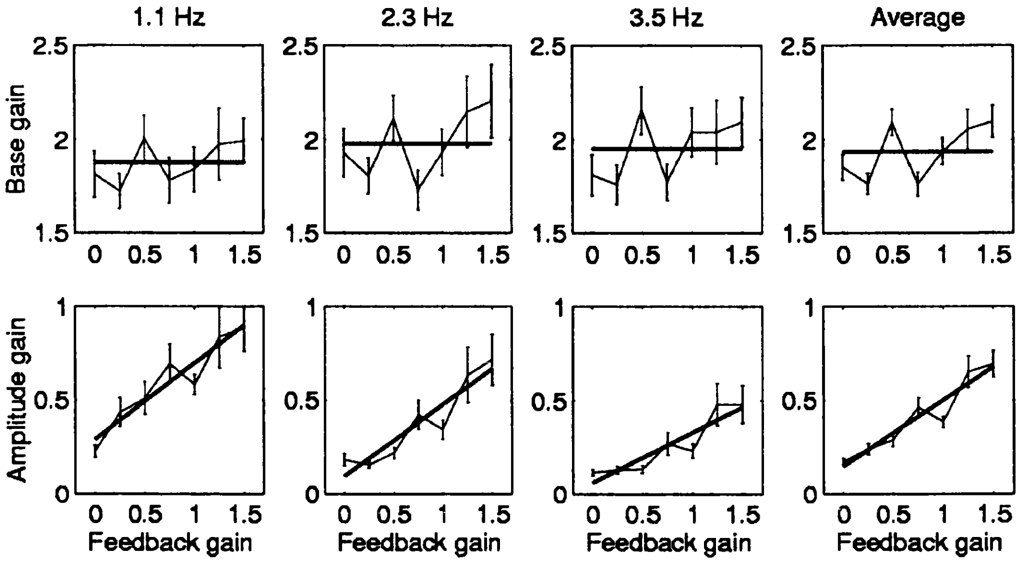
Figure 4-7



Phase, lag and coherence at different frequencies at feedback gains *g*=1 (solid lines) and *g*=0 (dashed lines). a) average phase b) average lag c) average coherence between load force and grip force.

Figure 4-8 & 4-9 compare the grip force responses to different frequency load forces applied to the object by the left hand via a second robot with different levels of force feedback gain (*g* varied between 0 and 1.5). The ANOVA performed on the measures as a function of gain showed a significant difference between the 7 levels of gain for lag ($P<0.01$), phase ($P<0.05$), coherence ($P<0.01$) and amplitude gain ($P<0.05$). There was no significant difference between the 7 levels of gain for baseline gain ($P=0.669$). A polynomial contrast on the gains showed a significant fit for the quadratic term for lag ($P<0.01$), phase ($P<0.01$) and coherence ($P<0.05$), and for the linear term for amplitude gain ($P<0.05$). A comparison of the extreme values of gain ($g=0$ and $g=1.5$) with $g=1$ showed a significant difference for phase ($P<0.01$ for $g=0$; $P<0.05$ for $g=1.5$), lag ($P<0.01$ for $g=0$; $P<0.05$ for $g=1.5$) and coherence ($P<0.01$ for $g=0$; $P<0.05$ for $g=1.5$). For the combined frequencies, therefore, the highest significant term for the amplitude gain was linear and for the phase, lag and coherence it was quadratic. For baseline gain a linear fit was not significant.

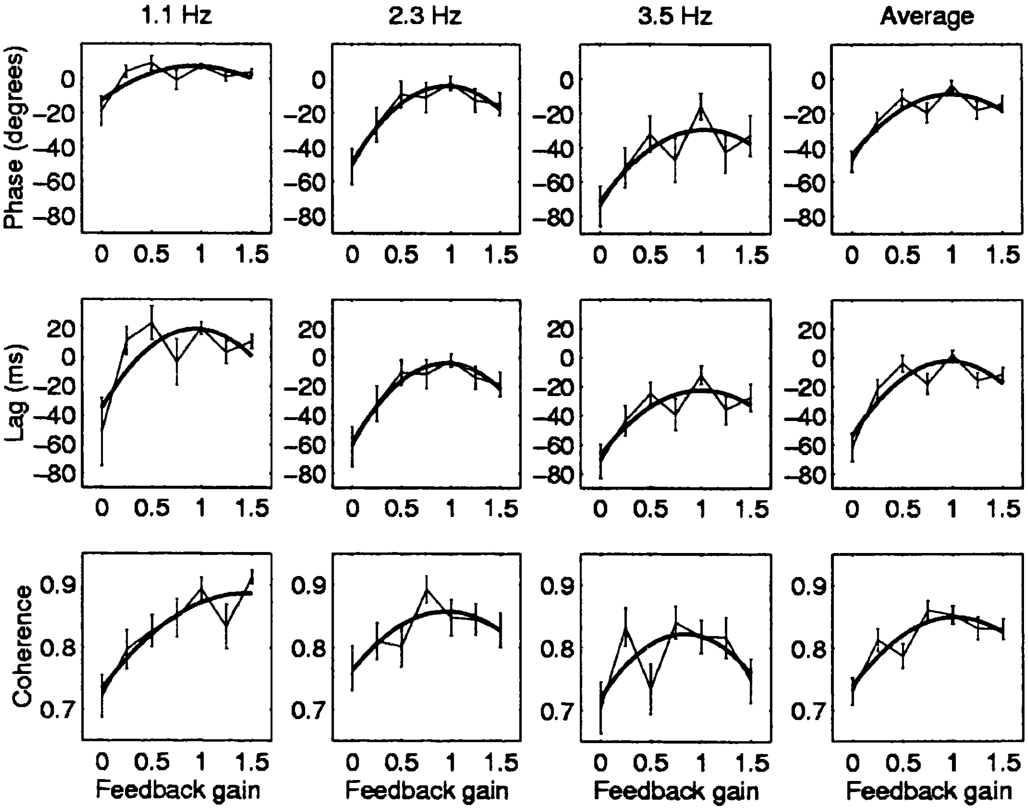
Figure 4-8



Baseline gain and amplitude gain of grip force modulation at different frequencies with different force feedback coupling, *g*, between the two robots held in either hand. Graphs show the baseline gain (solid line shows the mean) and the amplitude of grip force modulation (solid line shows linear regression fit) at different feedback gains at 3 different frequencies and the average over all six frequencies.

An analysis of the location of the maxima of the quadratic fits for lag and phase (**Figure 4-9**) showed that they occurred at a feedback gain value not significantly different from 1 at each frequency. For lag this value was 1.10±0.22 (standard error) at 1.1 Hz; 0.92±0.07 at 2.3 Hz; 0.87±0.11 at 3.5 Hz; and on average (combining all 6 frequencies) 1.05±0.09. The mean lag value at which the peaks occurred was -0.3±12.0 ms. Therefore with feedback gains less or more than g=1, grip significantly lagged behind load. Similarly, coherence significantly decreased at feedback gains of less or more than one. The mean location of the peak (combining frequencies) in coherence was at a feedback gain of 0.81±0.06. As the feedback gain g increased the amplitude of modulation increased significantly (P<0.05) for the ensemble data.

Figure 4-9



Phase, lag and coherence at different frequencies with different force feedback coupling between the two robots held in either hand. Graphs show phase, lag and coherence at different feedback gains at 3 different frequencies and the average over all six frequencies). The solid line shows the quadratic fits to the data.

4.5 Discussion

While previous studies have demonstrated predictive modulation of grip force to self-generated load forces, the results of the current experiment show that this self-generation in itself is not sufficient to produce precise predictive grip force modulation. Precise prediction was only seen when the left hand experienced force feedback that was equal and opposite to the force exerted on the right hand, a situation consistent with the presence of a real rigid object between the hands. However, when the force feedback to the left hand was either greater or less than the force experienced by the right hand, grip lagged behind load force.

In order to prevent a gripped object from slipping during movement without maintaining an excess safety margin, grip force must change with load force. The present results demonstrate that when load force is generated by the hand holding the object, grip force is modulated in parallel with load force, in line with previous findings (Johansson & Westling, 1984; Johansson *et al*, 1992; Flanagan & Wing, 1995; Flanagan & Wing, 1997a). Grip force anticipated load force even at frequencies as high as 3.5 Hz (**Figure 4-4**) and, as demonstrated by the high coherence (**Figure 4-4-C**), the phase relationship showed minimal variability within each trial. The large amplitude and parallel nature of the grip force modulation allows a small safety margin to be achieved while preventing the object from slipping and may be important in economising muscular effort (Johansson & Westling, 1984). However, when the load force was externally produced by the robot, the grip force modulation lagged about 100 ms behind load force. This lag is similar to that seen in response to unpredictable load force perturbations (Cole & Abbs, 1988; Johannson *et al*, 1992; Johannson *et al*, 1992), showing that even for a repetitive sinusoidal movement of the object there is no predictive modulation if the movement is externally produced. If, in the presence of such a large delay, the amplitude of modulation and the baseline force were similar to that in the self-produced condition, the object would slip. Therefore, when little grip force prediction is seen there is a concomitant increase in the baseline grip force and a reduction in grip force modulation amplitude (**Figure 4-3**-Robot). In addition, the phase relationship, as indicated by the low coherence, is more variable in this externally produced condition compared to the self-generated condition.

When the load force was generated by the left hand pushing directly on the object, grip force modulation was predictive but of a smaller amplitude than when the load force was generated by the right hand. This parallel modulation suggests that the motor command sent to the left hand can be used to produce precise predictive modulation by the right hand. The phase relationship was strikingly similar to the relationship when the right hand produced the load. In contrast, when the load force was indirectly generated by the left hand controlling the robot via a low-friction joystick, grip force lagged significantly behind load force by over 100 ms - this is comparable to the *externally produced* condition. Therefore, although the load force was self-generated by the left hand in both the *direct* and *indirect (joystick)* conditions only the former elicited precise predictive grip force modulation. The present study extends this finding by examining the reasons behind such a discrepancy in anticipatory responses.

Previous studies have shown anticipatory responses to discrete events such as loading the limb by dropping a ball (Johannson & Westling, 1988; Lacquaniti *et al*, 1992) or unloading the limb using the opposite hand (Lum *et al*, 1992). For example, when subjects are required to remove an object held in one hand with the other, anticipatory deactivation of the forearm muscles occurs prior to the unloading and the position of the loaded hand, therefore, remains unchanged (for a review see Massion, 1992). However, when the subjects were required to press a button which caused the load to be removed from their other hand, no anticipatory behaviour was seen (Dufosse *et al*, 1985). These two paradigms can be thought of as analogous to the *self-produced left hand* and *joystick* conditions of the current study.

Two possible reasons were hypothesised to account for the lack of precise prediction in the *indirect (joystick)* condition when compared to the direct action of the left hand on the object. The first was that the coordinate transformation between joystick action, which was both remote to the right hand and in the sagittal direction, prevented precise prediction. Alternatively the difference in sensory feedback received by the left hand in the two conditions might have produced the differential results. In the *direct* condition the left hand received force feedback that was equal and opposite to that experienced by the right hand whereas in the *joystick* case the left hand received minimal force feedback.

To investigate this issue grip force modulation was examined when the force feedback to the left hand was parametrically varied. This was achieved by simulating a virtual object between the two hands, whose properties did not necessarily conform to normal physical laws. The first hypothesis was rejected as precise prediction was not observed in the condition $g=0$ even though both hands acted in the same coordinate system. However, it was found that the lag between load and grip force was minimal (0.3 ms) when the feedback gain to the left hand simulated a normal physical object ($g=1$). Furthermore, the lag increased in a systematic way as the virtual object deviated further from normal physical laws, supporting the second hypothesis.

Burstedt *et al.* (1997) have recently demonstrated that grip force is modulated in parallel with load force when subjects lifted an object between the index finger of their left and right hands, and cooperatively with another subject using the right index finger. Performance was similar in both these conditions, and was comparable to that when subjects lifted the object between the thumb and index finger of their right hand. The authors suggest that this result demonstrates that the forward model can be adjusted to account for a variety of situations. The results of the current study show that the context of the movement, as coded by the haptic feedback to each hand, critically modulates the nature of the grip force response.

The present results suggest that predictive mechanisms rely on there being sensory feedback to the two hands that obey the physical laws normally encountered in objects. Knowledge of the mechanical properties of objects is probably learned by handling and manipulating objects (Gordon *et al*, 1993) as is demonstrated by prediction improving throughout development (Eliasson *et al*, 1995) suggesting a continual refinement of the internal models.

4.5.1 Multiple internal forward models

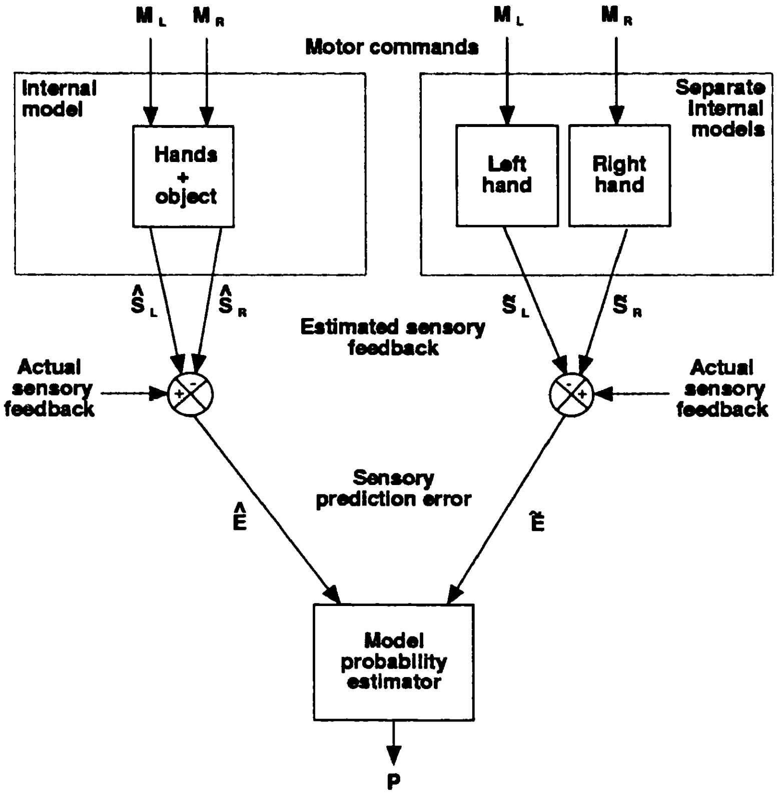
In the introduction of this thesis it was argued that forward models capture the causal relationship between actions and their sensory outcome. Such a sensory outcome is the load force of an object manipulated by self-produced movements. Here it is suggested that a forward model is used to predict the sensory consequences of the motion of one hand. Based on this prediction an appropriate anticipatory grip force in the other hand can be generated, despite sensory feedback delays associated with the detection of load force by the fingertips (Johansson & Westling 1984).

The present results can be interpreted within a computational framework of multiple forward models (Wolpert & Kawato 1998; Wolpert *et al.* 1998). One problem the CNS faces when both hands are in contact with objects is determining whether the hands are manipulating a single object or are acting on separate objects in order to select the appropriate control strategy. Only when the hands are manipulating a single object should the motor commands to each limb be used in a predictive manner to modulate the grip force of the other hand. For example, when holding a cup in one hand and a saucer in the other there is no reason why one hand should take account of what the other is doing in terms of grip force modulation. However, if the cup and saucer were rigidly joined then it would be desirable for each hand to take account of the other hand's actions.

One computational solution to this problem is to use multiple internal forward models each predicting the sensory consequences of acting within different sensorimotor contexts (**Figure 4-10**). Firstly, sensory contextual cues are used to determine which module to use before movement initiation. For grip force, contextual cues include object weight and shape as judged visually (Jenmalm & Johansson 1997; Johansson & Westling 1988), experience from previous lifts (Gordon *et al.* 1993), and perceived friction from the object's surface (Johansson & Westling 1984, 1987). Once the movement of an object is initiated the forward model's predictions are used. As each forward model captures a distinct dynamic behaviour of the limb or object, their prediction errors can be used during movement to determine in which context the motor system is acting. The signal derived from the forward models can be used to adjust the prior selection of the modules that occurs before the movement is initiated and sensory feedback is available. For example, for an object that appears heavy, prior selection will predict that a large grip force is needed to lift the object. However, feedback processes, based on comparing the predicted (from the forward model) with the actual consequences of action (such as hand acceleration) can indicate that the object is in fact light, requiring a module appropriate for a lower grip force. These feedback processes are used to adjust the predictive feed-forward control and are separate from the feedback control processes, which can provide reactive responses.

In the case of the current study, one internal model could capture the relation between the motor commands and subsequent sensory feedback when the hands manipulate a single object (**Figure 4-10,** *left*), while another model captures the condition in which the hands act on separate objects (**Figure 4-10,** *right*). Each forward model predicts the sensory consequences, based on its particular model of the context and the motor command, and these predictions are then compared with the actual sensory feedback. The discrepancies in these predictions are then used to estimate the probability that each model captures the current behaviour. In the present study, for example, when the feedback is equal and opposite to both hands ($g=1$) the internal model of a single object between the hands would have a small error compared to the model of separate objects. This would give rise to a high probability that the hands are manipulating a single object thereby allowing the efference copy of the command to the left hand to modulate predictively the grip force in the right hand, as was observed. As the sensory feedback deviates from the prediction of the model ($g>1$ or $g<1$), the probability of this model capturing the behaviour would fall, leading to an increase in the lag between grip and load force, as was observed. The current results therefore suggest that an internal model exists that captures the normal physical properties of an object and is used to determine the extent to which the two hands are manipulating this object. While it is probably not possible to have a model for every context we are likely to experience, it is proposed that by selectively combining the outputs of multiple simple forward models we could construct predictions suitable for many different contexts.

Figure 4-10



A model for determining the extent to which two hands are acting through a single object. For simplicity only two internal models are shown. On the *left* is an internal forward model which captures the relationship between the motor commands sent to the left (M_L) and right (M_R) hands and expected sensory feedback when the two hands act on a single object. On the *right* is shown two internal forward models which capture the behaviour when the hands are manipulating separate objects. Both models make predictions of the sensory feedback from both the left (S_L) and right (S_R) hands based on the motor commands. These predictions are then compared with the actual sensory feedback to produce the sensory prediction discrepancies (E). The errors from each model, $\hat{E}$ and $\tilde{E}$, are then used to determine the probability P that each model captures the current behaviour. This probability determines the extent to which the motor command to one hand can be used for predictive grip force modulation of the other hand.

The observed relationship between lag and feedback gain, g, constrains the way in which sensory prediction errors could be used to select between the internal models. The current results rule out a model selector producing a hard classification in which grip force modulation corresponds to the hands acting either on a single object or separate objects. Such a relationship would have led to a binary distribution of the lags consistent either with predictive modulation (lag of zero) or no prediction (lag approx. 100 ms). However, the results of the current experiment show that the lag was minimal when the feedback gain to the left hand was 1 and increased smoothly when the feedback gain was either greater or less than 1. Prediction is therefore graded by the similarity between the force feedback expected for a real rigid object and the feedback actually received.

Forward models must be adaptable in order to cope with the changing dynamics of the limb and the many new objects experienced throughout life. A recent study that explored learning of internal models supports the notion of multiple internal models proposed above (Witney *et al.*, 1999). Witney and colleagues compared the grip force responses when an object held in a precision grip was pulled, either by the action of the other hand (*self-produced*) or externally by a robot, either unpredictably (*non-cued*) or predictably (*cued* by a tone). Anticipatory grip force modulation only occurred when the load force was self-produced. In contrast, in both the cued and non-cued conditions grip force modulation was reactive in response to the imposed load force, with a grip force lag of ~70 ms in each condition. The researchers then introduced a 250-ms delay between the pull exerted by one hand and the consequential production of the load force on the object. In this *delayed self-produced* condition, a grip force profile with two peaks was initially observed, comprising an early grip force peak, appropriately timed for a non-delayed load, followed by a grip force reactive to the delayed load force. Over the course of 250 trials, the grip force became anticipatory while the early, and now inappropriate, grip force peak decreased in amplitude. In contrast, when a delay was introduced between the tone and the load force produced by the robot (*cued*), the grip force remained reactive in response to the load force.

Witney and colleagues argued that the new predictive peak to the delayed load force observed in the self-produced condition suggests the development of a new internal model, appropriate for the novel situation. Their results show that an internal model can be learned for the situation in which the consequences of a motor action are delayed, but cannot be learned for a sensorimotor context in which a tone determines the sensory outcome. Therefore it may be that internal models for grip force modulation can adapt to new dynamics relating the motion of one hand to the other, but arbitrary pairings such as tone with load force cannot be incorporated into a new internal model.

4.6 Conclusion

Forward model prediction is evident in the precise anticipatory modulation of grip force seen when one hand pushes on an object gripped in the other hand (Johansson and Westling, 1984; Flanagan and Wing, 1993). The current experiment demonstrates that self-generation is not in itself sufficient for such prediction. Two robots were employed to simulate virtual objects held in one hand and acted upon by the other. Using this robotic interface, the sensory (force) feedback from the object held by the moving hand was parametrically varied. Precise predictive grip force modulation of the restraining hand was highly dependent on the sensory feedback to the hand producing the load. Predictive modulation requires not only that the movement is self-generated, but also that the efference copy and sensory feedback are consistent with a specific context; in this case the manipulation of a single object. Precise prediction was seen when the feedback to both hands was consistent with a single object and declined smoothly as the feedback became inconsistent with this context. The results are interpreted in terms of a computational mechanism whereby the CNS uses multiple internal models, each corresponding to a different sensorimotor context, to estimate the probability that the motor system is acting within each context. It is proposed that each context (the dynamics of the limbs and object properties) can be learned from experience of manipulating objects throughout life. In the following chapter the behavioural consequences of forward models operating in non-learned contexts is examined. The relationship between the accuracy of the forward model's sensory predictions and the perception of self-produced stimulation is investigated by manipulating the sensorimotor context in which self-produced stimulation occurred.

5 CHAPTER 5: SPATIOTEMPORAL PREDICTION MODULATES THE PERCEPTION OF SELF-PRODUCED STIMULI

5.1 Introduction

In the introduction of this thesis, it was proposed that forward models can use accurate sensory predictions to cancel the sensory consequences of self-generated movements. In contrast, externally produced sensations cannot be accurately predicted and therefore cannot be cancelled by the forward model. In this way, externally produced sensations should be perceptually enhanced relative to self-produced stimuli.

Many studies have shown that self-generated movement attenuates sensory stimulation. Evidence suggests that in humans sensory stimulation is perceptually attenuated when it occurs simultaneously with self-generated movement compared with when no movement is made (Angel & Malenka, 1982; Chapman *et al.*, 1987; Milne *et al.*, 1988; Collins *et al.*, 1998). Chapman *et al.* (1987) demonstrated that detection thresholds for tactile stimulation are increased during movement of the stimulated arm. Both active and passive movement of the stimulated limb increased detection thresholds, with active movement having a slightly greater and more consistent effect than passive movement. This suggests that both central and peripheral feedback factors play a role in reducing the ability to detect tactile stimulation during movement. Collins *et al.* (1998) tested muscular sense (defined as the ability to detect an electrically-induced twitch of the right forearm muscle) during arm movements in humans. They found that muscular sense was attenuated by voluntary wrist movements. Passive movements of the wrist reduced perceptual ratings of twitch amplitude, but to a lesser extent. Reaching with the stimulated, but not the contralateral arm also significantly reduced muscular sense. The findings suggest that both peripheral receptors and central sources play a role in this movement-related perceptual attenuation. Firstly, attenuation occurred during cyclic stretching of the skin on the hand suggesting that signals from peripheral receptors may play a role. Secondly, attenuation occurred prior to a single wrist flexion movement, which indicated that central sources also contribute to the sensory attenuation. These findings demonstrate that the perception of a sensory stimulus is attenuated if movement occurs simultaneously with the stimulus.

Furthermore, it has been found that the sensory consequences of self-produced sensory stimulation are perceived differently from identical sensory stimulation when it is externally produced. An example of the differential perception of self- and externally generated stimulation is the phenomenon that people cannot tickle themselves (e.g. Weiskrantz *et al*, 1971; Claxton, 1975). It has been argued that efference copy produced in parallel with the motor command underlies this phenomenon. In Weiskrantz *et al.* (1971)'s psychophysical study, a tactile stimulus that transversed the sole of the subject's foot was administered by the experimenter, the subject or both. Subjects rated the self-administered tactile stimulus as less tickly than the externally administered tactile stimulus. When the stimulation was associated with passive arm movements the tickliness of the sensation was reduced, but not to the level of the self-administered tactile stimulus. The authors attributed the differences in response to the mode of delivery: self-administered tactile stimulation produces both efference copy in accordance with the motor command and re-afference produced by the arm movement; passive arm movement produces only re-afference and externally administered tactile stimuli produces neither efference copy nor re-afference. The authors therefore concluded that although re-afference plays a role, the attenuation signal is based mainly on the efference copy signal produced in concordance with a self-generated movement.

Claxton (1975) investigated the effect of predictability on tickliness by asking subjects to rate tickliness of a stimulus while being tickled by an external stimulus with their eyes closed or open, by active and by passive movement. Like Weiskrantz *et al.* he found that active movement reduced the tickle sensation and attributed this movement-induced perceptual attenuation to the presence of corollary discharge during active movement. Stimulus predictability was manipulated by having subjects open or shut their eyes. Claxton found that the more predictable the stimulus the lower the tickliness rating.

One explanation of the results by Weiskrantz *et al.* (1971) and Claxton *et al.* (1975) is that all incoming sensory stimulation is attenuated when it occurs at the same time as self-generated movement. This might due to a general 'gating' of all incoming sensory information during movement, akin to the perceptual attenuation of sensory feedback that occurs during movement, as described above (Angel & Malenka, 1982; Chapman *et al.*, 1987; Milne *et al.*, 1988; Collins *et al.*, 1998). Such findings suggest that the perception of a sensory stimulus might be attenuated simply if self-generated movement occurs simultaneously with the stimulus – the movement does not necessarily have to produce the sensory stimulus in order for it to be attenuated. This, however, is inconsistent with the theoretical approach to forward models outlined, which posits that in order for sensory attenuation to occur, the specific sensory consequences of the movement must be accurately predicted.

The focus of the present study was to determine whether sensory attenuation is due to a precise prediction of the sensory consequences of movement, or to a movement-induced non-specific attenuation of all sensory signals. On the one hand, it is possible that movement is the only requirement for the sensation to be attenuated. On the other hand, according to the hypothesis formulated in the introduction of this thesis, the sensory stimulation would have to correspond exactly to the movement producing it in order for perceptual attenuation to occur. If this latter hypothesis is true, there are two further possibilities. Firstly the sensory stimulation might have to correspond exactly to the movement producing it for any perceptual attenuation to occur. Alternatively, the perceptual attenuation might be proportional to the accuracy of the sensory prediction.

To investigate this, in an experiment that was based on Weiskrantz and colleagues' study, subjects were asked to rate the sensation of a tactile stimulus on the palm of their hand, and examined the perceptual effects of altering the correspondence between self-generated movement and its sensory (tactile) consequences. This was achieved by introducing parametrically varied degrees of delay or trajectory rotation between the subject's movement and the resultant tactile stimulation. The result of increasing the delay or trajectory rotation is that the sensory stimulus no longer corresponds to that which would be normally expected based on the efference copy produced in parallel with the motor command. Therefore as the delay or trajectory rotation increases, the sensory prediction becomes less accurate and the level of sensory discrepancy increases.

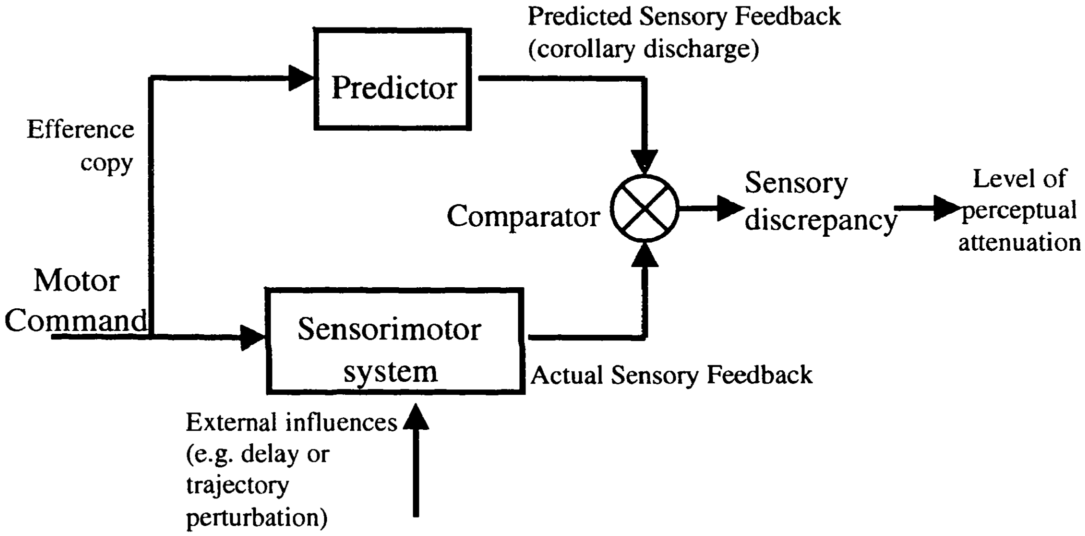
In one condition, a robotic motor was programmed to produce the tactile stimulation across the subjects' right palm – this was the *externally produced* tactile stimulation condition. In all the remaining conditions the tactile stimulus was self-produced. In these conditions the subjects held an object attached to the end of a second robot and were required to move this over their right palm sinusoidally. The motion of the left hand determined the position of the first robot attached to which was the piece of foam, which made contact with the subject's right palm. The motion of the left hand therefore produced the tactile stimulus on the right palm.

In the *self-produced* tactile stimulation condition, the tactile stimulus corresponded exactly to the movement of the subject's left hand. This condition corresponds to the normal situation in which subjects use their left hand to move a physical rod across the palm of their right palm (equivalent to the self-produced tickling condition in the study by Weiskrantz and colleagues). By using this robotic interface so that the tactile stimulus could be delivered under remote control by the subject, *delays* of 100, 200 and 300 ms were introduced between the movement of the left hand and the tactile stimulus on the right palm. In a further condition *trajectory perturbations* (rotations) of 30°, 60° and 90° were introduced between the direction of the left hand movement and the direction of the tactile stimulus on the right palm.

Increasing the delay or trajectory perturbation has three possible effects on the sensation. Firstly, if sensory attenuation is due to a general movement-induced sensory gating, then since movement occurs under all delays and trajectory perturbations the sensation would remain at the same level of attenuation in all conditions. Secondly, if sensory attenuation relies on a completely accurate prediction of the sensation, then no attenuation would occur under any delay or trajectory perturbation. Thirdly, sensory attenuation could be proportional to the accuracy of the prediction, in which case as the delay or trajectory perturbation is increased then the intensity of the sensation would increase (**Figure 5-1**).

Under all delays and trajectory perturbations the left hand makes the same movement. Only the temporal or spatial relationship between the action of the left hand and the sensory effect on the right hand is altered. Any perceptual modulation observed in the delay and trajectory perturbation conditions must be due to the use of precise predictions of the sensory consequences of movement, rather than a movement-induced non-specific attenuation of all sensory signals.

Figure 5-1



A model for determining the sensory consequences of a movement, in the present study whether the left hand is causing the tactile sensation on the right hand. An internal forward model makes predictions of the sensory feedback based on the motor commands sent to the left hand. These predictions are then compared to the actual sensory feedback to produce the sensory discrepancy errors. It is proposed that the lower the sensory discrepancy the greater is the attenuation of tactile sensation. In the current study, when there is no delay or trajectory perturbation the model correctly predicts the sensory consequences of the movement so no sensory discrepancy ensues between the predicted and actual sensory information. In this case the motor command to the left hand can be used to attenuate the sensation on the right hand. As the sensory feedback deviates from the prediction of the model (by increasing the delay or trajectory perturbation) the sensory discrepancy between predicted and actual sensory feedback increases. This leads to a decrease in the level of perceptual attenuation possible and a relative increase in the intensity of sensation experienced on the right hand.

One possible reason why subjects in previous studies have rated self-produced tactile stimulation as less tickly than externally produced tactile stimulation is that in the former case subjects know exactly when and where the next touch will occur. Perhaps the tickle sensation requires an element of surprise. Previous studies have attempted to control for this by making the tactile stimulus as predictable as possible. However, none has used robots to control the tactile stimulus precisely. In the present study robots were employed to produce the tactile stimulation, so the stimulus was highly controlled and highly predictable in time and space in the externally produced tactile sensation condition. Therefore lack of stimulus predictability could be ruled out as a factor responsible for increasing the intensity of the percept in this condition. Furthermore, to avoid biasing subjects towards tickling and minimising the likelihood of them using their tacit knowledge about tickling oneself, the experiment was not framed as pertaining to tickling or ticklishness *per se.* Instead the experiment was referred to as concerning 'tactile sensation' and subjects were asked to rate the stimulus in terms of several sensations including 'tickliness' ('painful,' 'intense,' 'pleasant,' 'irritating,' and 'tickly').

5.2 Method

5.2.1 Subjects

A total of 16 normal right-handed subjects (mean age 23), who were naive to the issues involved in the research, gave their informed consent and participated in the present study, which was approved by the National Hospital for Neurology and Neurosurgery Ethics Committee.

5.2.2 Apparatus

Subjects sat at a table with their right forearm on the table with the palm facing upwards. A tactile stimulus constituting a piece of soft foam (radius 1 cm and length 2.5 cm) attached to the end of a lightweight robotic manipulator (Phantom Haptic Interface, Sensable Devices, Cambridge, MA) was positioned above their right palm. The robot was controlled by a PC and was capable of generating forces in three dimensions, and its position was updated at 1 KHz. The subject gripped a cylindrical object (radius 1 cm and width 4 cm) with the thumb and index finger of their left hand. This object was held directly above the tactile stimulus and was attached to a second robotic device (see **Figure 5-2**). In each trial of each condition the tactile stimulus on their right palm moved sinusoidally at a frequency of 2 Hz and amplitude 1.5 cm in the lateral (horizontal) direction, with a downward force of 0.5 N.

5.2.3 Procedure

In the self-produced tactile stimulus conditions subjects were required to move the object held in their left hand sinusoidally (frequency 2 Hz and amplitude 1.5 cm), which, via two robots, produced the same movement of the tactile stimulus above their right hand. Subjects practised this until they were proficient at producing the desired frequency and amplitude of movement. This took between 30 and 60 seconds for each subject. In the conditions in which the movement of the tactile stimulus above their right hand was produced by the movements of their left hand subjects were told of this relationship.

Figure 5-2

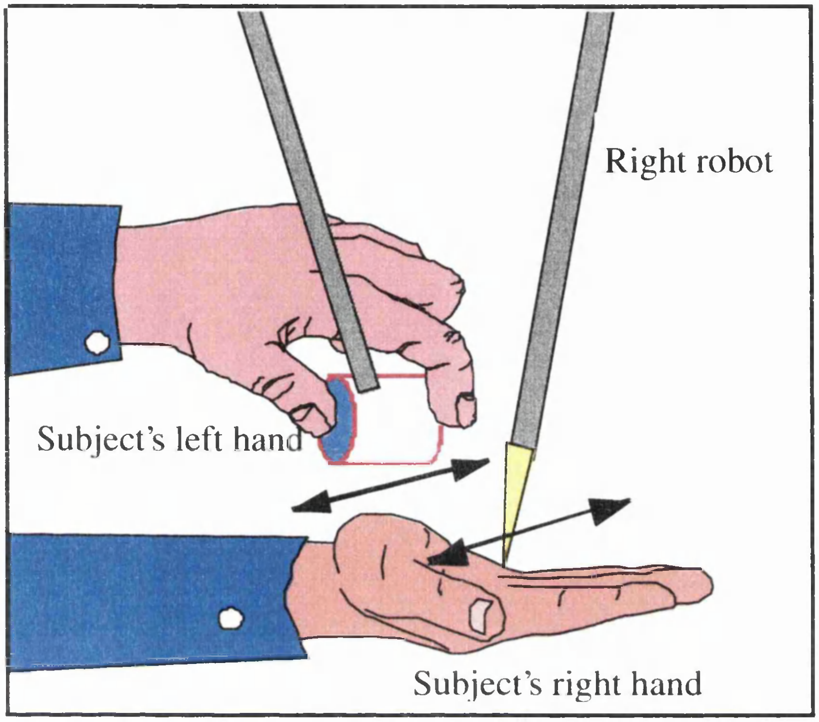


Diagram of experimental set-up. A tactile stimulus constituting a piece of foam attached to the end of a robotic manipulator was positioned above the subject's right palm. The subject gripped a cylindrical object with the thumb and index finger of their left hand. This object was held directly above the tactile stimulus and was attached to a second robotic device. Delays and trajectory perturbations were introduced between the movement made by the left hand and the resultant tactile stimulation of the right palm. Subjects were asked to rate the stimulus on several perceptual scales.

Trials consisted of two 10 second sub-trials. Two points were marked on the subjects' right palm, and subjects were instructed (by a tone) to move their hand from one point to other during the 3 second delay between the two sub-trials in order to limit the amount of sensory adaptation that took place. Apart from during this inter-trial delay, subjects shut their eyes during the experiment.

Externally produced tactile stimulation

In the externally produced tactile stimulation condition the right robot was programmed to produce the 2 Hz sinusoidal, amplitude 1.5 cm, tactile stimulus on the subjects' right hand. With their left thumb and index finger subjects gripped the left robot, which remained still throughout.

Self-produced tactile stimulation

In the self-produced tactile stimulation condition subjects were required to move the object in their left hand sinusoidally at 2 Hz to the desired amplitude. This movement was transmitted to the tactile stimulus via the right robot, which produced the same trajectory, frequency and amplitude of movement above the subject's right palm.

Parametric delays

Subjects were required to move the object in their left hand sinusoidally at 2 Hz. This movement was transmitted to the tactile stimulus via the right robot and 100 ms, 200 ms and 300 ms delays were introduced between the movement made by the subject's left hand and the resultant movement of the right robot. Subjects were not informed of the presence of these delays.

Parametric trajectory perturbations

Subjects were required to move the object in their left hand sinusoidally at 2 Hz. This movement was transmitted to the tactile stimulus via the right robot and perturbations of 30°, 60° and 90° rotations were introduced between the direction of movement made by the subject's left hand and the direction of movement of the right robot. The tactile stimulus always moved in the same (lateral) direction on the palm of the subject's right hand but subjects were instructed to move the left hand along different trajectories. Straight lines drawn on paper corresponding to 30°, 60° and 90° rotations from the lateral direction indicated to the subjects in which direction they should move their left hand in each condition.

The conditions were randomised and counter-balanced within and between subjects and subjects were blind to the order. Each condition was repeated 5 times per subject. Therefore subjects underwent a total of 40 trials.

Rating scale

After each trial subjects were instructed to rate the sensation on their palm on a scale from 0 (not at all) to 10 (extremely) intense, painful, tickly, pleasant and irritating. Subjects were told that a rating of zero indicated a neutral perception for that particular scale. Subjects were told that it was important to maintain the same scale all the way through the experiment and that the emphasis was on the relative values of their judgements, not the absolute values.

5.2.4 Data analysis

Since each subject used their own subjective rating scale, the ratings need not be normally distributed. Therefore the perceptual ratings were converted to ranks for each condition for each subject and the significance of the differences between the ranks was calculated in each condition. Wilcoxon non-parametric matched-pairs signed-ranks test was used to examine the difference between the self-produced tactile stimulation and externally produced tactile stimulation conditions for each scale.

Friedman's non-parametric ranking test was used to rank the ratings, and to calculate the coefficient of rank correlation, in the following conditions:

- Self-produced tactile stimulation, 100 ms, 200 ms and 300 ms delays, and externally produced tactile stimulation
- Self-produced tactile stimulation, 30^{o}, 60^{o} and 90^{o} trajectory perturbations, and externally produced tactile stimulation.

In addition, a repeated measures multivariate analysis of variance (ANOVA) was performed to assess the effects of self-generated movement, delays and trajectory perturbations on the ratings. Results were taken as significant if $P<0.05$.

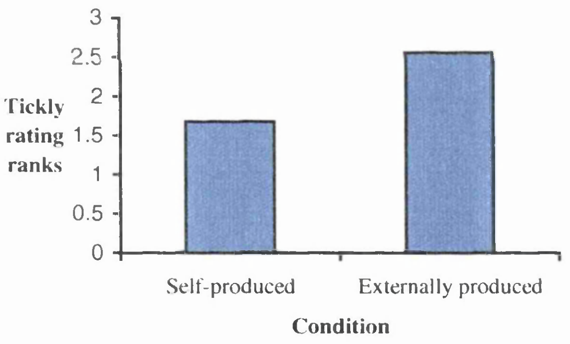
5.3 Results

After practice each subject was able to produce the desired movement of the left hand with reasonable accuracy. 'Painful' received zero ratings in all conditions by all subjects, and was therefore excluded from the analysis. 'Irritating' received very few ratings, so was also excluded from the analysis.

5.3.1 Self- versus externally produced tactile stimulation

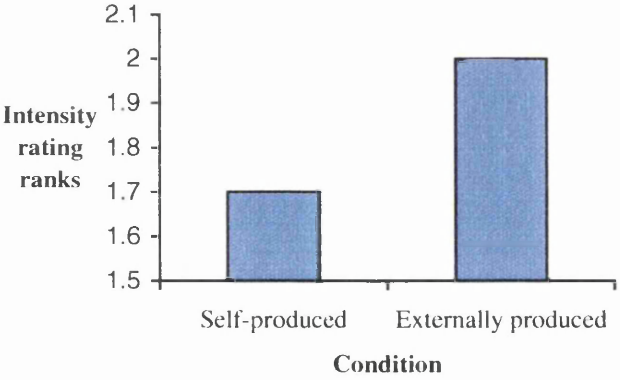
Subjects rated the self-administered tactile stimulus as significantly less tickly (F=41.21; P<0.0001), intense (F=112.948; P<0.0001), and pleasant (F=60.157; P<0.0001) than the externally administered tactile stimulus. Tickly, intense, and pleasant rating ranks for self-produced and externally produced tactile stimulation are shown in **Figures 5-3, 5-4 & 5-5**.

Figure 5-3



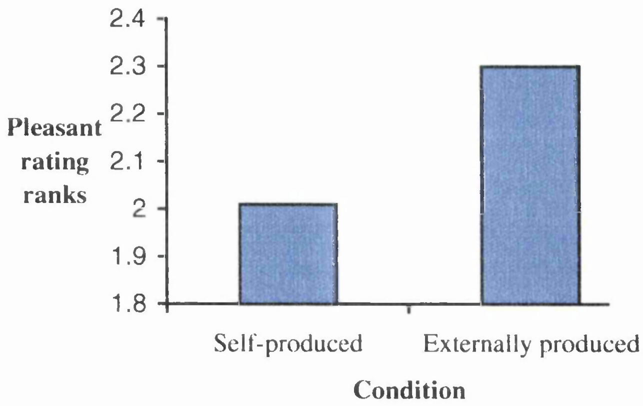
Graph to show 'tickly' rating ranks for self-produced and externally produced tactile stimulation conditions in normal subjects.

Figure 5-4



Graph to show 'intense' rating ranks for self-produced and externally produced tactile stimulation conditions in normal subjects.

Figure 5-5



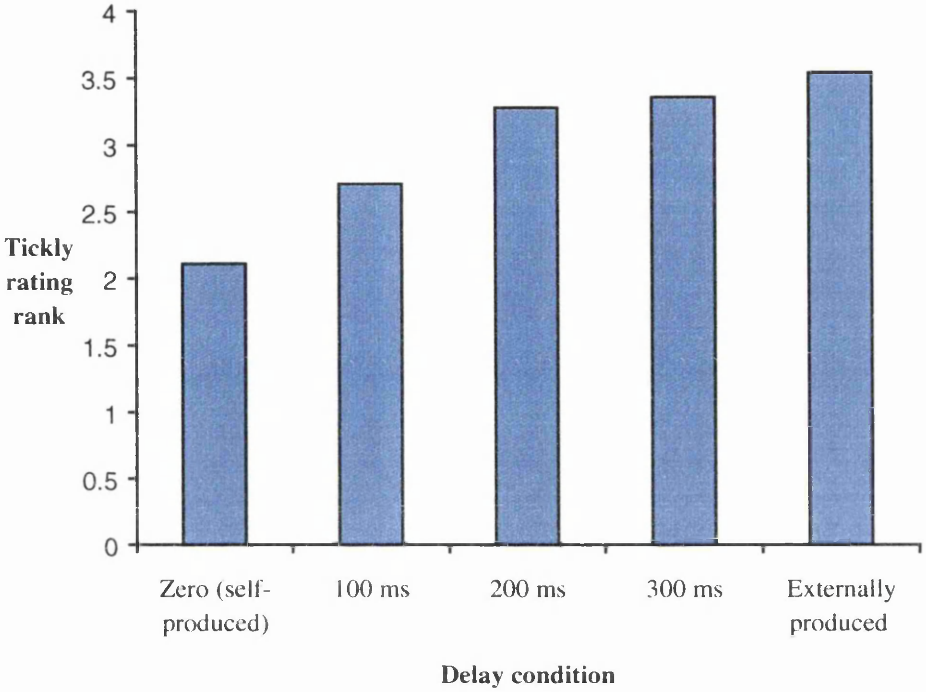
Graph to show 'pleasant' rating ranks for self-produced and externally produced tactile stimulation conditions in normal subjects.

5.3.2 Parametric delays between movement and tactile stimulation

Two subjects reported noticing the delay in the delay conditions in the post-experiment debriefing. The other 14 subjects claimed to be unaware of the delays.

There was a significant increase (F=24.93; P<0.0005) in the tickly rating as the delay between the movement of the left hand and the tactile stimulus increased from 0 to 200 ms. There was no significant difference between ratings at 200 ms and 300 ms delay and in the externally produced tactile stimuli condition. **Figure 5-6** shows tickly rating ranks with increasing delay between the movement of the left hand and tactile stimulus on right hand.

Figure 5-6

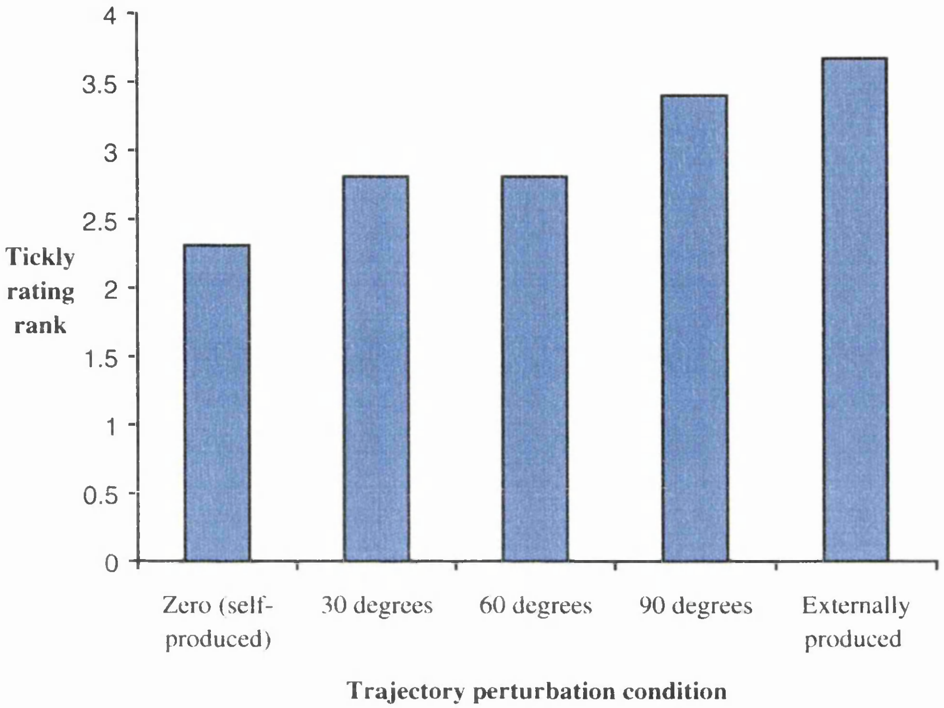


Graph to show that the perception ('tickliness') of a tactile stimulus increase with increasing delay (up to 200 ms) between the movement of the left hand and the tactile stimulus on the right hand.

5.3.3 Parametric trajectory perturbations between movement and tactile stimulation

There was a significant increase in the tickly (F=9.37; P<0.01) rating as trajectory perturbation between movement and tactile stimulation increased from 0^{o} to 90^{o}. There was no significant difference between ratings at 90^{o} trajectory perturbation and in the externally produced tactile stimuli condition. **Figure 5-7** shows tickly rating ranks with increasing trajectory perturbation between the movement of the left hand and tactile stimulus on right palm.

Figure 5-7



Graph to show that the 'tickliness' of a tactile stimulus increase with increasing trajectory perturbation (up to 90°) between the movement of the left hand and the tactile stimulus on the right hand.

5.3.4 Difference between rating scales

As a measure of the precision with which subjects could rate the different percepts the variance of the rating of each percept for each subject and condition was calculated. The average variance across all subjects and conditions was significantly higher for 'pleasant' (0.40±0.005) and 'intense' (0.46±0.006) than for 'tickly' (0.26±0.012) ratings.

5.4 Discussion

The present study sought to investigate how subjects perceive the sensory consequences of their own actions and under what conditions the perception of self-produced sensations changes. The results support and expand on work by Weiskrantz *et al.* (1971) demonstrating that the perception of a tactile stimulus is modulated by a causative self-generated action: subjects consistently rated a self-produced tactile sensation as being less tickly, intense and pleasant than when it was externally produced. These results were interpreted as supporting Weiskrantz and colleagues' claim that when a tactile stimulus is self-produced it can be predicted accurately on the basis of the efference copy produced in parallel with the motor command, and the prediction can be used to attenuate the sensation. In contrast, when a tactile stimulus is externally produced it cannot be predicted because it is not associated with any efference copy, and therefore no perceptual attenuation occurs.

In addition, it was demonstrated that a tactile sensation becomes increasingly tickly the further the tactile stimulus diverges from the motor command producing it. By introducing delays and trajectory perturbations between the movement of the left hand and the resultant tactile stimulus on the right palm it was demonstrated that an increase in these two parameters produces a corresponding increase in the tickliness rating. It is argued that increasing the delay and trajectory perturbation increases the intensity of the sensation because the stimulus no longer corresponds (in time or space) to the motor command producing it.

In contrast to the tickliness rating, while there was a trend, there was no correlation between the degree of delay or trajectory perturbation and the intense or pleasant ratings. This might be due to the higher variance of ratings shown by subjects on these measures compared to the 'tickliness' rating. This lower consistency for 'intense' and 'pleasant' suggests that subjects found assessing and quantifying these sensations more difficult than assessing and quantifying the 'tickliness' of a stimulus.

It might be argued that the greater the delay or trajectory perturbation between the active and passive hands the less predictable the stimulus becomes, and that decreasing predictability is responsible for increasing 'tickly' ratings. However, in the delay and trajectory perturbation conditions the stimulus was still predictable in the sense that the stimulus on the right hand is entirely determined by the movement of the left hand. Furthermore, it was possible for subjects to learn after a few seconds the exact relationship between the action of their left hand and the stimulus on their right hand. Indeed, in the debriefing following the experiment only two subjects reported having noticed the presence of any kind of anomaly in the delay conditions. Thus most subjects were unaware of the delay and the tactile stimulus was as expected in these conditions as in the zero delay condition. In those conditions in which trajectory perturbations were used, subjects were aware of them (they were instructed to move their left hand in a different direction) but the tactile stimulus became predictable after the first few seconds in which it was possible to learn this relationship. A more plausible explanation of the results other than stimulus predictability is that as the tactile stimulus diverges temporally or spatially from the motor command producing it, the forward model is less able to predict precisely and cancel the sensory feedback from the movement.

Under all delays and trajectory perturbations the left hand made the same movement and the right hand experienced the same stimulus. Only the spatiotemporal relationship between the action of the left hand and the sensory effect on the right hand was altered. The results suggest that the perceptual attenuation of self-produced tactile stimulation is due to a precise modulation of the sensory feedback, based on specific sensory predictions, rather than a non-specific attenuation of all sensory signals. If this latter hypothesis were true, the same level of perceptual attenuation would have been observed during all the delay and trajectory perturbation conditions as in the self-produced tactile stimulation condition since the same movement was made by the subject during all these conditions.

The present results can be interpreted in terms of the sensory discrepancy errors made by a forward model (**Figure 5-1**). Normally when movement occurs the system predicts a sensation based on zero delay and trajectory perturbation between the movement and the resultant tactile stimulation. This prediction is based on years of experience manipulating rigid objects in which delays and trajectory perturbations do not occur. Thus, the closer the system is to direct contact between the hands, the higher the accuracy of the prediction will be, and more of the sensory re-afference will be cancelled. When there is no delay or trajectory perturbation the model correctly predicts the sensory consequences of the movement so a low level of discrepancy ensues between the predicted and actual sensory information. In this case the motor command to the left hand can be used to attenuate the sensation on the right hand. As the sensory feedback deviates from the prediction of the model (by increasing the delay or trajectory perturbation) the sensory discrepancy between predicted and actual sensory feedback increases. This leads to a decrease in the amount of attenuation possible and a relative increase in the intensity of sensation experienced on the right hand. The present results demonstrate that the 'tickly' rating is minimal with zero delay or trajectory perturbation and increases smoothly as the (imperceivable) delay or the trajectory perturbation increases up to a certain point (200 ms or 90° respectively). At this point the sensation becomes as tickly as an externally produced sensation. This suggests that a precise forward model is in operation that is sensitive even to small changes in the correspondence between movement and its sensory consequences, including those unavailable to conscious awareness.

5.4.1 Comparison with oculomotor system

Unlike in the oculomotor system, complete cancellation of incoming sensory information may not be appropriate for the somatosensory system since it would result in anaesthesia during self-produced movements. It is proposed that prediction-based modulation acts as a filter on incoming sensory signals which can enhance the afference to re-afference ratio (akin to increasing the signal-to-noise ratio). This modulation (not complete cancellation) of incoming sensory input might have the effect of accentuating features of importance (for example those due to external events). Another difference between the comparator studied in this experiment and the oculomotor comparator is that the latter operates only on direct commands to move the eyes. When the eye is moved by pressing on the eyeball with a finger the percept is that the world moves. However, this sort of interaction is rare in everyday life and there would be little advantage of it being modelled by the CNS. In contrast, interactions between other body parts such as the limbs are common and for such interactions the results of the current study show that predictions of the sensory consequences of the motion of one hand are used to attenuate the sensation on the other hand.

5.4.2 Forward model learning

The human motor system is capable of very flexible, modular adaptation. It is possible that delays and trajectory perturbations could be learned and new forward models incorporating delays or trajectory perturbations acquired. Forward model learning is the subject of much research, as discussed in previous chapters (Mano *et al*, 1986; Mano *et al*, 1989; Bauswein *et al*, 1983; Wang *et al*, 1987; Ojakangas *et al*, 1992 Wolpert & Kawato 1998; Witney *et al.*, 1999; Imamizu *et al*, 2000). In the study by Witney and colleagues subjects learned over the course of 250 trials to adjust their grip-force modulation appropriately to incorporate a 250-ms delay between the pull exerted by one hand and the consequential production of the load force on the object. Whether experience with the delays or trajectory perturbations between movement and tactile stimulation in this study would affect the perceptual attenuation would make an interesting future study. It is predicted that over a large number of trials the system would be able to learn to predict a certain delay or trajectory perturbation between movement and its sensory consequences, and cancel the sensation appropriately.

5.4.3 The nature of ticklishness

What is the purpose of this perceptual attenuation of self-produced tactile stimuli? Firstly, externally produced stimuli normally carry more biological significance than self-produced stimuli. An animal must be attuned to sensory events that indicate the actions of other animals, and this can only be achieved by being able to ignore the sensory events that arise as a consequence of the animal's own actions. This allows unexpected stimulation to be selectively detected. The attenuation of self-produced tactile stimuli might distinguish them from biologically more important (externally produced) stimuli.

Secondly, the current results might have implications for the nature of tickliness, a subject that has been the centre of considerable debate, mainly with reference to tickle-induced laughter. The debate is split between those who argue that tickle-induced laughter is purely reflexive (Sully, 1902; Stearns, 1972; Fridlund and Loftis, 1990; Harris and Christenfeld, 1997; Harris, 1999), and those who propose that it is socially-induced and results from close physical contact with another person (McDougall, 1922; Darwin, 1872; Hecker, 1873). The former argument, that tickle-induced laughter is purely reflexive, something that happens without our voluntary control, has recently received empirical support from a study by Harris and Christenfeld (1997). They found that people laugh out loud when they are being tickled by (what they believe is) a robotic hand even when no other person is around to hear them. If the function of tickle-induced laughter was purely social, the subjects would not laugh in the absence of another person.

On the other hand, the inability to tickle oneself has been taken to support the social bonding theory (Gregory, 1924; Shultz, 1976; Hoshikawa, 1991). It has been argued that tickle-induced laughter depends on a second person doing the tickling (Levine, 1979) and as such has been termed a purely psychological process (McDougall, 1922): the person's cognitions about the situation determine whether laughter occurs or not (Darwin, 1872; Hecker, 1873; Koestler, 1964; Foot and Chapman, 1976). This view was argued by Charles Darwin over a century ago. He wrote that ticking is an important aspect of social and sexual bonding, and prominent in the development of communication between mothers and babies. Tickle-induced laughter, he argued, is socially induced and results from close physical contact with another person.

It is possible that the findings of the current study support both sides of the debate. It has been argued throughout this chapter that one function of the attenuation of self-produced tactile stimulation is to differentiate self-produced from externally produced tactile stimulation. A consequence of this is that tickle-induced laughter is more likely to occur to an externally produced tactile stimulus because it feels more tickly than a self-produced tickle. The physiological theory of tickle-induced laughter implies that it is simply the tactile stimulation during tickling per se that induces tickle-induced laughter. However, if this were the case, laughter would not depend on the tickliness of the stimulus, which seems unlikely. Speculatively, the current results suggest that there is both a physiological and a social element to tickling. The physiological response that reduces the sensation of a self-produced tickle and enhances it when someone else does the tickling makes social bonding (in terms of tickle-induced laughter) with oneself unlikely and with someone else likely.

5.5 Conclusion

This experiment sought to investigate when self-produced tactile stimulation is perceived as less intense than the same stimulus produced externally. The results suggest that an internal forward model is able predict the sensory consequences of the motor commands sent to one hand, which are used to cancel the resultant tactile sensation on the other hand. The 'tickliness' rating of the self-produced tactile stimulus increased significantly with increasing delay and trajectory perturbation between self-produced movements and the resultant tactile stimulation. It is argued that the tickliness of a self-produced tactile sensation is proportional to the sensory discrepancy produced by the comparison between the predicted and the actual sensory feedback from a movement. As the tactile stimulus diverges temporally or spatially from the motor command producing it, the forward model is less able to predict precisely and cancel the sensation, which is therefore perceived as increasingly tickly. In the following chapter, the neural correlates of the reduced intensity and tickliness of self-produced relative to externally produced tactile stimulation are evaluated using fMRI.

6 CHAPTER 6: CENTRAL CANCELLATION OF SELF-PRODUCED TACTILE STIMULATION

6.1 Introduction

The psychophysical study in the previous chapter demonstrated that self-produced and externally produced tactile sensations are perceived differently. Subjects consistently rated a self-produced tactile sensation on their right palm as being significantly less 'tickly', 'intense' and 'pleasant' than an identical stimulus produced by a robot. This is an example of the perceptual attenuation associated with self-generated movements, which has been documented by several researchers (e.g. Weiskrantz *et al.*, 1971; Collins *et al.*, 1998). In the experiment described in this chapter the neural correlates of this perceptual attenuation of self-produced tactile stimulation were investigated using fMRI.

Neurophysiological data from animals demonstrate that neuronal responses in somatosensory cortex are attenuated by self-generated movement. Active touch is 'gated' in primary somatosensory cortex of rats (Chapin & Woodward, 1982) and monkeys (Jiang *et al.*, 1991; Chapman & Ageranioti-Belanger, 1991; Chapman, 1994) compared to passive and external touch of an identical tactile stimulus. For example, neuronal activity in somatosensory areas 3b, 1 and 2 in monkeys is attenuated when monkeys move their hand over a surface texture compared to when their hand is passively moved over the same surface, or when the surface moves underneath their hand (Chapman, 1994). Furthermore, Chapman and her colleagues have found neurons that signal changes in texture only during active tactile discrimination. This texture-related discharge disappeared when the cell was tested with passive movements. The authors argued that these neurons signal the behavioural significance of a stimulus: when an animal is actively exploring a tactile surface, changes in texture are likely to be behaviourally relevant. Chapman *et al.*(1988) demonstrated that responses in the primate medial lemniscus, sensory thalamus (ventral posterior lateral nucleus, caudal division, VPLc) and somatosensory cortex evoked by natural (air puff) or electrical percutaneous stimulation to the arm are diminished prior to and during active arm movements. Passive movement of the forearm significantly decreases all but the lemniscal evoked potential. The authors argue that prior to and during movement there is a centrally mediated suppression of somatosensory transmission and, during movement, re-afferent signals from the moving arm decrease transmission at the thalamocortical level.

In addition, many researchers have found that somatosensory evoked potentials (SEPs) are reduced in amplitude during movement in humans (Staines *et al*, 1998; Tinazzi *et al*, 1998; Rossini *et al*, 1999; Shimazu *et al*, 1999; Valeriani *et al*, 1999). In the study by Shimazu and colleagues, subjects heard a warning sound followed one second later by an electric stimulus to the right median nerve at the wrist. The latter served both as a cue to start a finger movement and as stimulation to evoke SEPs. Somatosensory gating occurred and since finger movement began after the stimulus, the authors concluded that such gating must have been purely central in origin, and may reflect motor preparation. Valeriani *et al.* (1999) found that somatosensory gating occurs, but is weaker during passive than during active movement, and therefore suggested that both peripheral and central mechanisms contribute to the gating.

Whether such movement-related somatosensory gating is responsible for the reduced perception of self-produced tactile stimuli in humans is unknown. Furthermore, the neural processes underlying movement-related gating in SI are undetermined. In order for somatosensory cortex activity to be attenuated to self-produced sensory stimuli, these stimuli need to be predicted accurately. The cerebellum is a likely site for a forward model of the motor apparatus that provides predictions of the sensory consequences of motor commands, which are then compared with the actual sensory feedback from the movement (Ito, 1970; Paulin, 1989; Miall, *et al.*, 1993; Wolpert, *et al.*, 1998). The main input to the cerebellum, the climbing fibres from the inferior olive, has been proposed to act as a comparator between intended and achieved movement, signalling errors in motor performance (Oscarsson, 1980). Evidence for this comes from electrophysiological studies demonstrating that neurons in the inferior olive of cats respond to passively applied cutaneous stimuli but not to similar stimuli produced by a voluntary movement of the cat (except when stimuli were unexpectedly encountered during movement; Gellman *et al.*, 1985). Similarly, Andersson & Armstrong (Andersson & Armstrong, 1985; 1987) found that inferior olive neurons fire when a cat walking on a horizontal ladder encounters a rung that unexpectedly gives way. Therefore inferior olivary neurons have been proposed to act as somatic 'event detectors' responding particularly reliably to unexpected stimuli (Oscarsson, 1980; Simpson *et al.*, 1995). The error signals are sent from the inferior olive to the cerebellum. They may be used to modify motor commands during performance, to modulate neural responses to the sensory consequences of the movement, and to update the forward model.

In the present study, fMRI was used to examine the neural basis of the differential perception of self- and externally produced tactile stimuli. On the basis of the neurophysiological data described above, it was predicted that activity in the somatosensory cortex would increase when the tactile stimulation was externally generated relative to when it was self-generated. In addition, it was predicted that activity in the cerebellum would be increased during externally produced tactile stimulation relative to self-produced tactile stimulation. This hypothesis was based on the proposal that externally produced tactile stimulation can not be predicted accurately by the forward model. This type of stimulation will therefore result in a higher level of sensory discrepancy resulting from the comparison process than a self-produced tactile stimulus, which can be accurately predicted by the forward model.

A tactile stimulation device (**Figure 6-1**) allowed a sinusoidal tactile stimulus to be applied to the subject's left palm either by the subject's right hand or by the experimenter. To examine the neural correlates of self-produced relative to externally produced tactile stimuli a factorial design was employed with the factors of 1) self-generated movement of the right hand vs. rest, and 2) tactile stimulation on the left palm vs. no stimulation. There were four conditions: self-generated tactile stimulation; self-generated movement without tactile stimulation; externally generated tactile stimulation; and rest (**Figure 6-2**). Using this design it was possible to assess what brain activity is unique to self-generated tactile stimulation by factoring out activity associated with self-generated movement and tactile stimulation alone.

6.2 Methods

6.2.1 Subjects

Six normal right-handed volunteers (4 females and 2 males; mean age 33 years) gave informed consent and participated in the study, which was approved by the National Hospital for Neurology and Neurosurgery Ethics Committee.

6.2.2 Experimental Design

The experiment was split into two 12-minute sessions. Each subject underwent 200 fMRI scans in each session. Within each session the subject lay supine on the MRI bed with their right arm fixed over their chest to limit movement to the fingers. Their left arm was secured to a perspex sheet with the left hand perpendicular to the scanning bed about 5 cm from the fingers of the right hand. Attached to the perspex sheet was the tactile stimulus device (**Figure 6-1**). The tactile stimulus device consisted of a piece of soft foam attached to a plastic rod (length 70 cm) which could pivot vertically about its centre. The rod was situated inside a plastic box. A pulley system allowed the foam stimulus to be retracted or exposed, under the experimenter's control, during the scanning. When exposed the foam made light contact with the subjects left palm and could be moved by the movement of the rod. The rotation of the rod was mechanically limited to vertical sinusoidal movements of amplitude 1.5 cm. The rod could be moved either by the subject using their right hand or, from the other end of the rod, which was outside the scanner, by the experimenter.

Figure 6-1

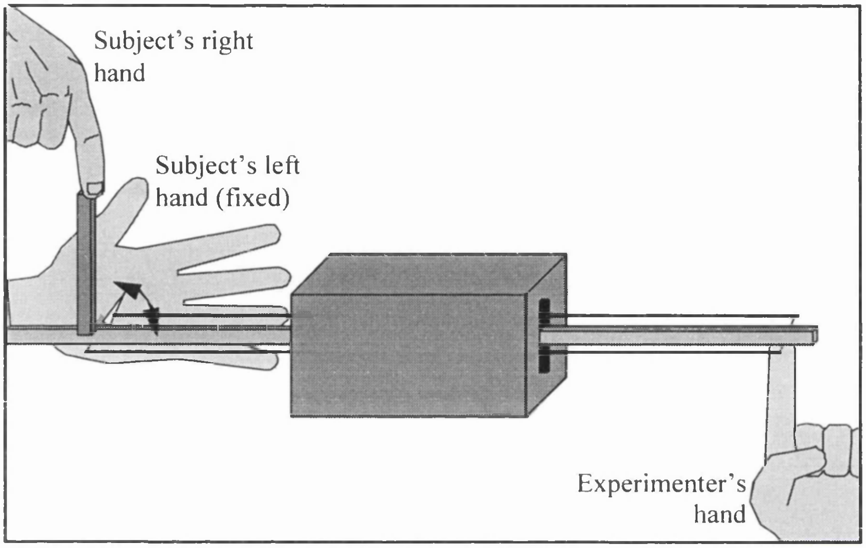


Diagram of experimental set-up. A tactile stimulus device consisted of a piece of soft foam attached to a plastic rod which could pivot about its centre. The rotation of the rod was mechanically limited to vertical movements of amplitude 1.5 cm. The rod could be moved either by the subject using their right hand or, from the other end of the rod, which was outside the scanner, by the experimenter. A pulley system allowed the foam stimulus to be retracted or exposed, under the experimenter's control, during the scanning. When exposed the foam made light contact with the subjects left palm. See text for details.

There were two experimentally manipulated variables: whether the subjects were required to make movements and whether or not a tactile stimulus occurred. In the self-generated movement conditions movements of the rod were always made with the index and third fingers of the right hand. Subjects were instructed to move the rod up and down to its full extent at a frequency of 2 Hz and practised beforehand to ensure that they could reliably generate the desired movements. The apparatus minimised variation in force, amplitude and frequency of the tactile stimulus throughout the experiment.

There were four conditions using a within-subject factorial design, with a total of 12 replications of each condition per subject (**Figure 6-2**). Each condition lasted 30 seconds, and was followed in immediate succession by the next condition.

Subjects were told which condition to perform through earphones (corresponding to the words in parenthesis following each condition name).

Figure 6-2

	Tactile stimuli	**No tactile stimuli**
Self-generated movement	A: Self-produced tactile stimuli	B: Self-produced movement without tactile stimuli
No self-generated movement	C: Externally-produced tactile stimuli	D: Rest

2x2 factorial design used in the present study. There were four conditions – see text for details.

Condition A: self-generated movements producing tactile stimulation ('touch')

Subjects made vertical sinusoidal movements of the rod with their right hand. This movement produced tactile stimulation on the palm on their left hand. Subjects were told that in the 'touch' conditions, their right hand movements would produce tactile stimulation on their left palm.

Condition B: self-generated movements without tactile stimulation ('move')

Subjects made vertical sinusoidal movements of the rod with the their right hand. The tactile stimulus was removed from the subject's left palm so no tactile stimulation occurred. Subjects were told that in the 'move' conditions their right hand movements would not produce any tactile sensation.

Condition C: externally produced tactile stimulation ('feel')

No subject movement occurred. The experimenter moved the tactile stimulus sinusoidally across the subject's left palm at a frequency of 2 Hz. Subjects were told that in the 'feel' conditions they would receive tactile stimulation on their left palm.

Condition D: no movement, no tactile stimulation ('rest')

Neither subject movement nor tactile stimulation occurred. The experimenter moved the rod sinusoidally at a frequency of 2 Hz (in order to control for any confounds caused by movement of the rod), but the tactile stimulus did not make contact with the subject's palm.

The order of conditions was randomised and counterbalanced within and between subjects. Scanning took place in a darkened room and subjects were asked to keep their eyes closed throughout the experiment. The number of movements made in each condition was counted by the experimenter. There was no significant difference between the total number of movements produced by subjects in conditions A and B and by the experimenter in conditions C and D. The average frequency of movements of the four conditions was 2.25 Hz.

6.2.3 Data acquisition

A Siemens VISION system (Siemens, Erlangen) operating at 2 T was used to acquire both axial gradient-echo, echo-planar T2* weighted image volumes with blood oxygenation level- dependent (BOLD) contrast and axial T1 weighted structural images for anatomical co-registration. The experiment began with the acquisition of a T1 weighted anatomical image from each participant. Functional imaging was then performed in two separate runs with a 3 minute break in between sessions. Each functional-image volume comprised 48 3 mm axial slices with in-plane resolution of 3x3 mm positioned to cover the whole brain. During each run, volumes were acquired continuously every 4.1 s, while participants performed either epochs of the experimental task lasting 32.8 s (eight volumes) or epochs of rest (lasting 32.8 s or eight volumes). Each run began with eight 'dummy' volumes, which were subsequently discarded to allow for T1 equilibration effects. The total duration of the experiment was around 35 mins, during which time 400 functional-image volumes were acquired, of which 384 were subsequently analysed.

6.2.4 Statistical analysis

Functional imaging analysis used the technique of statistical parametric mapping, implemented in SPM97 (Friston *et al*, 1997b). For each subject, the imaging time series was realigned using sinc interpolation using a 11x11x11 kernal (Friston *et al.*, 1995b). The data were adjusted to remove any signal correlated with head rotation and motion. The scans were then stereotactically normalised using affine registration followed by non-linear registration using 1196 parameters. The data were resampled using sinc interpolation into the space of Talairach & Tournoux (Talairach & Tournoux, 1988). The scans were then smoothed with a Gaussian kernel of 6 mm full-width half maximum.

The analysis of functional imaging data entails the creation of statistical parametric maps that represent a statistical assessment of condition-specific effects hypothesised by the experimenter (Friston, *et al.*, 1990; Friston *et al.*, 1995a; Friston, 1997b). Condition-specific effects were estimated with the General Linear Model with a delayed boxcar wave-form. Low-frequency sine and cosine waves modelled and removed participant-specific low-frequency drifts in signal, and global changes in activity were removed by proportional scaling. Areas of significant change in brain activity were specified by appropriately weighted linear contrasts of the condition-specific effects and determined using the t-statistic on a voxel to voxel basis. See chapter 2 (Methods) for details of SPM.

Statistical analysis was performed to examine the main effects of movement [(A+B)-(C+D) in **Figure 6-2]** and tactile stimulation [(A+C)-(B+D)], the interaction of these two factors [(A-B)-(C-D) and (C-D)-(A-B)]. Examination of the interaction reflects the differential effects of self- vs. externally produced tactile stimuli while factoring out activity due to movement or tactile stimuli alone. 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). Resultant areas of activation were characterised in terms of their peak heights.

6.3 Results

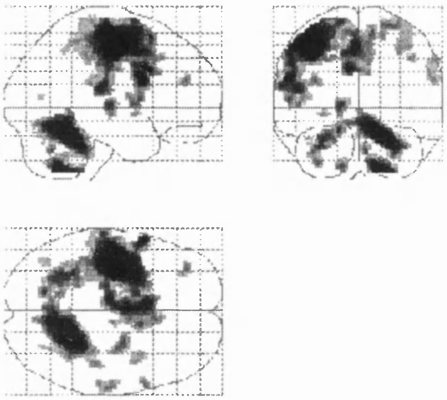
6.3.1 *Main effect of self-generated movement* (Table 6-1)

The main effect of movement of the right hand [(A+B)-(C+D) in **Figure 6-2**] revealed activity in a number of contralateral motor, premotor, and prefrontal areas and bilateral cerebellar areas (**Figure 6-3**). The range of activated areas is consistent with previous studies that have examined self-generated movements (e.g. Deiber *et al.*, 1991; Jahanshahi *et al.*, 1991; Frith *et al.*, 1991), and is similar to the areas activated by self-generated movement in the PET study described in **Chapter 3**. Relative deactivations, where activity was greater in the conditions where no movement occurred [(C+D)-(A+B)] were seen in the inferior parietal lobe, insular cortex, right inferior frontal cortex, right middle temporal gyrus, and the left superior frontal gyrus (BA 8 and 9), as shown in **Figure 6-4**.

Table 6-1: Table showing regional changes in activity in the comparison of the self-generated movement conditions and those without movement.

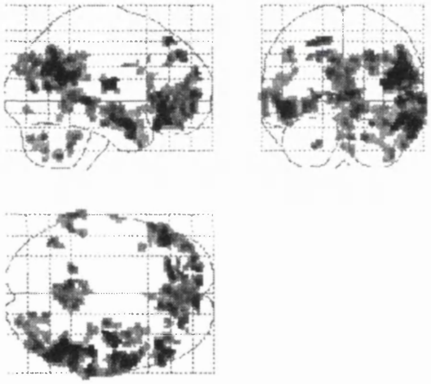
Area	Tailarach coordinates (x,y,z)	Z value and corrected P value
Increases in BOLD signal		
Cerebellum (R)	18 -46 -22	9.20 (P<0.0001)
Cerebellum (L)	-28 -52 -24	7.53 (P<0.0001)
Precentral gyrus (BA 4) (L)	-34 -12 58	9.17 (P<0.0001)
Precentral gyrus (BA 4) (R)	26 -6 68	6.44 (P<0.0001)
Postcentral gyrus (BA 3) (L)	-48 -16 52	8.61 (P<0.0001)
Thalamus (L)	-14 -16 2	7.06 (P<0.0001)
Medial frontal (BA 10) (L)	-34 44 22	5.68 (P<0.001)
Putamen (L)	-28 4 -4	4.98 (P<0.0001)
Decreases in BOLD signal		
Inferior parietal (BA 40) (R)	42 –52 20	7.75 (P<0.0001)
Insula sulcus (R)	40 –10 16	7.62 (P<0.0001)
Inferior frontal (R)	50 32 -12	7.32 (P<0.0001)
Middle temporal (BA 21) (R)	60 2 –18	7.26 (P<0.0001)
Dorsal frontal (R)	8 58 8	6.94 (P<0.0001)
Superior frontal (BA 8) (L)	-14 38 54	6.87 (P<0.0001)
Superior frontal (BA 9) (L)	-8 46 36	6.43 (P<0.0001)

Figure 6-3



Sagittal, coronal and axial views of statistical parametric maps showing significant (P<0.05 corrected for multiple comparisons) activations associated with those conditions where there was self-generated movement compared to those where there was not: (A+B)-(C+D).

Figure 6-4



Sagittal, coronal and axial views of statistical parametric maps showing significant (P<0.05 corrected) activations associated with those conditions where there was no self-generated movement compared to those where there was self-generated movement: (C+D)-(A+B).

6.3.2 Main effect of tactile stimulation (**Table 6-2**)

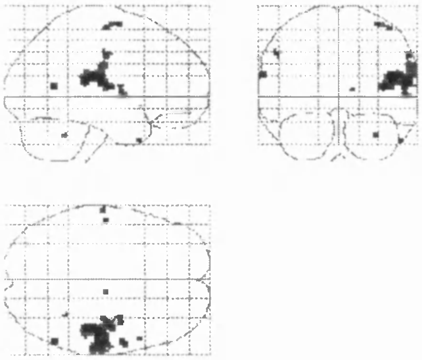
The main effect of tactile stimulation [(A+C)-(B+D) in **Figure 6-2**] on the left palm revealed activity in contralateral primary (SI) and bilateral somosensory (SII) cortices (**Figure 6-5**). Somatosensory representations occupy the postcentral gyrus (SI) and lateral parietal-opercular cortex (SII). The activated areas correspond to those reported in other studies using magnetoelectroencephalography (Kakigi *et al*, 2000), PET (Burton *et al*, 1997), and fMRI (Krubitzer *et al.*, 1995; Paulesu *et al.*, 1997; Polonara *et al*, 1999). Polonara and colleagues (1999) used fMRI to map somatosensory areas activated by unilateral tactile stimulation of the palm and fingers with a rough sponge. The current results are very similar to the results of Polonara and colleagues. In particular the activated areas ipsilateral to the tactile stimulation - the posterior parietal and opercular cortices, roughly symmetrical to those activated in the contralateral hemisphere - were in very similar in both studies.

Relative deactivations, where activity was greater in the conditions in which no tactile stimulation occurred [(B+D)-(A+C)] were seen in the left precentral gyrus (BA 6), superior parietal (BA 7) and inferior parietal (BA 40) cortex, as shown in **Figure 6-6**.

Table 6-2 Table showing regional changes in activity in the comparison of the tactile stimulation conditions and those without tactile stimulation (A+C)-(B+D).

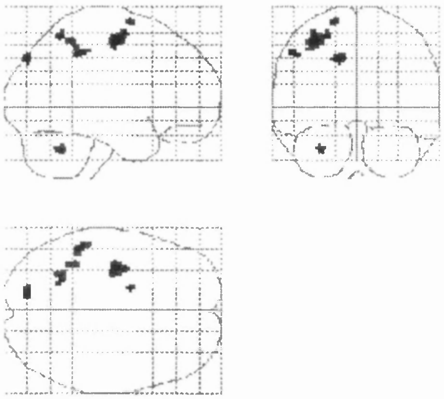
Area	Tailarach coordinates (x,y,z)	Z value and corrected P value
Increases in BOLD signal		
Postcentral gyrus (BA 2) (R)	58 -18 14	6.92 (P<0.0001)
Parietal operculum (R)	46 -22 18	7.43 (P<0.0001)
Parietal operculum (L)	-52 -24 18	5.01 (P<0.01)
Medial Temporal (BA 39)	56 -58 10	6.64 (P<0.0001)
Inferior Temporal (R)	52 14 -38	5.39 (P<0.01)
Cerebellum (R)	32 -48 -34	5.29 (P<0.01)
Decreases in BOLD signal		
Precentral gyrus (BA 6) (L)	-34 –10 56	5.37 (P<0.01)
Superior parietal (BA 7) (L)	-12 –82 40	5.25 (P<0.05)
Inferior parietal (BA 40) (L)	-50 –40 44	4.78 (p<0.05)

Figure 6-5



Sagittal, coronal and axial views of statistical parametric maps showing significant (P<0.05 corrected) activations associated with those conditions where there was tactile stimulation compared to those where there was not: (A+C)-(B+D).

Figure 6-6



Sagittal, coronal and axial views of statistical parametric maps showing significant (P<0.05 corrected) activations associated with those conditions where there was no tactile stimulation compared to those where there was tactile stimulation: (B+D)-(A+C).

6.3.3 *Interaction between self-generated movements and tactile stimulation* (**Table 6-3**)

Examination of the interaction and reflects the differential effects of self- vs. externally produced tactile stimuli while factoring out activity due to movement and tactile stimuli alone (**Figure 6-7**). No a priori predictions were made regarding the activated regions in the first interaction analysis (A-B)-(C-D) and no activation reached a level significance that was corrected for multiple comparisons.

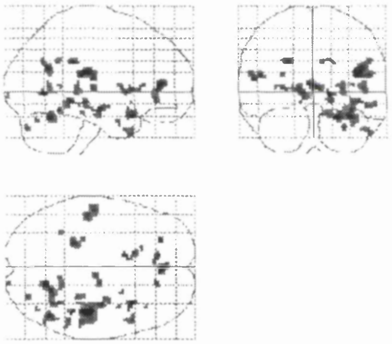
The second interaction analysis (C-D)-(A-B) enabled us to investigate the neural correlates of the reduced intensity and tickliness of a self-produced tactile stimulus that was described in Chapter 5 and previously reported by other researchers (Weiskrantz *et al.*, 1971; Claxton, 1975). This analysis demonstrated that there was significantly less activity in bilateral secondary somatosensory cortex, the anterior cingulate (Area 24/32) and the anterior lobe of the right cerebellum when the tactile stimulation was self-produced relative to when it was externally produced (**Figures 6-8, 6-9 & 6-10**).

As can be seen from the parameter estimates the pattern of activity in each of these areas is different. Self-generated movements that touched the hand (condition A), and movements that did not (B), resulted in similar activation of somatosensory and anterior cingulate cortex. In contrast there was a significant difference between the relative BOLD signal in the right cerebellum in these two conditions: this area was significantly less activated by self-generated movements that touched the hand (condition A) than by movements that did not (condition B).

Table 6-3: Table showing regional changes in activity in externally produced tactile stimulation conditions relative to the self-produced tactile stimulation (C-D)-(A-B).

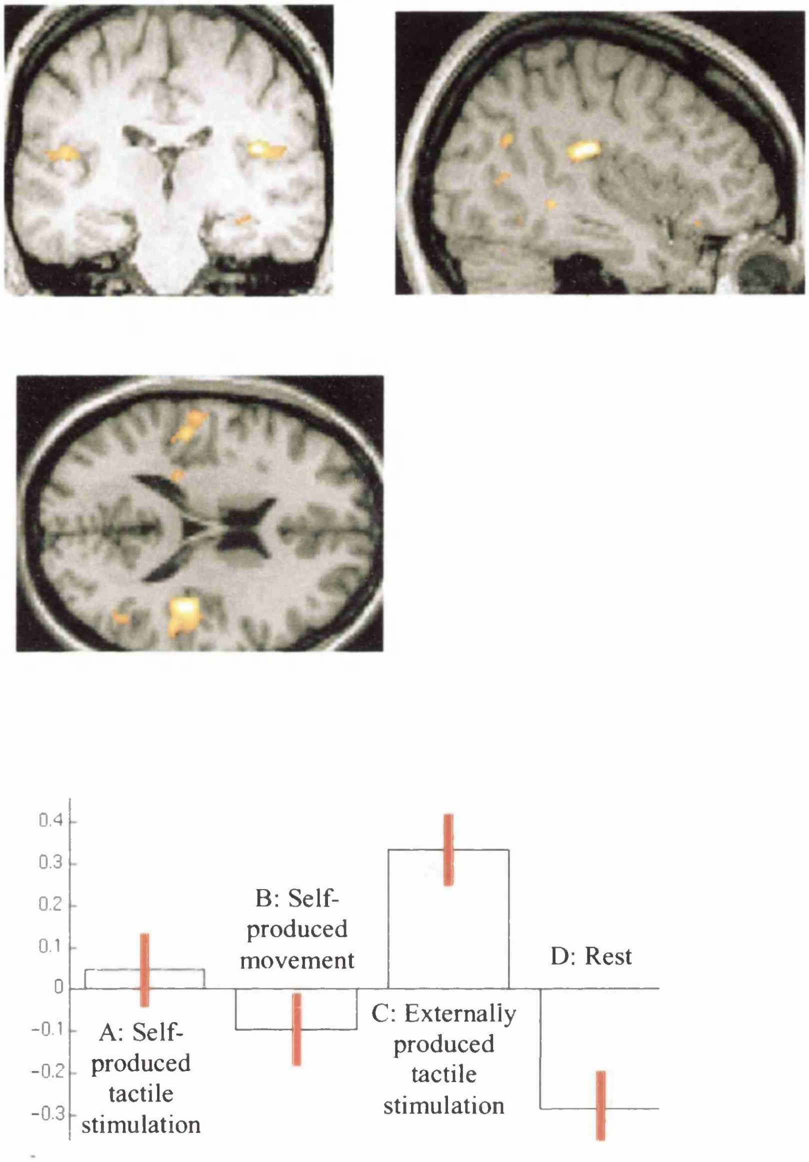
Area	Tailarach coordinates (x,y,z)	Z value and corrected P value
Parietal operculum (R)	42 -24 18	6.42 P<0.0001
Parietal operculum (L)	-22 -36 30	5.08 P<0.05
Cerebellum (R)	22 -58 -22	5.45 P<0.005
Anterior cingulate (BA24/32)	2 42 6	5.41 P<0.006

Figure 6-7



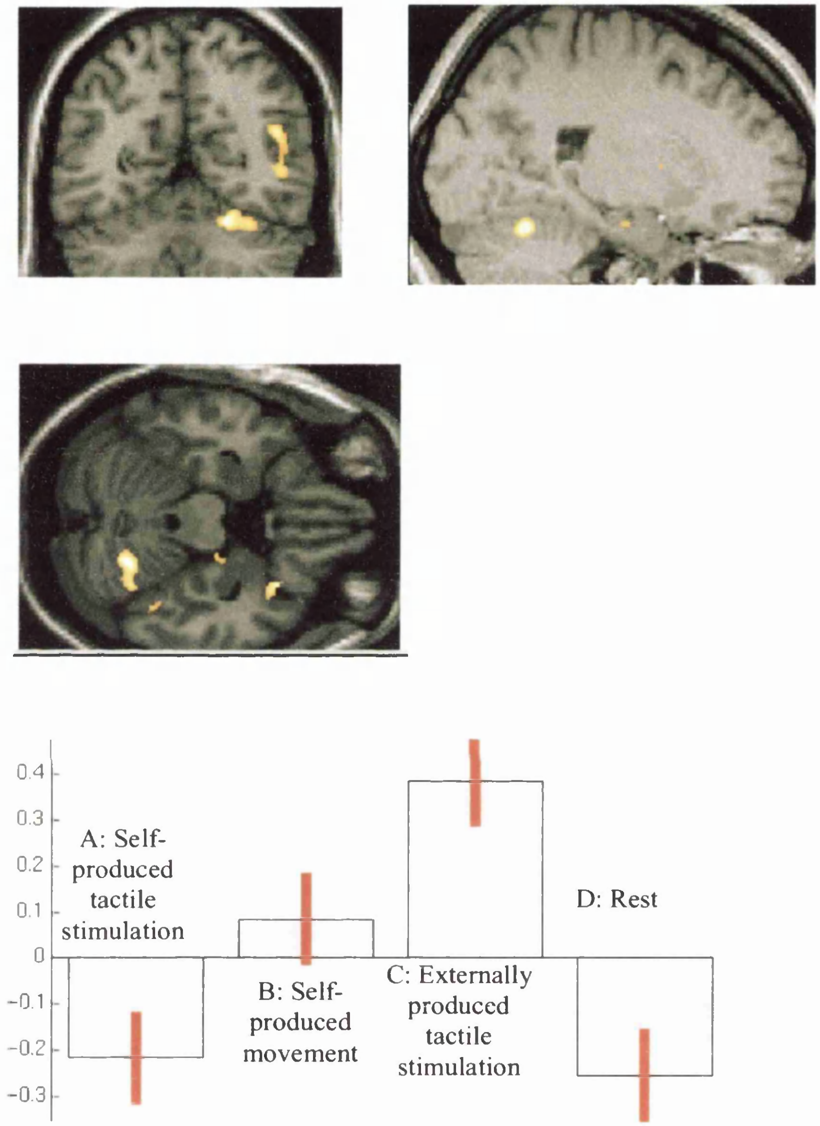
Sagittal, coronal and axial views of statistical parametric maps showing significant ($P<0.05$ corrected) activations associated with externally produced tactile stimulation relative to self-produced tactile stimulation: (C-D)-(A-B).

Figure 6-8



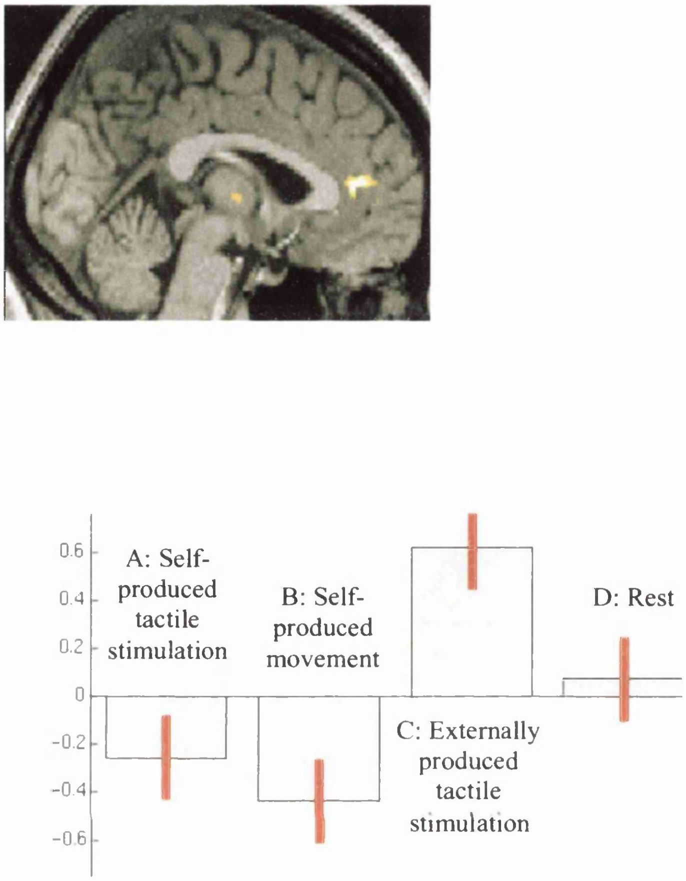
Significant (P<0.05 corrected for multiple comparisons) decreased activity in bilateral secondary somatosensory cortex associated with the interaction between the effects of self-generated movement and tactile stimulation. Condition-specific parameter estimates, which reflect the adjusted BOLD contrast signal relative to the fitted mean and expressed as a percentage of whole brain mean activity are shown. The effects at voxels in the right (42, -24, 18) and left (-22, -36, 30) parietal operculum are shown, for illustration, for a single subject in the lower panel. Similar parameter estimates were obtained for the remaining subjects in this statistical model. The labelling of the conditions corresponds to A=self-generated tactile stimulation; B=self-generated movement without tactile stimulation; C=externally generated tactile stimulation; D=rest.

Figure 6-9



Significant (P<0.05 corrected) decreased activity in right anterior cerebellar cortex associated with the interaction between the effects of self-generated movement and tactile stimulation. Condition-specific parameter estimates at the voxel 22, -58, -22 are shown, for illustration, for a single subject in the lower panel.

Figure 6-10



Significant (P<0.05 corrected for multiple comparisons) decreased activity in anterior cingulate cortex associated with the interaction between the effects of self-generated movement and tactile stimulation. Condition-specific parameter estimates at the voxel 2, 42, 6 are shown, for illustration, for a single subject in the lower panel.

6.4 Discussion

The results demonstrate that self-produced tactile stimulation results in less activation of bilateral secondary somatosensory cortex and anterior cingulate cortex than externally produced tactile stimuli. In addition, activity in the anterior cerebellar cortex was attenuated by self-produced movements that generated tactile stimuli relative to movements that did not. It is proposed that the cerebellum is involved in predicting the specific sensory consequences of movements and comparing these sensory predictions to the actual sensory re-afference from the movement. In this way the cerebellum provides the signal that is used to cancel the somatosensory response to self-produced tactile stimulation.

In the current study self-produced tactile stimuli resulted in less activation of somatosensory and anterior cingulate cortex than identical tactile stimuli that were externally produced. The reduction of activity in these areas to self-produced tactile stimuli is likely to be the physiological correlate of the reduced perception associated with this type of stimulation that was described in Chapter 5 and previously reported by other researchers (Weiskrantz et al., 1971; Claxton, 1975). The finding that somatosensory cortex is activated more by externally produced than by self-produced tactile stimulation is in accord with neurophysiological experiments demonstrating that active touch results in less neuronal firing in SI than passive and external touch of the same surface (Chapman, 1994).

The anterior cingulate cortex (BA 24/32) was also significantly activated by externally produced, relative to self-produced, tactile stimuli (**Figure 6-10**). Previous studies have implicated this area in affective behaviour (Vogt et al, 1992; Vogt & Gabriel, 1993; Coghill et al, 1994) and have shown that rats will self-stimulate this site, suggesting it is a site of positive reinforcement (Porrino, 1993). The activity in the anterior cingulate in the present study may have been related to the finding that externally produced tactile stimuli are perceived as more tickly and pleasant than self-produced tactile stimuli in the previous study described in **Chapter 5**. Phillips and her colleagues have found area 32 activation in response to happy facial expressions (Phillips et al, 1998a), and to emotional vocal expressions (Phillips et al, 1998b). This suggests that this area is involved in processing emotionally salient stimuli, including stimuli of positive emotions. In support of this suggestion, John Morris and his colleagues (personal communication) have found that a similar region of the anterior cingulate was activated when subjects looked at happy versus sad faces using fMRI.

While the changes in somatosensory and anterior cingulate cortex are likely to underlie perception of tactile stimuli, the pattern of brain activity observed in the cerebellum suggests that this area is the source of the somatosensory modulation. In somatosensory areas activity was attenuated by all self-generated movement: they were equally activated by movement that did and that did not result in tactile stimulation (**Figure 6-8**). This is in line with an intriguing fMRI result reported by Jansma et al. (Jansma et al., 1998). In their experiment subjects were instructed to make finger/thumb opposition movements. Whether subjects did or did not make contact between their fingers and thumb did not affect brain activity, which was equivalent everywhere, including somatosensory cortex, in both conditions.

In contrast, the right anterior cerebellar cortex was selectively deactivated by self-produced movement which resulted in a tactile stimulus, but not by movement alone, and significantly activated by externally produced tactile stimuli (**Figure 6-9**). Therefore the cerebellum responds differently to movements depending on their sensory consequences and might be involved in predicting the specific sensory consequences of movement. The pattern of activity within the cerebellum suggests that it might be involved in signalling the sensory discrepancy between the predicted and actual sensory feedback of a movement. In the current study, when the actual sensory feedback of a movement matches the predicted sensory feedback (when the tactile stimuli are self-produced), cerebellar activity decreases and the somatosensory cortex is not activated (relative to rest). In contrast when there is a sensory discrepancy between the predicted and actual sensory feedback of a movement (when the tactile stimuli are externally produced), cerebellar activity increases and the somatosensory cortex is activated.

Gao et al.(1996) found that the cerebellum dentate nucleus was activated more when subjects had to make sensory discriminations between objects by moving the objects with their fingers than when sensory stimuli were moved externally, or when no sensory discrimination was required. This suggests that the cerebellum dentate nucleus is involved in the acquisition and discrimination of sensory stimuli. Our results showed that the cerebellar cortex was activated more by external tactile stimuli than by tactile stimuli produced by the subject's movement. Although this appears to contradict the findings of Gao et al., this could be explained by the different cerebellar regions investigated in both studies. Gao et al. investigated the dentate nucleus, whereas we refer to the cerebellar cortex in our study. Since the output of the cerebellar cortex to the dentate is inhibitory, these regions would be predicted to show opposite patterns of activity to the same stimuli. Therefore, our results might not be in contradiction to those of Gao et al.

This reasoning is consistent with the theory that the cerebellum is a component of a system that uses forward models to provide precise predictions of the sensory consequences of movements. When congruent with the actual sensory consequences these predictions can be used to cancel the percept of the stimulation that results from the movement (Ito, 1970; Paulin, 1989; Miall, et al., 1993; Wolpert et al., 1998). It has been argued that the main input to the cerebellum, the climbing fibres from the inferior olive, acts as a comparator between intended and achieved movement (Gellman et al., 1985; Andersson & Armstrong, 1985; 1987), detecting unexpected sensory events (Oscarsson, 1980; Simpson et al., 1995).

It is proposed that by correctly predicting the tactile consequences of self-produced movements, the cerebellum mediates the somatosensory gating, and the decreased perception, associated with self-produced tactile stimulation. Since Purikinje cells in the cerebellar cortex are inhibitory and innervate the cerebellar nuclei, decreased activity in the cerebellar cortex (when sensory stimulation is self-produced) would cause an increase in the firing of the cerebellar nuclei. The cerebellar nuclei output is also inhibitory so in this case there would be an decrease in inhibition of the thalamus, which would increase its activity, causing an decrease in activity of the somatosensory cortex. An interesting, and undetermined, issue is what local blood flow and BOLD signal in the cerebellar cortex reflects in terms of neuronal activity. This issue will be addressed more fully in the following chapter.

The cerebellar activation in the current study was ipsilateral to the moving (not the stimulated) hand. There are two alternative explanations for this laterality. The right cerebellum activity might correspond to the movement of the right hand rather than to the tactile information on the left hand. Alternatively the activity in the right cerebellar might be part of a bilateral response to tactile stimulation observed in recent studies (Peeters et al, 1999). Cerebellar cells have long been thought of as having ipsilateral receptive fields (Llinas & Sotelo, 1992) but more recently bilateral responses have been noted to sensory stimulation (Peeters et al, 1999). The proposal that the cerebellum is involved with predicting of the sensory consequences of motor commands and comparing those predictions with the actual sensory feedback is consistent with research demonstrating the role of the cerebellum in processing sensory information on line (Morrissette & Bower, 1996; Leiner et al., 1995; Gao et al., 1996; Bower, 1997a; Bower, 1997b).

6.5 ***Conclusion***

The experiment in the previous chapter demonstrated that self-produced tactile stimulation is perceived as less intense and ticklish than the same stimulation generated externally. fMRI was used to examine neural responses when subjects experienced a tactile stimulus that was either self-produced or externally produced. More activity was seen in bilateral secondary somatosensory cortex and anterior cingulate cortex when the tactile stimulus was externally produced relative to when it was self-produced. The responses in these areas might mediate the differential perception of self- and externally produced stimulation. In the cerebellum there was less activity associated with a self-produced movement that generated a tactile stimulus than with a movement that did not. This difference suggests that the cerebellum is involved in predicting the specific sensory consequences of movements, providing the signal that is used to cancel the somatosensory response to self-generated stimulation. In the following chapter this hypothesis is specifically investigated by evaluating the influence of the cerebellum over somatosensory cortices when tactile stimulation were self-produced compared to when it was externally produced.

7 CHAPTER 7: THE CEREBELLUM CONTRIBUTES TO SOMATOSENSORY CORTICAL ACTIVITY DURING SELF-PRODUCED TACTILE STIMULATION

7.1 Introduction

In the previous chapter, fMRI was employed to investigate the neural basis of the differential perception of self- and externally produced tactile stimuli. The study demonstrated an increase in activity of secondary somatosensory cortex when subjects experienced an externally produced tactile stimulus on their palm relative to a self-produced tactile stimulus (**Figure 6-8**). It was proposed that the inhibition of somatosensory cortex activity by self-generated movements could result from the accurate prediction of the sensory feedback when a tactile stimulus is self-produced. In the cerebellum there was less activity associated with a movement that generated a tactile stimulus than with a movement that did not (**Figure 6-9**). In other words, the cerebellum responded differently to movements depending on their sensory consequences. Therefore the cerebellum might be involved in predicting the specific sensory consequences of movement and signalling the sensory discrepancy between the predicted and actual sensory feedback of a movement. In the fMRI study, when the actual sensory feedback of a movement matched the predicted sensory feedback (when the tactile stimuli were self-produced), cerebellar activity decreased and the somatosensory cortex was not activated (relative to rest). In contrast when there was a sensory discrepancy between the predicted and actual sensory feedback (when the tactile stimuli were externally produced), cerebellar activity increased and the somatosensory cortex was activated above rest. It was therefore proposed that the cerebellum provides the signal that is used to attenuate the somatosensory response to self-produced tactile stimulation.

In this chapter regression analyses are used to test this hypothesis, based on the following principles. If the activity in one region (area A) predicts the activity in another region (area B) then the strength of the prediction reflects the influence area A could be exerting on area B. If the strength of the prediction (measured by regression analysis) varies with the psychological context in which the physiological activity is measured then this is evidence for a 'psychophysiological interaction' (Friston *et al.*, 1997a). Significant psycho-physiological interactions have been demonstrated in several previous functional neuroimaging studies. For example, Morris *et al.*(1998) demonstrated that the regression of activity in occipital cortex on activity in the amygdala depends on the emotional context: the regression was positive when subjects viewed fearful faces, and negative when they viewed happy faces.

Linear regression was used to test the anatomically constrained prediction (the cerebellum innervates somatosensory cortices via the ventral thalamus; see **Figure 7-1**) that the influence of the cerebellum on the ventral thalamus and somatosensory cortex would be strong in conditions where the sensation could be predicted from movement (self-generated tactile stimuli), but weak when the sensation could not be predicted (externally generated tactile stimuli).

7.2 Methods

7.2.1 Subjects and Design

The data from the six subjects in the experiment reported in the previous chapter were used for the current analysis. Refer to **chapter 6** for information regarding subjects, design, procedure and data acquisition used in the experiment.

7.2.2 Conditions

There were four conditions using a within-subject factorial design (see **Figure 6-2**):

- Condition A - self-generated movements producing tactile stimulation
- Condition B - self-generated movements without tactile stimulation
- Condition C - externally produced tactile stimulation
- Condition D - no movement, no tactile stimulation

7.2.3 Regression analyses testing for psychophysiological interactions

The hypothesis concerning psychophysiological interactions was constrained on the basis of established anatomical pathways between the cerebellum and somatosensory cortex in the monkey (Waxman & DeGroot, 1995; **Figure 7-1**).

First a target area in the cerebellum that showed a significant interaction between self-generated movement and tactile stimulation was identified for each subject, that is the area in which activity was greater when tactile stimulation was externally produced than when it was self-produced: (C-D)-(A-B). SPM was then used to identify brain areas within the subset shown in **Figure 7-1** where activity was predicted by activity in the target area (the cerebellum) during self-generated tactile stimulation, but not during externally generated stimulation.

Figure 7-1

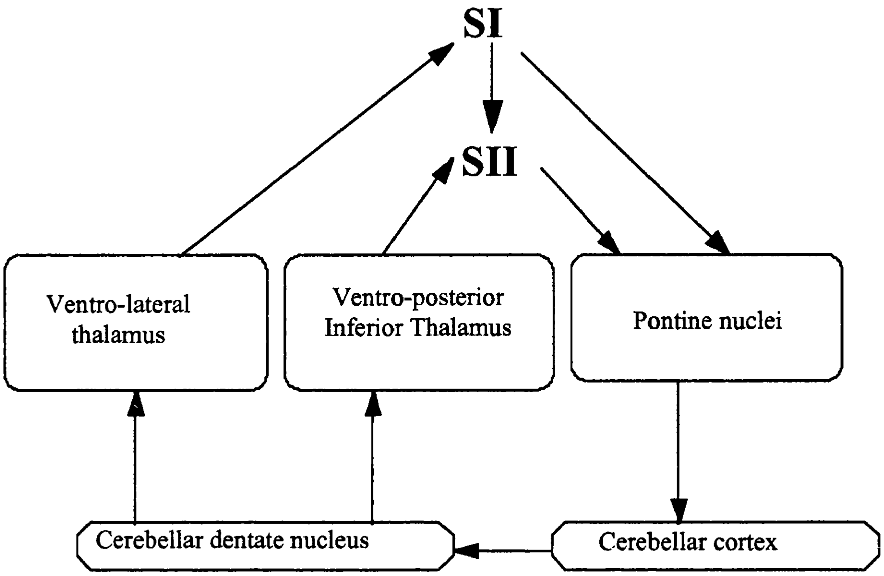


Diagram of anatomical pathways between the cerebellum and somatosensory cortex in the monkey, taken from Waxman & deGroot (1995).

This analysis was performed in several stages:

Step 1

From the original factorial analysis the results from the interaction between the two factors self-generated movement and tactile stimulation [(C-D)-(A-B)] was chosen for each subject. The voxel of maximum intensity in the region of the cerebellum that showed a significant interaction was selected.

Step 2

The activity in this target voxel of the cerebellum was plotted as a function of scan or time. This resulted in a vector that corresponded to the BOLD signal in this region (adjusted for confounds) in each scan over the time course of the experiment (384 scans). This vector, called S, was mean-corrected and comprised the physiological factor to be used in the analysis. A psychophysiological interaction (PPI) simply means that the ability of S to predict changes in the areas identified by the PPI depends on the context, either 1: self-produced tactile stimulation, or 2: externally produced tactile stimulation.

Step 3

A regressor P is created, which corresponds to the interaction term in the experimental design. The order of the vector P is the same in terms of scans as that assumed by S. The value 1 was given to all scans corresponding to conditions B and C (see **Figure 6-2**), and -1 to all scans corresponding to conditions A and D. This leaves a vector of equal size to the vector from step 2 (the length of both is equal to the number of scans in the study), consisting of 1s and -1s. This vector has a mean = 0 so does not require mean-correction.

Step 4

These two vectors are multiplied together and the result is mean corrected. There are now three vectors:

a) BOLD activity in a particular voxel in the cerebellum over the time course of the experiment. This is the physiological signal component, S.

b) the condition order of the experiment: this is the psychological component, P.

c) the interaction between activity in a particular voxel and the corresponding task. This is the psychophysiological component, SxP=PPI

Step 5

A further statistical analysis is carried out in SPM in which PPI is specified as the covariate of interest. The two other vectors (the physiological signal component S and the psychological component P) are entered as confounds.

Regression with the covariate of interest (PPI) after removing the two confounding effects (S and P) was calculated for every voxel in the relevant brain regions. The significance of the regression in all these voxels was displayed in a SPM[t] map. A significant value implies a difference in the regression slopes linking cerebellar activity to activity in other brain areas in different psychological contexts. Any region in which activity can be predicted from the covariate of interest shows a psychophysiological interaction of the kind hypothesised.

Where significant effects were found the two regression slopes were plotted in order to visualise the effects revealed by the psychophysiological interaction. It was predicted that activity in the thalamus and somatosensory cortex would show a positive regression on activity in the cerebellum during the experience of self-generated tactile stimuli, but not during the experience of externally generated tactile stimuli.

7.3 Results

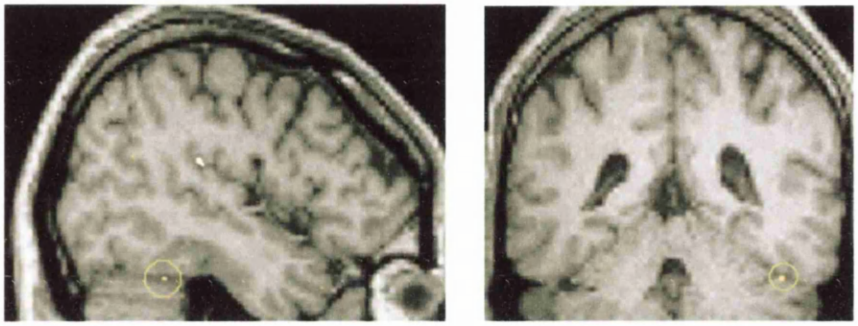
To test the hypothesis that the cerebellum can influence neural activity in other brain regions, regression analyses were performed to test for the presence of psychophysiological interactions. Brain regions of interest demonstrating significant ($P<0.001$) condition-specific changes in the influence of the cerebellum over the predicted brain regions (the thalamus and somatosensory cortices; **Figure 7-1**) in two subjects are shown in **Figure 7-2**. The data from these two subjects are representative of those from all six subjects, and are shown for illustration purposes.

Table 7-1: Regions showing an enhanced contribution from the cerebellum voxel used as the regressor during the administration of self-produced relative to externally produced tactile stimuli, in two representative subjects, for illustration.

	Coordinates (x, y, z)	Z value (P<0.001)
Subject 1		
Cerebellum voxel (regressor)	34, -56, -24	4.62
Post-central gyrus (R)	42, –12, 60	3.96
Parietal operculum (R)	38 -16 10	3.99
Parietal operculum (L)	-40 -16 2	3.75
Lateral Thalamus (R)	26,-16,-2	3.92
Medial Thalamus (R)	4,-18,6	5.02
Subject 2		
Cerebellum voxel (regressor)	38, -42, -44	2.62 (P<0.005)
Post-central gyrus (R)	-40, -6, 46	3.63
Parietal operculum (R)	46, -20, 16	4.09
Parietal operculum (L)	-46, -26, 10	3.88
Lateral Thalamus (R)	38, 2, 4	4.02
Lateral Thalamus (L)	-12, -19, 0	3.90

It is demonstrated here that, as predicted, activity in the thalamus, right SI and bilateral SII (**Figure 7-3**) showed a significant regression on activity in the cerebellum (**Figure 7-2**) during self-produced tactile stimuli conditions and not in conditions where tactile stimuli were externally produced.

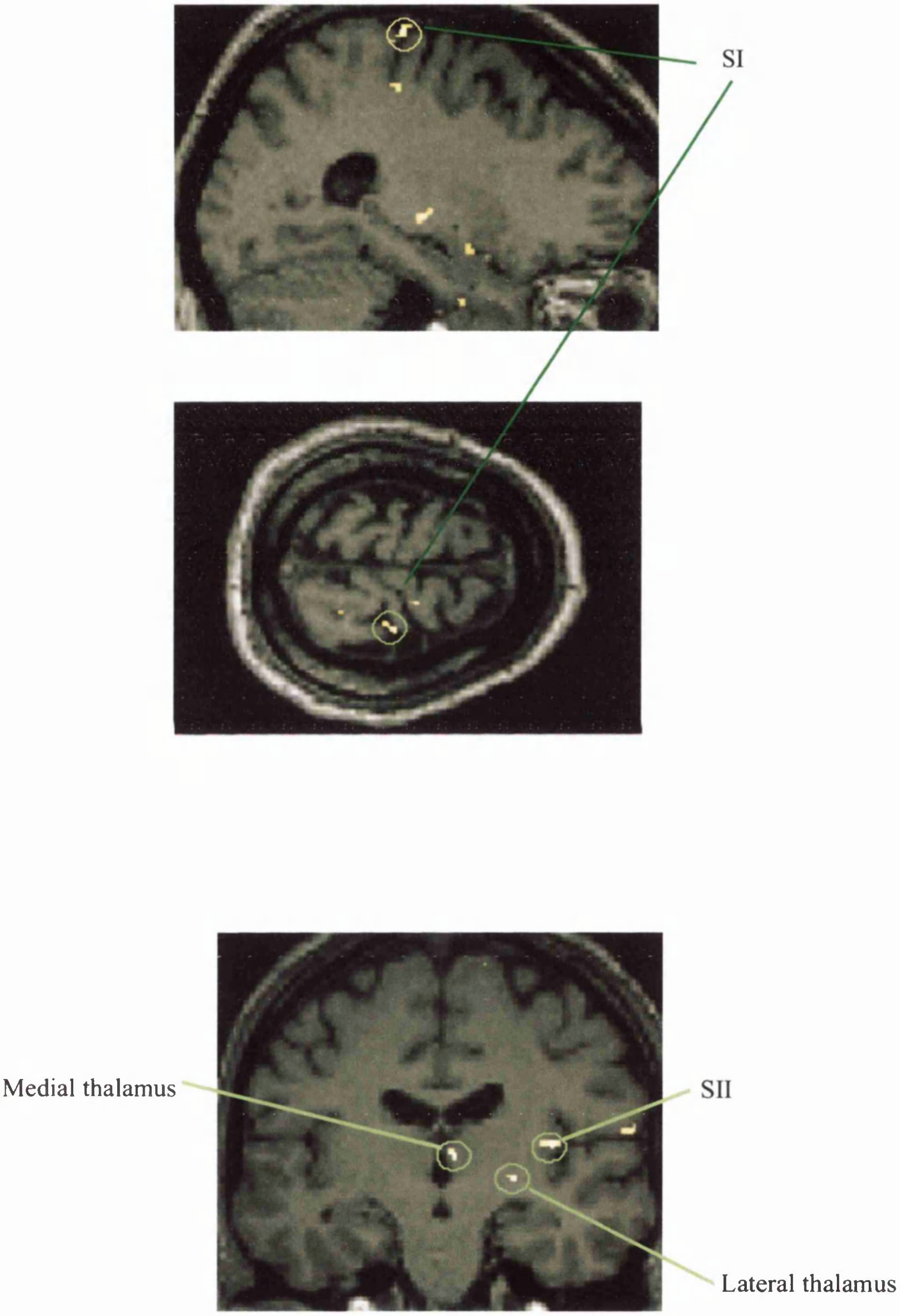
Figure 7-2



The cerebellum voxel (circled) used as the regressor in the psychophysiological interaction analysis. The voxel of maximum intensity in the cerebellum showing a significant interaction between the effects of self-generated movement and tactile stimulation was used as the regressor in the psychophysiological interaction analysis.

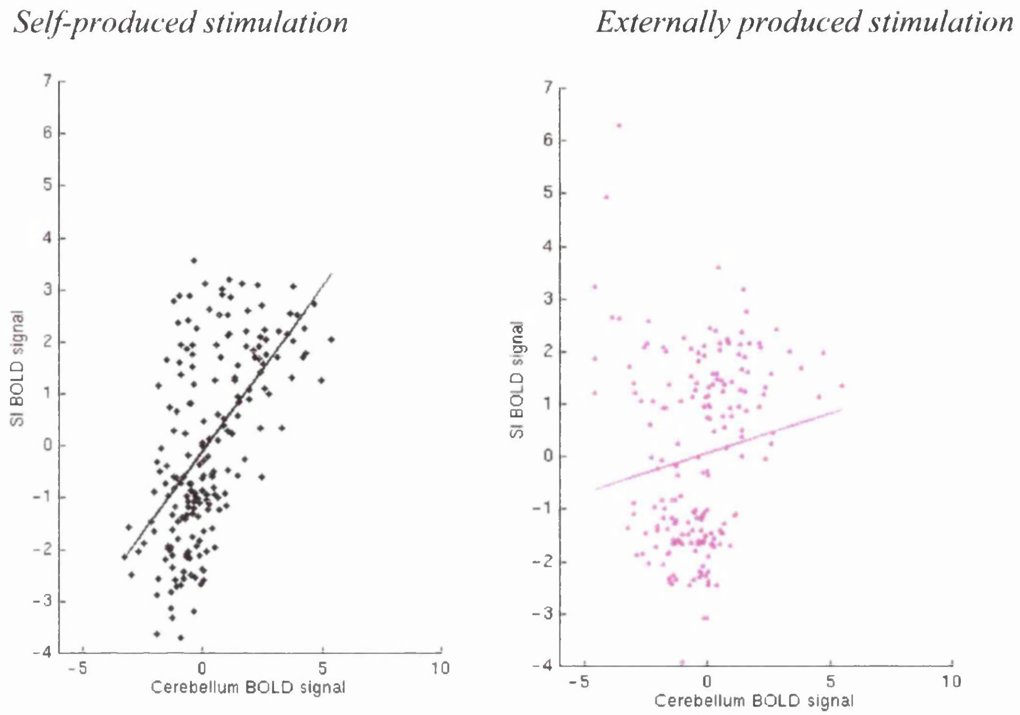
The context-specific nature of the inferred connectivity between the cerebellum and other brain areas is illustrated graphically in **Figures 7-4, 7-5 & 7-6**. These plots show a positive regression slope between cerebellum BOLD signal and the thalamus, right primary and secondary somatosensory cortex BOLD signal in the self-produced condition and a flat slope in the externally produced condition. The difference between these slopes was significant at $P<0.001$ in all six subjects. The images and graphical displays in **Figures 7-4, 7-5 & 7-6** illustrate the psychophysiological interaction between the cerebellum and the thalamus and somatosensory cortices in a single representative subject, for illustration.

Figure 7-3



Brain regions with an increased contribution from the cerebellum during the self-produced tactile stimuli. The primary somatosensory cortex, the secondary somatosensory cortex and the thalamus are shown.

Figure 7-4

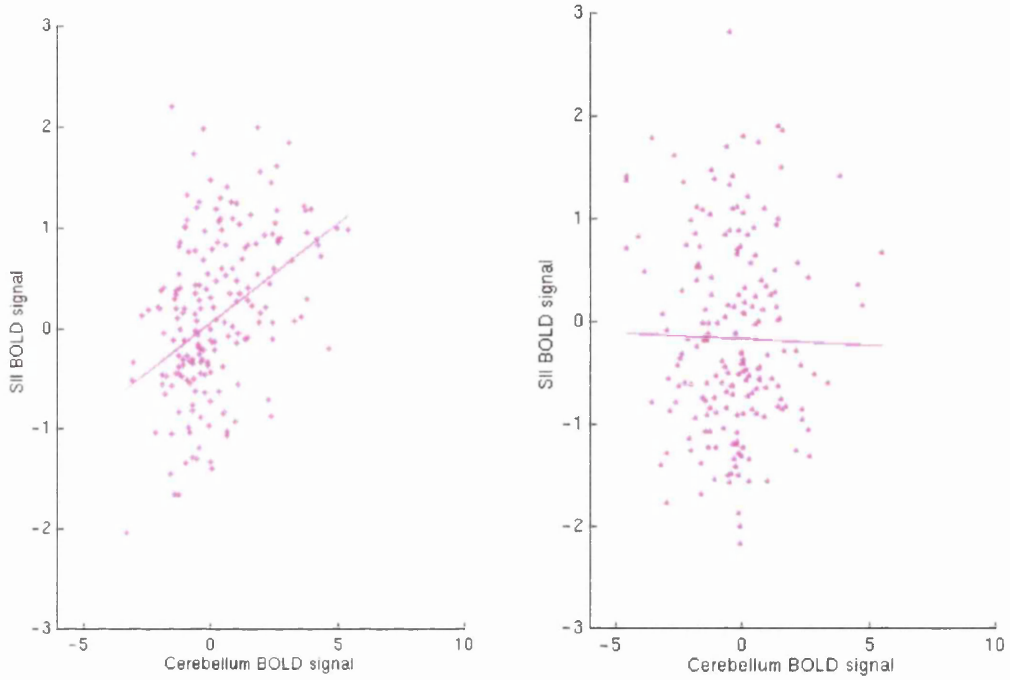


Self-produced stimulation

Externally produced stimulation

The BOLD values in the right cerebellum (34, -56, -24) and (42, -12, 60) in the right primary somatosensory cortex (SI) plotted against each other in the self-produced tactile stimuli and externally produced tactile stimuli conditions. Regression lines have been fitted to the data, demonstrating a positive gradient in the self-produced tactile stimuli condition and a negative gradient in the externally produced tactile stimuli condition. The correlation coefficient (r) between cerebellum and SI activity is 0.58 for the self-produced tactile stimuli condition and 0.14 for the externally produced tactile stimuli condition.

Figure 7-5

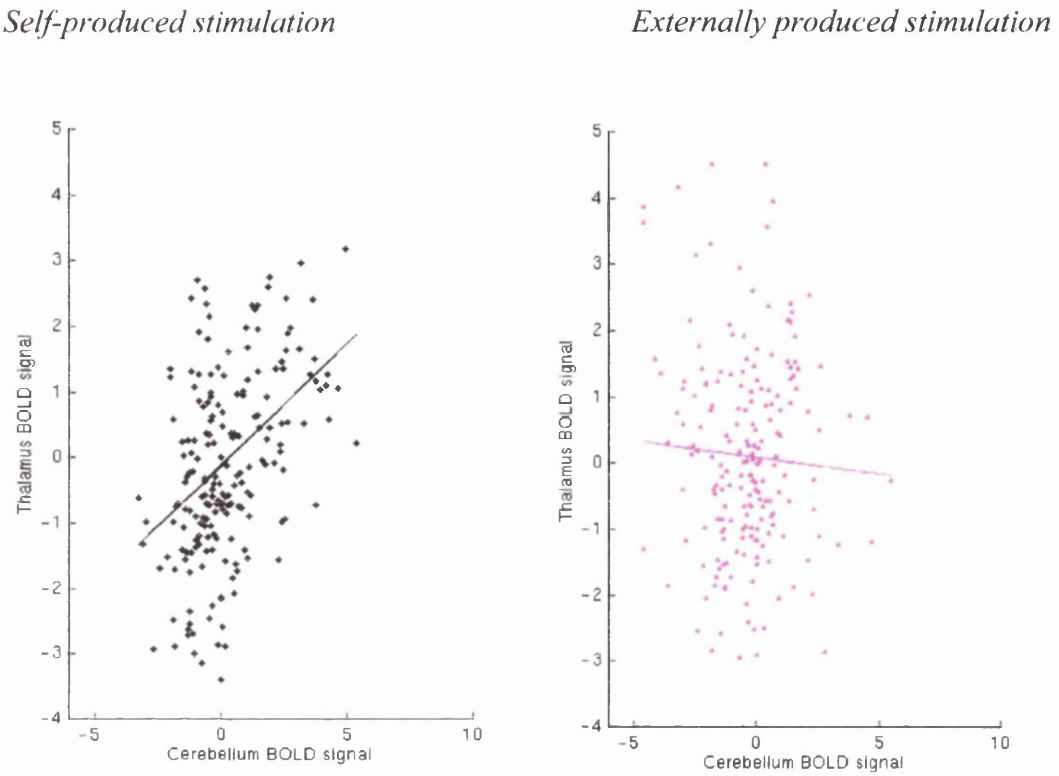


Self-produced stimulation

Externally produced stimulation

The BOLD values in the right cerebellum and (38, -16, 10) in the right secondary somatosensory cortex (SII) plotted against each other in the self-produced tactile stimuli and externally produced tactile stimuli conditions. The correlation coefficient (r) between cerebellum and SII activity is 0.42 for the self-produced tactile stimuli condition and -0.02 for the externally produced tactile stimuli condition.

Figure 7-6



Self-produced stimulation *Externally produced stimulation*

The BOLD values in the right cerebellum and (26, -16, 22) in the lateral thalamus plotted against each other in the self-produced tactile stimuli and externally produced tactile stimuli conditions. The correlation coefficient (r) between cerebellum and thalamic activity is 0.47 for the self-produced tactile stimuli condition and -0.06 for the externally produced tactile stimuli condition.

It is possible that the positive correlation between activity in the cerebellum and activity in the thalamus and somatosensory cortex is caused by activity in a third area. The only other area that was activated by externally produced but not by self-produced tactile stimulation was the ACC. Activity in the cerebellum and the somatosensory cortices did not significantly regress on activity in the voxel of maximum intensity in the ACC when this was used as the regressor. Therefore the hypothesis that activity in the ACC influenced activity in the cerebellum and the somatosensory cortices was not supported.

7.4 Discussion

It has been proposed that the cerebellum makes use of a forward model of the motor system, which provides a prediction of the specific sensory consequences of motor commands, and therefore distinguishes between movements depending on their specific sensory feedback. In the fMRI study described in the previous chapter, when the actual sensory feedback from a movement matched the predicted sensory feedback (when tactile stimuli were self-produced), cerebellar activity decreased and the somatosensory cortex was not activated. In contrast, when tactile stimuli were externally produced and could not be predicted based on efference copy, the predicted and actual sensory feedback did not match. It was proposed that the sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback is signalled by the cerebellum in the form of increased activity. In this case, activity in somatosensory cortex is not predictively attenuated.

To test the hypothesis that the cerebellum is the source of the somatosensory modulation, regression analyses were used to investigate the contribution of the cerebellum to the ventral thalamus and somatosensory cortices when tactile stimuli were self-produced relative to when they were externally produced. The resulting regression slopes reflect the influence of the cerebellum on the ventral thalamus and right primary and bilateral secondary somatosensory cortex. As can be seen in **Figure 7-4**, each regression slope changed when tactile stimuli were self-produced compared to when they were externally produced, thus constituting a significant psychophysiological interaction (Friston *et al*, 1997b). These results support the suggestion that the cerebellum output modulates activity in the somatosensory cortex via the thalamus when, and only when, the predicted and actual sensory information are matched i.e. when tactile stimuli are self-generated not when they are externally generated.

This reasoning is consistent with the theory that the cerebellum is component of a forward model system that provides predictions of the sensory consequences of motor commands, which are then compared with the actual sensory feedback from the movement (Ito, 1970; Paulin, 1989; Miall *et al*, 1993; Wolpert *et al*, 1998).

The sensory discrepancy, it has been argued, is signalled by the inferior olive, which via the climbing fibres innervates the cerebellum (Simpson *et al*, 1995). The proposal that the cerebellum provides predictions of the sensory consequences of motor commands is also consistent with research demonstrating the role of the cerebellum in processing sensory information on line. The current data support theories proposing that the cerebellum is involved in the acquisition and discrimination of sensory data (Leiner *et al*, 1995; Gao *et al.*, 1996; Bower, 1997a; Bower, 1997b), a function that would be necessary for the comparison between the actual and predicted sensory consequences of the movement. This proposed role of the cerebellum is supported by Jueptner & Weiller (1998) who conclude that, based on the results of three PET studies, the cerebellum may be concerned with monitoring the sensory outcome of movements.

When tactile stimulation is self-produced it can be accurately predicted and the comparison between predicted and actual sensory feedback will result in low level of sensory discrepancy. In this case activity in the cerebellum will decrease. Conversely when the tactile stimulation is externally produced it cannot be accurately predicted and the comparison between the predicted and actual sensory feedback will result in higher levels of sensory discrepancy. In this case activity in the cerebellum will increase.

This study demonstrates that when the BOLD signal in the cerebellum increases, so does the BOLD signal in the thalamus and somatosensory cortices. A crucial question is to what increases in blood flow (or in BOLD signal) in the cerebellum correspond in terms of neuronal activity. One possibility is that the principal cells of the cerebellar cortex, the Purkinje cells, which are inhibitory, account for changes in blood flow in the cerebellum. Albus (1971) and Marr (1969) propose that the Purkinje cells compute the error signal between an actual sensory 'context' (the set of incoming data from sensory afferents) and the context that the brain had been expecting. If this is correct, then in the current experiments self-generated stimulation would be expected to produce no error signal in the Purkinje cells, but externally generated (unexpected) stimulation would be expected to produce a Purkinje cell output.

However, recently it has been found that, in rats, there is no simple correlation between blood flow and Purkinje cell firing (Mathiesen *et al*, 1998). Mathiesen and colleagues had two important findings. Firstly, they found that there is a blood flow *increase* evoked by stimulating the parallel fibres (i.e. the granule cell axons), which is inhibited by AMPA receptor blockers. Since glutamate acts on the AMPA receptors, this suggests that it is glutamate release from the granule cell terminals, which acts on AMPA receptors to evoke a blood flow increase. In the cerebellar cortex there are AMPA receptors on Purkinje cells, inhibitory cells, and on Bergmann glia, and in principle it could be any of these, or the downstream consequences of their activation, that trigger the blood flow increase.

Secondly, however, the authors showed that parallel fibre stimulation *decreases* Purkinje cell spiking. This is because stimulating the parallel fibres activates inhibitory interneurons, which send inhibitory synapses to Purkinje cells. This inhibitory innervation outweighs the effect of the direct excitatory input from the parallel fibres. Indeed, blocking GABA receptors (which mediate the inhibition) blocks the effect on Purkinje cell firing but not the increase of blood flow. Therefore, it is not Purkinje cell firing that leads to the blood flow increase.

The authors suggest that it is the inhibitory inter-neuronal firing that causes an increase in blood flow. However, the cerebellum is a multi-layered structure containing various types of cell and there are also other possibilities that could cause an increase blood flow, including the following:
(i) glutamate acts on AMPA receptors on Purkinje cells, which then release a messenger that dilates blood vessels. This is independent of whether Purkinje cell firing actually increases or decreases.
(ii) glutamate acts on AMPA receptors on Bergmann glia, which release a factor that controls blood flow (Llinas & Sotelo, 1992).
(iii) glutamate acts on AMPA receptors on cells that release dopamine, which has been found to be a key regulator of blood flow in the cortex (Leonid *et al*, 1998).

A likely downstream messenger that could be produced after glutamate activates the AMPA receptors is nitric oxide. There is evidence that in the cerebellum nitric oxide dilates blood vessels by generating cGMP in the cells controlling vessel diameter (e.g. Yang *et al*, 1998). Thus, glutamate that is released from parallel fibres and acts on Purkinje cells can raise calcium locally in Purkinje cell dendrites. This brings about a release of nitric oxide, which dilates blood vessels, independently of the change in Purkinje cell firing that occurs.

In summary, the blood flow increase could be triggered either by inhibitory inter-neuronal firing or by glutamate, which is released from the parallel fibres and acts on AMPA receptors, or by both of these factors. Which of these factors controls blood flow in the cerebellum is unknown and this question is further complicated by the interaction with activity in other cerebellar cells. For example, an increase of granule cell firing might lead to an increase or decrease of Purkinje cell firing. Therefore if blood flow correlates with granule cell firing, it might also correlate with Purkinje cell firing. In addition it is possible that granule cell firing might also correlate with mossy fibre input firing if an increase of mossy fibre input always leads to an increase of granule cell firing. This is complicated because the mossy fibres both excite the granule cells directly and inhibit them through Golgi cells. Thus, it is unlikely that BOLD signal, or blood flow, in the cerebellum corresponds simply to an increase in firing of the Purkinje cells. At present it is unknown whether BOLD signal, and blood flow increases, in the cerebellum represents inhibitory or excitatory output. This question is as yet unanswered and requires further research.

7.5 Conclusion

In this chapter, regression analyses were used to test the hypothesis the cerebellum is involved in predicting the specific sensory consequences of movements and providing the signal that is used to attenuate the sensory response to self-generated stimulation. It was predicted that activity in the cerebellum contributes to the decrease in somatosensory cortex activity during self-produced tactile stimulation. Evidence in favour of this hypothesis was obtained by demonstrating that activity in the ventral thalamus and primary and secondary somatosensory cortex showed a significant regression on activity in the cerebellum when tactile stimuli were self-produced, but not when they were externally produced. This supports the proposal that the cerebellum is involved predicting the sensory consequences of movements and signalling the sensory *discrepancy resulting from the comparison between the predicted and actual sensory feedback. In the present study, the prediction is more accurate and the comparison results in a lower level of sensory discrepancy when tactile stimuli are self-produced, compared to when they are externally produced. Therefore the sensory prediction can be used to attenuate the somatosensory response to self-produced relative to externally produced stimuli. In the following chapter PET is used to investigate further the hypothesis that the cerebellum is involved in signalling the sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback.*

8 CHAPTER 8: THE CEREBELLUM IS INVOLVED IN PREDICTING THE SENSORY CONSEQUENCES OF ACTION

8.1 Introduction

In chapter 5, a robotic interface was used to demonstrate that self-produced and externally produced tactile sensations are perceived differently. Furthermore, by using two robots so that the motion of the left hand on one robot determined the tactile stimulus (a piece of soft foam) on the right hand, computer controlled delays of 0, 100, 200 and 300 ms were introduced between the action of the left hand and the tactile sensation on the right. There was a progressive increase in the 'tickly' rating as the delay was increased between 0 ms and 200 ms. These results suggest that the perceptual attenuation of self-produced tactile stimulation is due to a precise attenuation of stimulation based on specific sensory predictions made by the forward model.

In chapter 6, fMRI was employed to examine the neural basis of the differential perception of self- and externally produced tactile stimuli in humans. There was an increase in activity of somatosensory cortex and the anterior cingulate gyrus when subjects experienced an externally produced tactile stimulus on their left palm relative to a self-produced tactile stimulus. In the cerebellum there was less activity associated with a movement that generated a tactile stimulus than with a movement that did not. This suggests that the cerebellum is involved predicting the sensory consequences of movements and signalling the sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback.

In the present study, PET was used to examine the brain responses to self-produced tactile stimuli during parametric perturbations of the correspondence between movement and its sensory consequences. Subjects were scanned while self-producing a tactile sensation on the palm of their left hand, by moving a robotic arm with their right hand. By using two robots so that the tactile stimulus could be delivered under remote control by the subject, delays of approximately 0, 100, 200 and 300 ms were introduced between the movement of the right hand and the tactile stimulus on the left palm. In all conditions the movement made by and the tactile stimulation experienced by the subject was the same (the motion of the right hand always determined the tactile sensation on the left palm). Only the temporal correspondence between the action of the right hand and the sensory effect on the left palm was altered. The 0 ms condition corresponds to the normal situation in which subjects use their right hand to move a physical rod across the palm of their left hand. As the delay is increased the resemblance to the normal situation decreases, and hence the prediction of the sensory feedback from the movement becomes increasingly inaccurate. This will lead to an increase in sensory discrepancy as the delay increases.

Two analyses were performed. Firstly, the data were analysed to investigate whether blood flow in the cerebellum regresses with estimated delay (0, 100, 200 and 300 ms). Secondly, the data were analysed using the movement parameters recorded by the PC during the experiment. In this second analysis, the data were analysed to investigate whether blood flow in the cerebellum regresses with the actual delay between the optical encoder and the robotic motor, as recorded by the PC. In addition, the frequency and amplitude of the movements made by the subjects in each condition were entered as confounding variables in the analysis. Therefore any brain activity associated with frequency and amplitude of the movements was removed. Any resulting activity that correlates with delay will thus be associated with the increasing sensory discrepancy between the predicted and actual sensory feedback from the movement. Based on the proposal that the cerebellum signals the sensory discrepancy between the predicted and actual sensory feedback, it was predicted that blood flow in the cerebellum will increase as the delay increases.

8.2 Method

8.2.1 Subjects

Six normal right-handed male volunteers (mean age 24 years) gave informed consent for the study, which was approved by the National Hospital for Neurology and Neurosurgery Ethics Committee. Permission to administer radioactive substances was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) U.K.

8.2.2 Procedure

Subjects lay supine in the scanner with their left forearm laid on a flat surface with the palm exposed. Subjects gripped a lightweight rod (radius 0.5 cm and length 4 cm) with the thumb and index finger of their right hand. This rod was attached to an optical encoder (Phantom Haptic Interface, Sensable Devices, Cambridge, MA, USA), and subjects were required to move it sinusoidally (frequency 2 Hz and amplitude 1.5 cm) in the vertical direction. The motion of this rod determined the position of a torque motor, on which was mounted a tactile stimulus constituting a piece of soft foam (radius 1 cm and length 2.5 cm), which made contact with the subject's stationary left palm (**Figure 8-1**). The motion of the rod held in the right hand was transmitted to the foam-tipped motor thereby ensuring that the motion of the right hand determined the tactile sensation on the left palm. The robot was controlled by a PC and its position was updated at 1 KHz. By delaying the transmission between the encoder and torque motor, computer controlled delays of approximately 0, 100, 200 and 300 ms were introduced between the movement of the right hand and the movement of the tactile stimulus on the left, constituting the four experimental conditions.

Figure 8-1

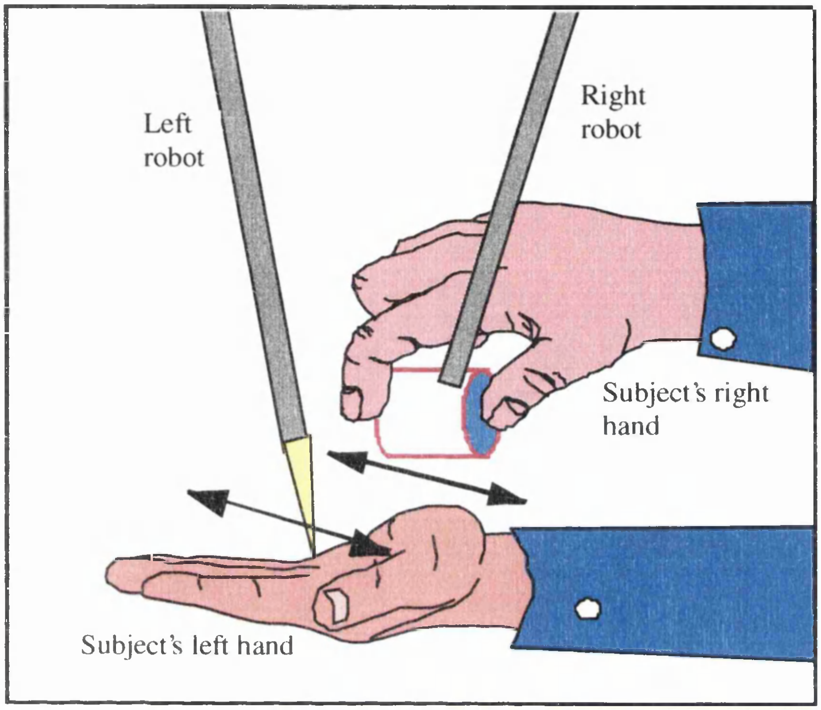


Diagram of experimental set-up. A tactile stimulus constituting a piece of foam attached to the end of a robotic manipulator was positioned above the subjects' left palm. The subject gripped a cylindrical object with the thumb and index finger of their right hand. This object was held directly above the tactile stimulus and was attached to a second robotic device. In all conditions subjects were required to move the object held in their right hand sinusoidally, which, via two robots, produced the same movement of the tactile stimulus above their left hand. Delays were introduced between the movement made by the right hand and the resultant movement of the left robot.

Subjects practiced the sinusoidal movement until they were proficient at producing it. This took between 60 and 120 seconds for each subject. In each condition the same movement was made and continuous tactile stimulation occurred. The only factor that was altered between conditions was the temporal relationship between the movement of the right hand and the sensory effect on the left palm. Subjects were informed that the movement of their right hand would produce the movements of the tactile stimulus on their left palm in each condition. Subjects were not informed of the presence of delays between the movement and the tactile stimulation.

Each subject underwent twelve PET scans in a single session, comprising three replications of each of the four condition, each lasting 90 seconds. There was an 8 minute interval between the start time of each scan. The order of conditions was randomised and counterbalanced within and between subjects. Scanning took place in a darkened room and subjects were asked to keep their eyes closed throughout.

8.2.3 Data acquisition

See **chapter 3** for details about PET scanning.

8.2.4 Statistical analysis

Functional imaging analysis used the technique of statistical parametric mapping, implemented in SPM99. For each subject, a set of twelve PET scans was automatically realigned and then stereotactically normalised into the space of Talairach & Tournoux (1988). The scans (72 in total) were then smoothed with a Gaussian kernel of 12 mm full-width half maximum.

The effects of global changes in blood flow between conditions were modelled as a confound using a subject-specific ANCOVA. SPM99 was used to identify brain areas where activity was predicted by delay between the movement and the tactile stimulation. Delay was used as a covariate (or regressor) and regression with this covariate was calculated for every voxel in the whole brain. The significance of the regression with delay was displayed in a SPM[t] map, which was then transformed into an SPM{Z} and thresholded at a Z-score of 3.09 ($P<0.05$ uncorrected). It was predicted that activity in the cerebellum would show a positive regression with delay. A small volume correction (Worsley *et al*, 1996) was made on the P values of the ensuing maxima in the cerebellum. Clusters of activated voxels were characterised in terms of their peak height and spatial extent conjointly.

8.2.4.1 Analysis without confounds

Firstly, the data were analysed to investigate whether blood flow in the cerebellum regresses with delay (0, 100, 200 and 300 ms).

8.2.4.2 Analysis using movement parameters as confounds

Delay, as recorded by a computer, was used as a covariate (or regressor) and regression with this covariate was calculated for every voxel in the whole brain. The amplitude and frequency of the movements over all conditions, which were recorded by the computer, were used as confounds in the analysis. Therefore any brain activity related to frequency and amplitude of the movements is removed.

8.3 Results

After practice each subject was able to produce the desired movement of the left hand with reasonable accuracy.

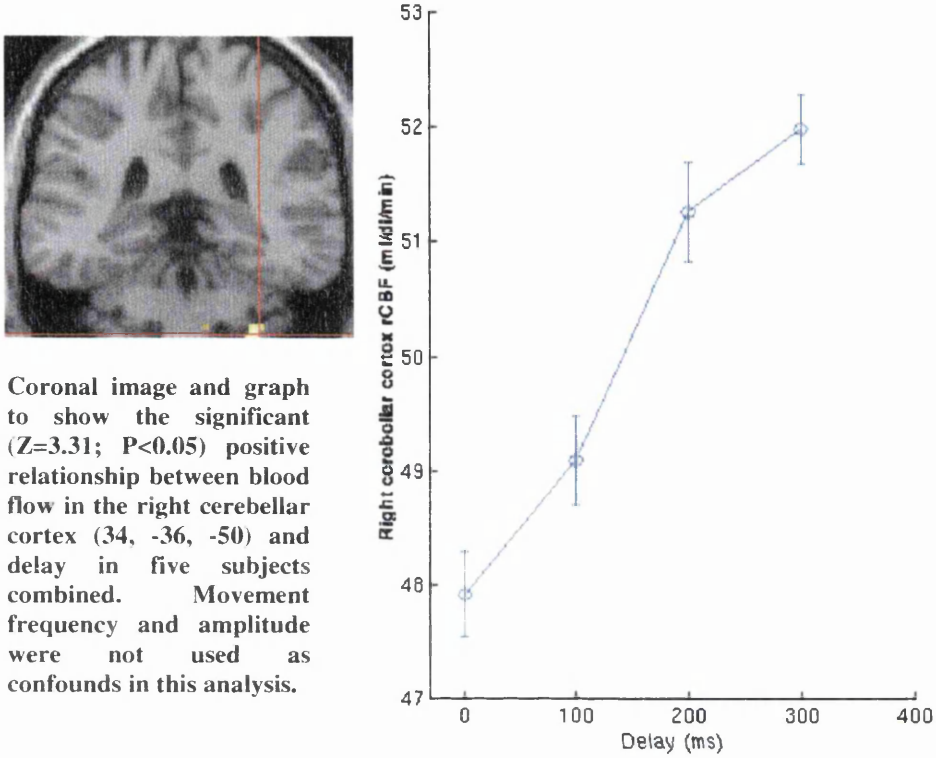
8.3.1 Regions that showed a positive correlation between blood flow and estimated delay (no confounds)

The regression analysis for all subjects combined demonstrated a significant ($P<0.05$ small volume corrected) positive regression on delay in the right cerebellar cortex (coordinates 34, -36, –50; $Z=3.31$) when movement frequency and amplitude were not used as confounding variables. In single subject analyses five subjects showed this positive relationship between delay and activity in the right cerebellum. In one subject activity in the left cerebellum correlated with delay. The localisation of the cerebellar activity differed slightly in each subject (**Table 8-1**). **Figure 8-2** shows the positive correlation between right cerebellar cortex blood flow and delay using the combined data of the five subjects showing such a correlation.

Table 8-1: Table to show the localisation of the cerebellar blood flow that showed a positive regression with delay in each subject. Movement frequency and amplitude were not used as confounds in the analysis.

Subject	Coordinates (x, y, z) in cerebellum	Z value (P<0.05)
1	44 -44 -38	3.46
2	24 -60 -50	2.77
3	-8 -54 -30	2.77
4	6 -66 -36	2.74
5	28 -54 -50	4.00
6	48 -42 -38	2.94

Figure 8-2



Coronal image and graph to show the significant (Z=3.31; P<0.05) positive relationship between blood flow in the right cerebellar cortex (34, -36, -50) and delay in five subjects combined. Movement frequency and amplitude were not used as confounds in this analysis.

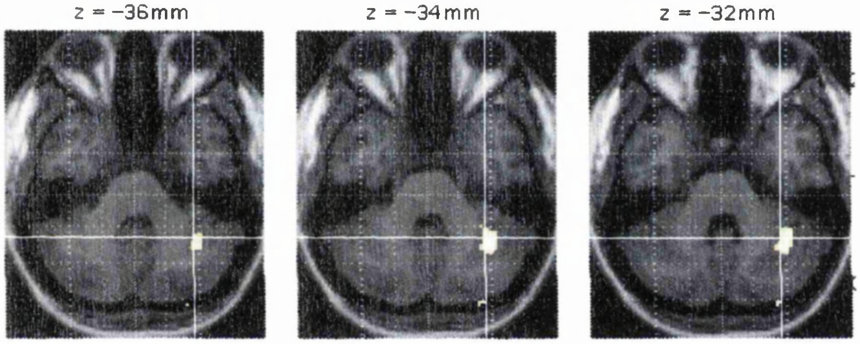
8.3.2 Regions that showed a positive correlation between blood flow and actual delay (using movement frequency and amplitude as confounds)

In this second analysis the actual delays (as recorded by the PC) were used as the covariate of interest and movement frequency and amplitude were used as confounding variables. The regression analysis for all subjects combined demonstrated a significant (Z=2.82; P<0.05 small volume corrected) positive regression on delay in the right cerebellar cortex (coordinates 38, -56, –34). In single subject analyses all six subjects showed this positive relationship between delay and activity in the right cerebellum. However in one subject this right cerebellar activation was only present at a lower significance threshold. The localisation of the cerebellar activity differed slightly in each subject (**Table 8-3**). **Figures 8-3 & 8-4** show the positive correlation between right cerebellar cortex blood flow and actual delay using the combined data of all subjects. Right cerebellar cortex blood flow is plotted against the actual delay, as recorded by the computer, in **Figure 8-4**.

Table 8-2: Table to show the localisation of the cerebellar blood flow that showed a positive regression with actual delay when movement frequency and amplitude were used as confounds in the analysis, in each subject.

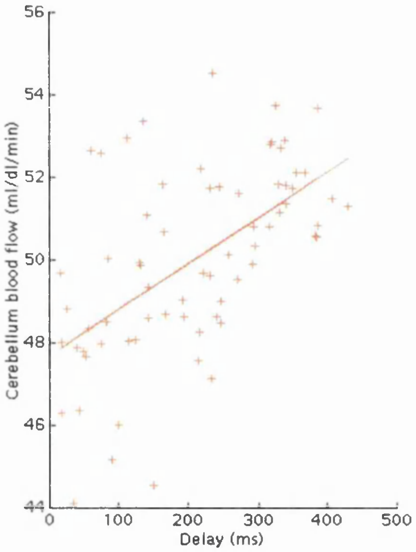
Subject	Coordinates (x, y, z) in cerebellum	Z value (P<0.05)
1	40 –48 –34	1.96
2	40 –68 –40	3.36
3	50 –70 –50	2.55
4	10 –72 –42	2.48
5	36 –36 –50	3.07
6	34 –30 –20	3.73

Figure 8-3



Axial slices through the region of the right cerebellar cortex (38, -56, -34) that showed a significant (P<0.05) positive relationship with actual delay in all subjects combined when movement frequency and amplitude were used as confounds in the analysis.

Figure 8-4



Graph to show the significant (Z=2.82; P<0.05) positive relationship between blood flow in the right cerebellar cortex (38, -56, -34) and delay in all subjects combined when movement frequency and amplitude were used as confounds in the analysis. The correlation coefficient between delay and cerebellar blood flow was r=0.57.

8.4 Discussion

The present study sought to investigate how blood flow is modulated by parametric perturbations in the correspondence between self-generated movements and their sensory consequences. Activity in the right cerebellum was positively correlated with delay. Under all delays in the current study the right hand made the same movement and the left hand experienced the same stimulus. Only the temporal relationship between the action of the right hand and the sensory effect on the left hand was altered. When movement amplitude and frequency were discounted from the (second) analysis, brain activity that correlated with delay was associated only with the temporal perturbation between an action and its consequences. It is proposed that as the delay increases the prediction of the sensory consequences of movements becomes less accurate, and the sensory discrepancy between predicted and actual sensory feedback increases. Therefore, these results support the proposal that the cerebellum is involved in signalling the sensory discrepancy between predicted and actual sensory consequences of movements.

When movement frequency and amplitude were used as confounding variables in the analysis, the area of the right cerebellum that regressed on delay was slightly inferior from the area that regressed on delay when movement frequency and amplitude were not used as confounding variables. This suggests that a component of the cerebellum activity that regressed on delay was due to the movement frequency and amplitude parameters.

The right cerebellum was the only area that correlated with delay that was predicted from the previous fMRI experiment, reported in chapter 6. In the fMRI study, the other areas that showed a significant difference between self- and externally generated tactile stimulation were the secondary somatosensory cortex and the ACC. Neither of these areas showed a significant correlation with delay in the present study. This result is not a surprising given the difference in activity in the secondary somatosensory cortex and the ACC during self-produced tactile stimulation (condition A) and self-produced movement (condition B) in chapter 6.

Self-generated movements that touched the hand (condition A), and movements that did not (B), resulted in similar activation of somatosensory and anterior cingulate cortex. Therefore, it would be predicted on the basis of the fMRI results that the somatosensory cortex and ACC would show the same level of activity as long as movement occurs. In the present study movement occurred in each condition.

8.5 Conclusion

This study was designed to test the hypothesis that the cerebellum is involved in predicting the sensory consequences of action, and signalling the sensory discrepancy between the predicted and actual sensory feedback from movements. PET was used to examine neural responses to parametrically varied degrees of sensory discrepancy between the predicted and actual sensory consequences of movement. This was achieved by introducing varying degrees of delay between the movement and its sensory consequences. Computer controlled delays of 0, 100, 200 and 300 ms were introduced between the action of the right hand and the tactile stimulation on the left. Activity in the cerebellum showed a positive correlation with the delay. This supports the proposal that the cerebellum signals the sensory discrepancy from the forward model.

9 CHAPTER 9: THE PERCEPTION OF SELF-PRODUCED SENSORY STIMULI IN PATIENTS WITH AUDITORY HALLUCINATIONS AND PASSIVITY EXPERIENCES: EVIDENCE FOR A BREAKDOWN IN SELF-MONITORING

9.1 Introduction

In **chapter 5** of this thesis, a study was described in which a group of healthy subjects were asked to rate the perception of a tactile sensation on the palm of their hand that was either self-produced by movement of their other hand, or externally produced by the experimenter. It was found that subjects rated self-produced tactile stimulation as less intense, tickly and pleasant than the externally produced stimulus. The results were interpreted in terms of an internal forward model, which predicts the sensory consequences of the motor commands sent to one hand, and uses the sensory prediction to cancel the resultant tactile sensation on the other hand. In the present study, the ability of psychiatric patients with auditory hallucinations and passivity experiences to differentiate perceptually between self- and externally produced tactile stimuli was investigated.

It has been proposed that a defect in central self-monitoring underlies auditory hallucinations and passivity phenomena experienced by people with schizophrenia (Frith, 1992). Auditory hallucinations are common in schizophrenia, and normally consists of hearing spoken speech or voices (Hoffman, 1986; Johnstone, 1991). Certain types of auditory hallucinations are included as 'first rank' features in schizophrenia, features that have been regarded as pathognomic of the disorder in most circumstances (Schneider, 1959). Passivity experiences or, delusions of control, are further 'first rank' features in schizophrenia (Schneider, 1959). The essence of this symptom is that the subject experiences his or her will as replaced by that of some other force or agency (Wing *et al.,* 1974). See **Table 1-1** in Introduction for examples of symptoms.

Frith (1992) suggested that these abnormal experiences arise through a lack of awareness of intended actions. Such an impairment might cause thoughts or actions to become isolated from the sense of will normally associated with them. This would result in the interpretation of internally generated voices or thoughts as external voices (auditory hallucinations and thought insertion) and of one's own movements and speech as externally caused (passivity phenomena). In a recent development of this idea it has been suggested that the experience of passivity arises from a lack of awareness of the predicted limb position based on the forward model (Frith *et al.,* 1999). As a result the patient is not aware of the exact specification of the movement. The patient is aware of his or her goal, of the intention to move and of the movement having occurred, but he or she is not aware of having initiated the movement. It is as if the movement, although intended, has been initiated by some external force.

In terms of the forward model, it is possible that an impairment of the prediction or the comparison process could cause auditory hallucinations and passivity experiences. If the comparison process were impaired and always produced a high level of sensory discrepancy despite the accuracy of the sensory prediction, then self-produced sensations would be associated with high levels of sensory discrepancy despite being accurately predicted. In this way, self-produced stimulation could be interpreted as being externally produced. Self-produced events could also be confused with externally generated events if the former were not predicted accurately.

There is nothing obviously abnormal in the motor control of patients with delusions of control. This suggests that accurate representations of predicted states are available and used by the motor system. However, these representations are not available to awareness. A number of experiments confirm that there are subtle problems consistent with a lack of awareness of predicted actions. Two experiments in which subjects had to correct their errors very rapidly in the absence of visual feedback, found evidence that central monitoring is faulty in schizophrenia (Malenka *et al.,* 1982; Frith and Done, 1989).

A breakdown in self-monitoring might result in failure in the attenuation of self-produced stimuli that is seen in normal subjects (as shown in **chapter 5** and by Weiskrantz *et al.,* 1971). In the present study, whether patients with auditory hallucinations and passivity experiences are able to differentiate perceptually between tactile stimuli that are self- and externally produced was evaluated. Patients with a diagnosis of schizophrenia, bipolar affective disorder or depression were divided into two groups according to the presence or absence of auditory hallucinations and passivity experiences. Subjects were asked to rate a tactile sensation (caused by a piece of soft foam) on the palm of their left hand that was produced either by movement of their right hand or by the experimenter. Based on the theory outlined above (Frith, 1992; Frith *et al.,* 1999) it was predicted that patients with auditory hallucinations and passivity experiences would be abnormally aware of the sensory consequences of their own movements, and thus would not show the normal attenuation of self-produced relative to externally produced sensations.

9.2 Method

9.2.1 Subjects

Patients with a diagnosis of schizophrenia (n=23; 16 males; mean age 33±1.8 years; 22 were right-handed), affective disorder (bipolar or depression; n=18; nine males; mean age 39±2.8 years; 16 were right-handed), and a group of normal control subjects (n=15; nine males; mean age 32±2.07 years; all were right-handed) gave informed consent to take part in the study. All patients were diagnosed by clinical interview using the ICD-10 (International Classification of Diseases; WHO, 1992). All subjects were tested at the Department of Psychiatry, The Royal Edinburgh Hospital, Morningside Park, Edinburgh, UK, in collaboration with Dr Joanna Smith, Dr Robby Steel and Prof. Eve C. Johnstone. The study was approved by the Psychiatry and Clinical Psychology Ethics Subcommittee of the Lothian Research Ethics Committee.

9.2.2 Division of patient groups

Patients were divided into two groups according to the presence or absence of auditory hallucinations and/or passivity experiences, according to a questionnaire given to each subject by a psychiatrist before the experiment. This questionnaire assessed general, background and clinical information. Subjects were asked about their symptomatology, specifically whether they had experienced auditory hallucinations, thought interference or passivity phenomena within the past six weeks. The questionnaire was given to, and externally validated for all (schizophrenic, manic and depressed) patients and normal control subjects[1].

The patients with a diagnosis of schizophrenia were also assessed by the PANSS interview (Kay *et al.,* 1987) conducted by a psychiatrist with video monitoring. A score of 3 ('mild') on the Hallucinatory Behaviour scale of the PANSS was taken to indicate the presence of auditory hallucinations. Patients who scored 1 ('absent') or 2 ('minimal') on this scale were classified as not experiencing auditory hallucinations. The average score on the Hallucinatory Behaviour scales

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[1] See Appendix 9 for questionnaire.

was 1.1 for the group of patients without auditory hallucinations, and 3.9 for the group classified as experiencing auditory hallucinations. There was 100% concordance between classification based on symptom ratings from the questionnaire and the PANSS ratings for patients with PANSS results. PANSS results were only available for patients with a diagnosis of schizophrenia.

According to the questionnaire a total of 17 (13 schizophrenic and four affective) patients had experienced auditory hallucinations and/or passivity phenomena within the past six weeks. While all 17 subjects had experienced auditory hallucinations, six had also experienced passivity phenomena within the past six weeks. 24 (ten schizophrenic and 14 affective) patients had not experienced either of these symptoms within the past six weeks.

For an overall picture of psychopathology within the patients with schizophrenia, the PANSS scales were divided into three categories corresponding to Reality Distortion, Disorganisation and Psychomotor Poverty, and the average score on each of these scales was calculated for the schizophrenic patients. They average scores were as follows: Reality Distortion 2.9; Disorganisation 2.0; Psychomotor Poverty 2.2.

9.2.3 Procedure

The tactile stimulus device consisted of a piece of soft foam attached to a plastic rod (length 70 cm) which could pivot about its centre (**Figure 6-1**). The rod was situated inside a plastic box attached to a perspex sheet, which was attached to a table. Subjects sat facing the table, with their left arm perpendicular to the table and secured to the perspex sheet. The piece of foam touched the subject's left palm, and could be moved by the movement of the rod. The rod could be moved either by the subject using their right hand or, from the other end of the rod, by the experimenter. The rotation of the rod was mechanically limited to vertical sinusoidal movements of amplitude 1.5 cm. Subjects were instructed to move the rod up and down to its full extent at a frequency of 2 Hz and they practiced beforehand to ensure that they could reliably generate the desired movements. This took between 1 and 4 mins for each subject. The frequency of stimulus movement in each trial was recorded by the experimenter throughout the experiment.

Condition A: Self-generated tactile stimulation

Subjects were required to make vertical sinusoidal movements of the rod with their right hand. This movement produced the tactile stimulation on the palm on their left hand.

Condition B: Externally produced tactile stimulation

The experimenter moved the tactile stimulus sinusoidally across the subject's left palm, while the subject rested their right hand.

Each trial lasted 10 secs. There were 10 repetitions of each condition for each subject, thus each subject underwent a total of 20 trials. The condition order was alternated. The apparatus was explained to each subject before the experiment. They were told that the piece of foam would touch their hand in each condition, and that on half the trials the foam would be moved by themselves, and in the other half by the experimenter.

Rating scale

After each trial subjects were instructed to rate the sensation on their palm on a scale from 0 (not at all) to 10 (extremely) 'intense', 'painful', 'tickly', 'pleasant' and 'irritating'. Subjects were told that a rating of zero indicated a neutral perception for that particular scale. Subjects were told that it was important to maintain the same scale all the way through the experiment and that the emphasis was on the relative values of their judgements, not the absolute values.

Sand paper control trials

In order to obtain an objective assessment of the ability of subjects to rate a tactile sensation, subjects were asked to rate the roughness of four grades of sandpaper (Grade Numbers 80, 120, 240, 460). The four different samples of sandpaper were attached to a sheet of card. Subjects were asked to close their eyes, move the fingers of their left hand over one piece of sandpaper and rate it in terms of its roughness on a scale from 0 (not at all rough) to 10 (extremely rough). The four samples of sandpaper were presented to the subjects in a randomised order. Subjects' perceptual rating data were excluded from the analysis if there was no difference between their ratings for the roughness of the four grades of sandpaper, or if their ordering was wrong for more than two grades.

9.2.4 Data analysis

Analyses were performed on the data to test the hypothesis that the presence of auditory hallucinations and/or passivity symptoms has a significant effect of the perception of self-produced stimuli. It was predicted that patients with auditory hallucinations and/or passivity phenomena would show no significant difference between their perceptual ratings in the two tactile stimulation conditions. By comparison, it was predicted that the patients without these symptoms and normal control subjects would show a significant difference between their ratings in the two conditions, rating self-produced tactile stimulation as less intense than externally produced stimulation.

Since each subject used their own subjective rating scale, the ratings need not conform to a normal distribution. Hence, Wilcoxon non-parametric matched pairs signed ranks test (Howell, 1997) was used to examine the difference between conditions for each scale within each subject group. Results were taken as significant if $P<0.05$.

9.3 Results

9.3.1 Sand paper control trials

All except three subjects performed the experiment satisfactorily and rated the four grades of sandpaper in the correct order of roughness. Two of the three subjects who failed the sandpaper control test had diagnoses of schizophrenia and had experienced auditory hallucinations and/or passivity phenomena within the past six weeks. The third patient who failed the test had a diagnosis of bipolar disorder, and had not experienced auditory hallucinations or passivity phenomena within the past six weeks. All three subjects rated all four grades of sandpaper as equally rough. Their perceptual ratings data were therefore excluded from further analysis.

9.3.2 Perceptual ratings analysis

After practice each subject was able to produce the desired movement of the left hand with reasonable accuracy. The scales 'Painful' and 'Irritating' both received few positive ratings, and were therefore excluded from the analysis.

The results of the Wilcoxon non-parametric ranking test demonstrated that auditory hallucinations and/or passivity symptoms had a significant effect on perceptual ratings in the two conditions. See **Tables 9-1, 9-2 & 9-3** for mean rating data.

Patients with auditory hallucinations and/or passivity experiences (n=15)

There was no significant difference between self-produced and externally produced tactile stimuli conditions for the intense ($Z=-1.54$; $P=0.12$), tickly ($Z=-1.88$; $P=0.06$) and pleasant ($Z=-1.08$; $P=0.28$) ratings in patients with auditory hallucinations and/or passivity experiences.

Patients without auditory hallucinations or passivity experiences (n=23)

Patients without auditory hallucinations or passivity experiences rated self-produced tactile stimuli as significantly less intense ($Z=-4.24$; $P<0.0001$), tickly

(Z=–5.10; P<0.0001) and pleasant (Z=–5.02; P<0.0001) than externally produced tactile stimuli.

Normal control subjects (n=15)

The normal control subjects rated self-produced tactile stimuli as significantly intense (Z=–2.66; P<0.01), tickly (Z=–3.10; P<0.005) and pleasant (Z=–5.54; P<0.0001) than externally produced tactile stimuli.

Table 9-1: Mean 'pleasant' ratings for all subjects combined in both conditions.

	Tactile stimulation condition	
Subject group	Self-produced	Externally produced
Patients with symptoms	3.16 ± 0.61	3.31 ± 0.53
Patients without Symptoms	2.38 ± 0.38	2.82 ± 0.42
Normal control subjects	1.85 ± 0.28	2.42 ± 0.28

Table 9-2: Mean 'tickly' ratings for all subjects combined in both conditions.

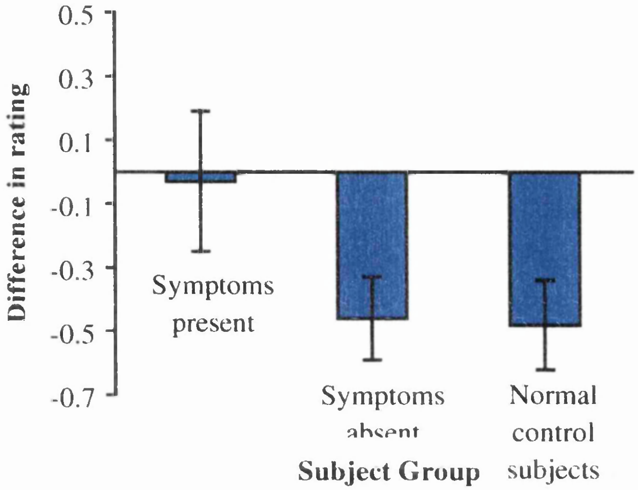
	Tactile stimulation condition	
Subject group	Self-produced	Externally produced
Patients with symptoms	3.34 ± 0.69	3.40 ± 0.69
Patients without Symptoms	2.27 ± 0.48	2.82 ± 0.50
Normal control subjects	2.10± 0.33	2.75 ± 0.47

Table 9-3: Mean 'intense' ratings for all subjects combined in both conditions.

	Tactile stimulation condition	
Subject group	Self-produced	Externally produced
Patients with symptoms	4.20 ± 0.57	4.12 ± 0.49
Patients without symptoms	3.6 ± 0.37	4.09 ± 0.41
Normal control subjects	2.54 ± 0.28	2.81 ± 0.32

Because the results were similar for the 'tickly', 'intense' and 'pleasant' rating scales, the average ratings from these three scales were combined to form one perceptual rating for each condition for each subject. The difference between this combined perceptual rating in each condition (Self-produced rating – Externally produced rating) was calculated for each subject, and these mean difference ratings were used in the subsequent analysis. Because these scores were not appropriately distributed the differences between the groups in terms of the number of subjects who showed the 'normal' pattern of responding was examined. The number of subjects showing the 'normal' response (a higher combined perceptual rating for externally produced tactile stimuli than for self-produced tactile stimuli) was compared with the number subjects not showing this normal response in each subject group. Overall comparison of the three groups revealed a marginally significant difference ($Chi^2(2)=4.74$, $P<0.09$). However, direct examination of the prediction showed that significantly fewer patients with auditory hallucinations and/or passivity phenomena showed the normal response than patients without these symptoms and normal control subjects ($Chi^2(1)=4.33$, $P<0.05$). See **Figure 9-1**.

Figure 9-1



Graph showing mean combined perceptual rating differences between self-produced and externally produced tactile stimulation conditions for the three subject groups: patients with auditory hallucinations and/or passivity experiences, patients without these symptoms, and normal control subjects. There was no significant difference between the perceptual ratings in these two conditions in patients with auditory hallucinations and/or passivity experiences, hence the mean rating difference was close to zero. In contrast, there was a significant difference between the perceptual ratings in the two conditions in patients without with these symptoms and in normal control subjects: both groups rated self-produced stimulation as significantly less tickly, intense and pleasant than externally produced stimulation.

9.4 Discussion

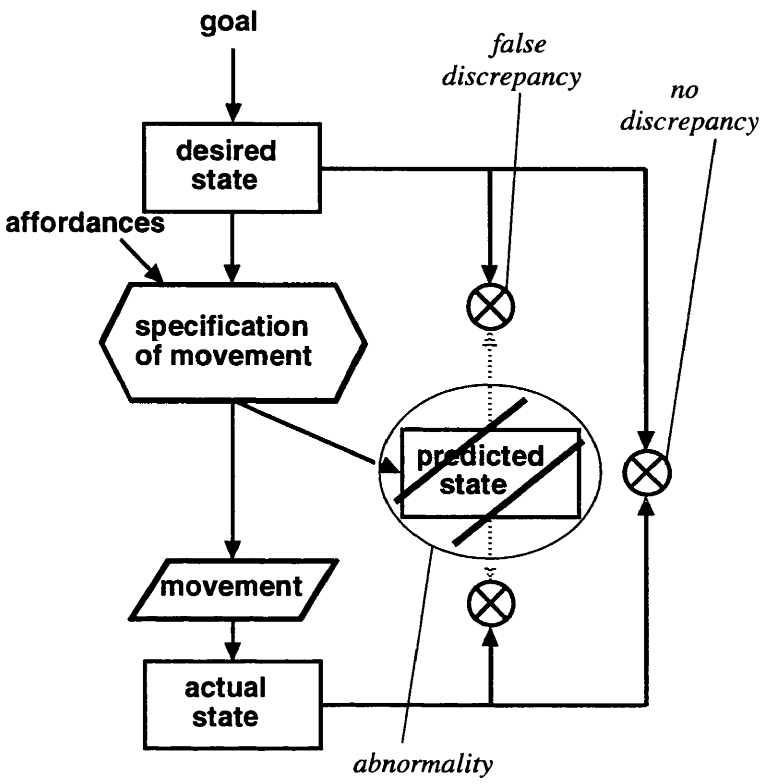
The present study sought to investigate how patients with auditory hallucinations and/or passivity experiences perceive the sensory consequences of their own actions. It was demonstrated that perception is not modulated by self-generated actions in patients with auditory hallucinations and passivity experiences. Patients without these symptoms and normal control subjects consistently rated a self-produced tactile sensation as being less intense, tickly and pleasant than when the sensation was externally produced. In contrast patients with these symptoms did not show a decrease in their perceptual ratings for tactile stimuli produced by themselves as compared to those produced by the experimenter (**Figure 9-1**).

In **chapter 5**, it was shown that normal control subjects perceive self-produced tactile stimuli as less intense, tickly and pleasant than externally produced tactile stimuli, supporting and expanding on a study by Weiskrantz *et al.*(1971). These results can be interpreted in terms of sensory predictions made by a forward model of the motor system (see **figure 5-1**). In terms of the current study, on the basis of the efference copy produced in parallel with the motor command sent to the right hand, the forward model predicts the sensory consequences of the movement. These sensory predictions are compared to the actual sensory feedback from the movement, and are used to attenuate the tactile consequences of the movement. Self-produced sensations can be correctly predicted on the basis of the motor command, and there will therefore be little or no sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback. When the sensory discrepancy is low it is possible to attenuate the effects on sensation induced by self-motion.

An impairment in this 'self-monitoring' mechanism could cause thoughts or actions to become isolated from the sense of will normally associated with them, leading to auditory hallucinations and passivity phenomena that are associated with schizophrenia (Frith, 1992). Frith suggested that these abnormal experiences arise through a lack of awareness of intended actions. The results of the present study support this notion. It was demonstrated that patients without auditory hallucinations and passivity experiences and normal control subjects perceived self-produced tactile stimuli as less intense, tickly and pleasant than externally produced tactile stimuli. In contrast patients with auditory hallucinations and/or passivity experiences showed no difference in their perception of self-produced and externally produced tactile stimuli. It was the presence of hallucinations and/or passivity experiences, rather than diagnosis, that was associated with a defect in self-monitoring. This suggests that patients who have hallucinations and/or passivity experiences have an abnormal awareness of the sensory consequences of their own movements. These results support the proposal that the experience of passivity arises from a lack of awareness of the predicted limb position based on the forward model (Frith *et al.,* 1999).

It has been proposed that patients with delusions of control formulate an action appropriate to their intention and the action is successfully performed. Such patients are aware that the action matches their intention, but they have no awareness of initiating the action or of its predicted consequences (Frith *et al.,* 1999). Patients with delusions of control therefore feel as if their intentions are being monitored and their actions made for them by some external force (**Figure 9-2**). This could arise if there were an impairment of either the prediction or the comparison process of the forward model. For example, if the comparison process were impaired and always produced a high level of sensory discrepancy despite the accuracy of the sensory prediction, then self-produced sensations would be associated with high levels of sensory discrepancy despite being accurately predicted. In this way, self-produced stimulation could be interpreted as being externally produced. Self-produced events could also be confused with externally generated events if the former were not predicted accurately.

Figure 9-2



The proposed underlying disorder leading to auditory hallucinations and passivity phenomena. The patient formulates the action or thought appropriate to his/her intention and the action or thought is successfully performed. The patient is aware that the action or thought matches the intention, but has no awareness of initiating the action or thought or of its predicted consequences. The patient therefore feels as if his/her intentions are being monitored and his/her actions made for him/her by some external force.

Jeannerod (1999) has suggested that conscious judgement about a movement requires a different form of representation from that needed for comparisons of predictions and outcomes within the motor system. Following Barresi & Moore (1996; see also Frith, 1995) he suggests that conscious judgements about movements require 'third-person' information while control of movement depends upon private 'first-person' information. Jeannerod suggests that schizophrenic patients fail to monitor the third-person signals that enable them to make judgements about their own actions. Frith *et al.* (1999) suggest that, in schizophrenia, something goes awry with the mechanism that translates the first-person representations that are involved in motor control into the third-person representations that are needed for conscious monitoring of the motor control system. This is part of more general problem that these patients have in escaping from a first-person, egocentric view of the world.

From the current results it is difficult to assert whether the lack of attenuation of self-produced tactile stimulation in patients with auditory hallucinations and/or passivity phenomena is a state or trait marker. The breakdown in self-monitoring might be considered a state marker because it is possible, if not likely, that some of the patients in the 'Without symptom' group would have had hallucinatory and/or passivity experiences in their past. It is impossible from this study to determine whether people 'With symptoms' at the time of the experiment would continue to show the same results when they are in remission. This is an important question that might be pursued in a future study.

The current results could be interpreted in terms of other sensorimotor gating abnormalities seen in people with schizophrenia. For example, prepulse inhibition, the reduction in startle produced by a prepulse stimulus, is diminished in schizophrenic patients, suggesting that schizophrenia is associated with impaired central inhibitory mechanisms (Grillon *et al.,* 1992; Swerdlow and Geyer, 1998; Braff *et al.,* 1999). However, although there is evidence that patients with auditory hallucinations and passivity experiences do show reduced prepulse inhibition, deficient prepulse inhibition has been shown to correlate with negative as well as positive symptoms (Braff *et al.,* 1999). It is unlikely that deficient prepulse inhibition accounts for the current results, because the schizophrenic subjects in both groups (with and without auditory hallucinations or passivity experiences) in the current study had negative symptoms.

9.4.1 Possible physiological mechanisms

Possible physiological mechanisms by which the attenuation of self-produced tactile stimuli is mediated have been investigated. Neurophysiological data demonstrate that neuronal responses in somatosensory cortex are attenuated by self-generated movement (Chapman, 1994). In addition, fMRI data from human subjects has demonstrated an increase in activity of the anterior cingulate and somatosensory cortex when subjects experienced an externally produced tactile stimulus on their palm relative to a self-produced tactile stimulus, as described in

chapter 6. It was proposed that this inhibition of anterior cingulate and somatosensory cortex activity by self-generated movements results from the comparison between predicted and actual sensory feedback, which results in less sensory discrepancy when a tactile stimulus is self-produced relative to when it externally produced. There is evidence that this comparison might take place in the cerebellum (Ito, 1970; Leiner *et al.,* 1995; Miall *et al.,* 1993; Paulin *et al.,* 1989; Wolpert *et al.,* 1998), a proposal supported by the functional imaging data (see **chapters 6, 7 and 8**). It has been suggested that this network of brain areas is involved in predicting the consequences of actions in order to distinguish self- and externally produced sensations. It is possible that this neural system, or part of it, operates abnormally in people with auditory hallucinations and/or passivity experiences.

Indeed, the hypothesis that there is a dysfunctional cortico-cerebellar circuit in schizophrenia has been supported by histological and imaging studies demonstrating abnormal neural processing in the cerebellum and the ACC in people with schizophrenia. Schizophrenia has long been associated with abnormal structure, metabolism and functioning of the frontal lobes. This became known as 'hypofrontality' (Ingvar & Franzen, 1974). Hypofrontality in schizophrenia has often been localised to the prefrontal cortex (PFC) in functional imaging studies (e.g. Ragland *et al*., 1998; Carter *et al*., 1998; Spence *et al*., 1998). However, there is now considerable evidence that the anterior cingulate might also be a significant focus of the frontal structural and rCBF changes in schizophrenia.

9.4.1.1 Evidence for abnormal anterior cingulate functioning in schizophrenia

Histological studies have shown evidence for abnormal synaptic function in the cingulate (Honer *et al*., 1997; Benes *et al.* 1991; Benes *et al.* 2000) in schizophrenia. Functional neuroimaging studies have also shown that the ACC functions abnormally during cognitive tasks in schizophrenia (see Tamminga *et al*, 2000 for review).

Abnormal metabolism in the right ACC has been associated specifically with the disorganisation syndrome (Liddle *et al*., 1992). The researchers correlated rCBF levels with symptom severity scores for Liddle's three clinical subdivisions in 30 schizophrenic patients. The disorganisation syndrome, which involves impaired suppression of inappropriate responses (e.g. in the Stroop test), was associated with increased perfusion of the right ACC at a location activated in normal subjects performing the Stroop test.

Dolan *et al.* (1995) and Fletcher *et al.* (1996) used a factorial design to test the effect of apomorphine, a non-selective dopamine agonist, which when given in very low doses as in this experiment acts primarily on auto-receptors thus decreasing the release of endogenous dopamine. Brain systems engaged by a paced verbal fluency task in unmedicated schizophrenic patients and normal control subjects were studied using PET. Activation of the dorsolateral PFC was normal, but the authors found a failure of task-related activation in the ACC and deactivation of the left superior temporal gyrus in the schizophrenic subjects. Fletcher and colleagues suggested that schizophrenia is associated with both segregated (ACC) and integrative (fronto-temporal) functional abnormalities. Low-dose apomorphine normalised both the cingulate activation and the fronto-temporal pattern of activation in schizophrenic subjects, making their pattern of brain activity more similar to that seen in control subjects. The interpretation of the apomorphine-induced reversal of the deactivation in the left temporal lobe in schizophrenic subjects is unclear. It might reflect a direct influence of apomorphine on the temporal lobe; alternatively the reversal could be due to a 'downstream' effect of the change in ACC function.

Spence *et al.*(2000) found no differences in functional connectivity between the frontal cortex and superior temporal cortex during a verbal fluency task in patients. However, patients exhibited significant disconnectivity between left PFC and anterior cingulate cortex in their study.

Fletcher *et al.* (1998) used PET to compare rCBF in memory-impaired and non-impaired schizophrenic patients with normal controls during a parametrically graded memory task. In this study, they found that dorsolateral PFC activity correlates with memory task difficulty and performance in the control group. In contrast, for both schizophrenic groups dorsolateral PFC activity levels plateaued as task difficulty increased despite a significant difference in performance between the two schizophrenic groups. The researchers then evaluated effective connectivity (Friston *et al.*, 1997a) between regions in the data from their PET study of a graded memory task in schizophrenia (Fletcher *et al.*, 1999). They demonstrated that in control subjects, but not in the schizophrenic patients, the product of PFC and ACC activity predicted a bilateral temporal and medial PFC deactivation. They interpreted these results as showing that in schizophrenia there is an abnormality in the way in which left PFC influences left superior temporal cortex, and this abnormality is due to a failure of the ACC to modulate the prefronto-temporal relationship. These results suggest that the ACC is part of a network of brain regions that function abnormally in schizophrenia.

9.4.1.2 Evidence for abnormal cerebellar functioning in schizophrenia

Cerebellar structure and volume has been found to be abnormal in people with schizophrenia. Wassink *et al.*(1999) examined whether brain morphology assessed early in the course of schizophrenia predicted psychosocial or symptomatic outcome. The authors acquired MRIs for 63 subjects with schizophrenia spectrum disorders. Subjects were then prospectively assessed every 6 months for an average of 7 years. Negative associations were found between cerebellar volume and three outcome measures: negative and psychotic symptom duration, and psychosocial impairment. The authors proposed a role of cerebellar abnormalities in the aetiology and pathophysiology of schizophrenia.

Many recent activation studies using PET, SPECT and fMRI have identified both decreased and increased activation in the cerebellum of schizophrenic patients compared with healthy controls (Kinney *et al*, 1999; Levitt *et al*, 1999; Loeber *et al*, 1999; Schultz & Andreasen, 1999). Andreasen and her colleagues suggest that the cerebellum plays a critical role in schizophrenia. They suggest that a disruption in the cortical-thalamic-cerebellar-cortical circuit leads to an impairment in the smooth co-ordination (or synchrony) of mental processes and may explain the 'loosening of associations' that Bleuler considered to be the fundamental cognitive phenotype of schizophrenia (Bleuler, 1969). Andreasen and her colleagues refer to this impairment in synchrony as 'cognitive dysmetria' and suggest that it defines the phenotype of schizophrenia and produces its diversity of symptoms (Andreasen *et al*, 1998; Andreasen *et al*, 1999). Evidence for this theory comes from several functional neuroimaging studies.

Andreasen *et al.* (1996), using PET, showed that a prefrontal-thalamic-cerebellar network is activated when normal subjects recall complex narrative material, but is dysfunctional in schizophrenic patients when they perform the same task. Wiser *et al.* (1998) measured rCBF during a long-term recognition memory task for words in schizophrenic patients and in healthy subjects using PET. The task was designed so that performance scores were similar in the patient and control subjects. The memory retrieval task did not activate the PFC, precuneus or cerebellum in patients as much as it did in the control group. This finding supports the notion of a dysfunctional cortico-cerebellar circuit in schizophrenia.

Andreasen and colleagues measured blood flow with PET in neuroleptic-naive patients experiencing their first episode of schizophrenia and in patients with chronic schizophrenia (Andreasen *et al*, 1997; Kim *et al*, 2000). Both sets of patients showed lower flow in prefrontal areas and higher flow in thalamic and cerebellar regions than normal comparison subjects, suggesting that a similar neural dysfunction occurs in both first-episode and chronic schizophrenia. Thus the authors suggest that the primary neural abnormalities in schizophrenia may occur in cortical, cerebellar, and thalamic regions and that the dysfunction in these regions results in cognitive dysmetria.

These studies highlight a dysfunctional fronto-anterior cingulate-cerebellar circuit in schizophrenia. The work by Spence and colleagues suggests that impaired functioning of the anterior cingulate is associated with passivity experiences. It would be interesting to investigate whether this circuit is particularly dysfunctional in patients with auditory hallucinations and passivity experiences while subjects are producing willed actions, as in the present study. This study would be particularly suitable for a scanning experiment because of the simplicity of the task and because it would be possible to ensure that there is no difference between the task performance of patients and control subjects.

This is an important issue because there is a conceptual problem with applying the approach of cognitive activation studies to patient groups. It is impossible to interpret patterns of brain activity that differ between control and patient groups when the performance of the two groups on tasks differs in terms of degrees of efficiency and success. Many functional neuroimaging studies have used unmodified frontal tasks, in which the performance of schizophrenic patients falls below that of control subjects. It is unclear how to interpret increases or decreases of regionally specific activation in these studies. Any difference in brain activity between the two tasks could represent a critical abnormality in schizophrenia and might cause poor task performance, or alternatively it might reflect poor performance. In other words, it is impossible to attribute cause or effect. Recent studies have employed tasks on which performance of the patient and control group is matched (e.g. Heckers *et al.*, 1998).

However, there is also a problem with interpreting the results of activation studies in which the task performance of the patient and control group is matched. What do differences in brain activity mean in the context of normal task performance? If an area is activated more in the control group than in the patient group during such a task, the functional significance of that activation is difficult to understand - it is clearly not necessary for performing the task. The most obvious interpretation is that patients and controls are using different strategies to achieve similar task performance. Therefore, interpretational difficulties remain: what is the nature of the relationship between differences in brain activity and behaviour? How do these two variables relate to the schizophrenic state? These problems have not been resolved, and remain when interpreting data from studies in which tasks performance of patient and control groups is matched.

9.5 Conclusion

To test the hypothesis that certain psychotic symptomatology is due to a defect in self-monitoring, the ability of groups of psychiatric patients to differentiate perceptually between self- and externally produced tactile stimuli was investigated. Three groups of subjects - psychiatric patients with auditory hallucinations and/or passivity experiences, psychiatric patients without those symptoms, and a group of normal control subjects - were asked to rate the *perception of a tactile sensation on the palm of their left hand. The tactile stimulation was either self-produced by movement of the subject's right hand or externally produced by the experimenter. Normal control subjects and psychiatric patients with neither auditory hallucinations nor passivity phenomena experienced self-produced stimuli as less intense, tickly and pleasant than identical, externally produced tactile stimuli. In contrast, psychiatric patients with these symptoms did not show a decrease in their perceptual ratings for tactile stimuli produced by themselves as compared to those produced by the experimenter. It is proposed that auditory hallucinations and passivity experiences are associated with an abnormality in the self-monitoring mechanism that normally allows us to distinguish self-produced from externally produced sensations. There is evidence that this self-monitoring mechanism involves the cerebellum and anterior cingulate, and that the interaction between these areas might be abnormal in schizophrenia. Whether this circuit is particularly dysfunctional in patients with auditory hallucinations and passivity would make an interesting future study.*

10 CHAPTER 10: DISCUSSION

10.1 Summary of studies described in this thesis

This thesis has described a series of experiments that evaluated behavioural and neural characteristics of internal forward models in human subjects. These experiments focused on how we distinguish sensory stimulation that is externally produced from sensory stimulation that is produced by our own actions. The experiments investigated such forward model mechanisms in auditory, sensorimotor and somatosensory modalities in healthy subjects using psychophysical paradigms and functional neuroimaging. In addition the ability of groups of psychiatric patients to differentiate between self- and externally produced sensory stimuli was investigated to test the hypothesis that auditory hallucinations and passivity experiences are caused by an impairment in the forward model.

10.1.1 Behavioural components of the forward model

It is proposed that forward models play a fundamental role in coordinative behaviour such as that used when manipulating objects. When subjects move an object, their grip force is modulated in parallel with the changes in load force of the object. Such anticipatory behaviour has been attributed to the ability to predict the consequences of one's own actions (Johansson and Cole 1994; Lacquaniti *et al.* 1992; Massion 1992), a process that requires internal models of both one's own body and the external world. Grip force modulation paradigms can be used to investigate the psychophysical consequences of the sensory predictions made by a forward model.

The experiment described in chapter 4 measured bilateral grip-force modulation when subjects manipulated objects. The first experiment was designed to test the hypothesis that provided the load force is self-generated, predictive grip force modulation will be observed. This was not found to be true. Precise predictive grip force modulation was seen in the conditions in which the load force was generated directly by motion of either the right or left hand. In contrast, when the left hand produced the load force indirectly, via a joystick, there was no prediction: grip force significant lagged behind load force. This was similar to the condition in which the load was externally generated by the robot. The second experiment was designed to investigate the reason for the lack of prediction in the joystick condition. Two robots were employed to simulate virtual objects held in one hand and acted upon by the other. Using this robotic interface, the force feedback from the object to the hand holding it was parametrically varied. Precise predictive grip force modulation of the restraining hand was highly dependent on the sensory feedback to the hand producing the load. The results showed that efference copy is not, in itself, sufficient for generalised prediction. Predictive modulation requires not only that the movement is self-generated, but also that the efference copy and sensory feedback are consistent with a specific context; in this case the manipulation of a single rigid object. Precise prediction was seen when the feedback to both hands was consistent with a single object and declined smoothly as the feedback became inconsistent with this context. The results were interpreted in terms of a computational mechanism whereby the CNS uses multiple internal models, each corresponding to a different sensorimotor context. Each context is assigned a probability. The highest probability indicates which context the motor system is acting within.

One such sensorimotor context in is that in which one hand produces a sensation on the other hand. In the experiment described in chapter 5 of this thesis the relationship between the accuracy of the forward model's sensory predictions and the perception of self-produced sensory stimulation was investigated by manipulating the sensorimotor context in which self-produced stimulation occurred. Subjects were asked to rate the perception of a tactile stimulus on the palm of their right hand that was either self-produced by the subject or externally produced by a robot. In the conditions in which the tactile stimulus was self-produced, the subject moved the arm of a robot with their left hand to produce the tactile stimulus on their right hand via a second robot. It was found that subjects rated self-produced tactile stimulation as less intense, tickly and pleasant than externally produced stimulation. The results suggest that an internal forward model predicts the sensory consequences of the motor commands sent to one hand, and this prediction is used to cancel the resultant tactile sensation on the other hand.

Using this robotic set-up it was possible to manipulate the correspondence between the action of the subject's left hand and the tactile stimulus on their right hand. Firstly, the delay between the movement of the left hand and the resultant movement of the tactile stimulus on the right hand was parametrically varied. Secondly, varying degrees of trajectory perturbation were implemented so the direction of the tactile stimulus movement as a function of the direction of left hand movement was manipulated. The 'tickliness' rating of the self-produced tactile stimulus increased significantly with increasing delay and trajectory perturbation between self-produced movements and the resultant tactile stimulation. These results suggest that the tickliness of a self-produced tactile sensation is inversely proportional to the sensory discrepancy produced by the comparison between the predicted and the actual sensory feedback from a movement. As the tactile stimulus diverges temporally or spatially from the motor command producing it, the forward model is less able to predict precisely and cancel the sensation, which is therefore perceived as increasingly tickly.

In summary, these results of these psychophysical studies demonstrate that:

- Forward models are used to predict and compensate for the sensory consequences of movements.
- When manipulating an object, self-generation of a movement is not in itself sufficient for the forward model to make accurate predictions of the sensory consequences of the movement. In addition the context must be consistent with our everyday experience - that is, the object must be conform to normal, physical laws.
- The sensory prediction made by a forward model can be used to attenuate self-produced sensory (tactile) stimulation relative to externally produced sensory stimulation.
- The extent to which self-produced tactile stimulation is attenuated is inversely proportional to the level of sensory discrepancy between the sensory prediction made by the forward model and the actual sensory feedback produced by the movement.

10.1.2 Neural correlates of the forward model

There is considerable evidence from several modalities that sensory stimuli are processed differently in the brain depending on whether they are self- or externally generated. In the auditory domain, evidence in human subjects suggests that auditory stimuli are processed differently depending on whether they are a consequence of self-generated actions (Shafer & Marcus, 1973; Shafer *et al*, 1981). However, whether this is due to the predictability of self-generated stimuli is unknown. Functional neuroimaging was used to explore this phenomenon. In chapter 3 PET was used to study brain responses to predictable sensory events (auditory tones) and to similar unpredictable sensory events. The study was designed to show how the processing of predictable sensory events is modified by the context of a causative self-generated action. Increases in activity when tones were unpredictable were seen in the temporal lobes, the right parahippocampal gyrus and right parietal cortex, and it was suggested that these areas might be involved with processing unexpected, 'novel' stimuli. A modulation of activity associated with self-generated auditory stimuli was observed in several areas including the medial posterior cingulate cortex, left insula, dorsomedial thalamus, and superior colliculus. It was proposed that areas where activity is greater during self-produced than during externally produced tones may be involved in predicting the sensory (auditory) consequences of self-produced movements.

In the somatosensory domain, it has been found that neurons in somatosensory cortex of monkeys are 'gated' during active self-produced tactile stimulation relative to passive or external tactile stimulation (Jiang *et al.*, 1991; Chapman & Ageranioti-Belanger, 1991; Chapman, 1994). fMRI was used in chapter 6 to examine neural responses when subjects experienced a tactile stimulus that was either self-produced or externally produced. More activity was seen in bilateral secondary somatosensory cortex and anterior cingulate cortex when the tactile stimulus was externally produced relative to when it was self-produced. The responses in these areas might mediate the differential perception of self- and externally produced stimulation. In the cerebellum there was less activity associated with a self-produced movement that generated a tactile stimulus than with a movement that did not. This difference suggests that the cerebellum is involved in predicting the specific sensory consequences of movements, providing the signal that is used to cancel the somatosensory response to self-generated stimulation.

This hypothesis was investigated in chapter 7 by using regression analyses to evaluate the influence of the cerebellum over somatosensory cortices when tactile stimulation were self-produced compared to when it was externally produced. Specifically, it was predicted that activity in the cerebellum contributes to the decrease in somatosensory cortex activity during self-produced tactile stimulation. Evidence in favour of this hypothesis was obtained by demonstrating that activity in the ventral thalamus and primary and secondary somatosensory cortex showed a significant regression on activity in the cerebellum when tactile stimuli were self-produced, but not when they were externally produced. This supports the proposal that the cerebellum is involved predicting the sensory consequences of movements and signalling the sensory discrepancy resulting from the comparison between the predicted and actual sensory feedback. It is proposed that when stimuli are self-produced the sensory prediction made by the forward model is accurate and can be used by the cerebellum to attenuate the somatosensory response to those stimuli. In contrast, externally produced stimuli cannot be accurately predicted by the forward model and therefore no somatosensory gating can occur.

To investigate further the hypothesis that the cerebellum is involved in signalling the sensory discrepancy, PET was used in chapter 8 to examine neural responses to parametrically varying degrees of sensory discrepancy between the predicted and actual sensory consequences of movement. Using the same robotic interface as was used in the psychophysical experiment in chapter 5, computer controlled delays of 0, 100, 200 and 300 ms were introduced between the action of the right hand and the tactile stimulation on the left. As predicted, activity in the cerebellum showed a positive correlation with the delay, a result that supports the proposal that the cerebellum signals the sensory discrepancy from the forward model.

In summary, the results of these functional neuroimaging studies demonstrate that:

- Certain brain regions respond differently to sensory stimuli that are self-produced and to the same stimuli when externally produced independent of their predictability.
- Activity in the somatosensory and ACC is reduced when tactile stimulation is self-produced relative to when it is externally produced. This might be the physiological correlate of the reduced perception associated with self-produced relative to externally produced stimulation.
- The cerebellum is involved in predicting the sensory consequences of movements and signalling the discrepancy that results from the comparison between the prediction with the actual sensory feedback from movements.
- This sensory prediction can be used to attenuate the response in somatosensory cortex –when the prediction is accurate, somatosensory activated is attenuated, when the prediction is inaccurate no somatosensory gating occurs.

10.1.3 Forward models in psychotic patients with auditory hallucinations and/or passivity experiences

It has been proposed that auditory hallucinations and passivity experiences associated with schizophrenia arise from an impairment in the forward model whereby patients are abnormally aware of the consequences of their own actions (Frith, 1992; Frith *et al*, 1999; Frith *et al*, 2000). To test the hypothesis that this psychotic symptomatology is due to a defect in the forward model, the ability of groups of psychiatric patients to differentiate perceptually between self- and externally produced tactile stimuli was investigated. In chapter 9, three age-matched groups of subjects - psychiatric patients with auditory hallucinations and/or passivity experiences, psychiatric patients without those symptoms, and a group of normal control subjects - were asked to rate the perception of a tactile sensation on the palm of their left hand. The tactile stimulation was either self-produced by movement of the subject's right hand or externally produced by the experimenter. Normal control subjects and psychiatric patients with neither auditory hallucinations nor passivity phenomena experienced self-produced stimuli as less intense, tickly and pleasant than identical, externally produced tactile stimuli. In contrast, psychiatric patients with these symptoms did not show a decrease in their perceptual ratings for tactile stimuli produced by themselves as compared to those produced by the experimenter.

It is proposed that auditory hallucinations and passivity experiences are associated with an abnormality in the forward model mechanism that normally allows us to distinguish self-produced from externally produced sensations. Specifically, it is suggested that these symptoms arise from a lack of awareness of the sensory prediction based on the forward model (Frith *et al.*, 1999; Frith *et al.* 2000). This might occur, for example, if the comparison process always results in a high level of sensory discrepancy error, however accurate the sensory prediction. In this case self-produced sensations (thoughts, movements, touch), despite being accurately predicted by the forward model, would result in a high level of sensory discrepancy, could not be cancelled, and would therefore be classified as arising from an external source. Self-produced events could also be confused with externally generated events if the former were not predicted accurately or were predicted accurately but associated with a high level of sensory discrepancy.

10.1.4 Summary

The experiments presented in this thesis have advanced our knowledge of the behavioural and neural correlates of forward models in humans. The experiments have demonstrated how we distinguish the sensory consequences of our own actions from sensations that are externally produced. The forward model mechanism that predicts the sensory consequences of self-generated actions is evolutionarily significant because it accentuates and picks out external (and potentially biologically important) events from sensations that arise as a necessary consequence of our own motor acts. The ability to monitor movements, sensations and even voices and thoughts caused by our own intentions allows the filtering of important information and gives sense to a world that otherwise might be sensorily confusing. Indeed, it is proposed that an impairment of this forward model mechanism might give rise to experiences in which self- and externally generated events are confused. If not classified as self-produced, and cancelled, thoughts might be interpreted as external voices (auditory hallucinations) and self-produced movements might be interpreted as externally generated (delusions of control or passivity phenomena). This theory of the aetiology of auditory hallucinations and passivity phenomena is supported by the final study described in this thesis.

10.2 Internal models and abnormalities in the control of action

Impairments in the components of internal models are a useful way of considering symptoms associated with schizophrenia. Internal models might also be useful when considering other types of motor and cognitive impairments. Firstly, a breakdown in the different components of the forward model might also be able to explain certain other abnormalities in the awareness and control of action, which will be discussed in this section. These theories have been discussed in Frith *et al* (2000). Secondly, internal models might be a useful way of characterising cognitive functions, such as understanding other people's intentions and desires. In this way, it is possible that certain cognitive deficits associated with autism might be considered in terms of an impairment of a component of the forward model.

10.2.1 Phantom limbs

After amputation of all or part of a limb many people report that they experience a phantom limb. Although they know that there is no limb they still feel the presence of the limb (Ramachandran & Hirstein, 1998). Some patients report being able to move their phantom limbs voluntarily, while others experience their phantom as paralysed and cannot move it even with intense effort. If the limb was paralysed before amputation the phantom normally remains paralysed. If not, then typically immediately after amputation patients can generate movement in the phantom. However, with time they often lose this ability (Ramachandran, 1993).

After amputation of a limb, reorganisation of the de-afferented region of sensory cortex occurs. As a result stimulation of the skin of distant areas such as the face or the chest can elicit sensation in a phantom arm (Ramachandran *et al.*, 1992; Aglioti *et al.*, 1994; Kew *et al.*, 1997). Thus the experience of a phantom limb can be supported by somatosensory signals coming from other parts of the body. However this sensory reorganisation does not explain why some patients can voluntarily move the phantom.

Voluntary phantom limb movement can be explained in terms of the forward model. It is proposed that the estimated position of a limb is not based solely on sensory information, but also on the stream of motor commands issued to the limb muscles. On the basis of these commands the forward model estimates the new position of the limb before any sensory feedback has been received. Even in the absence of a limb streams of motor commands can still be issued. If these commands lead to the prediction of movement, then the phantom will be experienced as moving. Since the limb does not actually move there will be a discrepancy between the predicted and the actual consequences of the motor commands. The motor control system is designed to adapt to changing circumstances, and with time the forward models will be modified to reduce this discrepancy. At this point the issuing of a stream of motor commands will not lead to the prediction of a change in limb position. Such adaptation of the forward model could explain why most patients eventually lose the ability to move their phantoms.

Such adaptation of the forward model would also explain how Ramachandran & Rogers Ramachandran (1996) were able to reinstate voluntary movement of the phantom by providing false visual feedback of a moving limb corresponding to the phantom. This was achieved by placing a mirror in the mid-saggital plain. With the head in the appropriate position it was possible for the patient to see the intact limb at the same time as the mirror reflection of this limb. This reflection so closely resembles the missing limb that the patient has the strong illusion of seeing the missing limb. If the intact limb is moved then the patient receives from the mirror visual feedback of movement in the missing limb. For most patients moving their hand in this mirror box rapidly leads to the perception that they are now able to move the phantom limb again. In some cases this perception continues even when the mirror box is no longer being used.

In a reformulation of the proposals of Ramachandran & Rogers Ramachandran (1996), it has been suggested that the false visual feedback supplied by the mirror box allows the forward model to be updated (Frith *et al*, 2000). In consequence, the efference copy produced in parallel with the motor commands now generates changes in the predicted position of the missing limb corresponding to what the patient sees in the mirror.

10.2.2 Missing limbs

After peripheral deafferentation of a limb patients will often develop a phantom even though the deafferented limb is still present. This phantom may be contained within the real limb, but, in some circumstances, may become separated from the limb and become supernumerary (e.g. Kew *et al.*, 1997; subject 2). In other cases patients do not develop phantoms, but rather are unaware of the existing limb unless it can be seen. The critical difference between deafferented patients who develop phantoms and those in whom the limb fades seems to lie in whether or not the deafferented limb is also paralysed. The cases described by Kew *et al.* (1997) who developed phantoms had limbs that were deafferented and paralysed. In contrast the patient described by Cole (1991) is completely deafferented for touch, but is not paralysed and has achieved a remarkable degree of motor control which is largely based on visual feedback. This patient has never developed a phantom, but for him and his body it is literally "out of sight, out of mind" (Cole, 1991).

Most deafferented patients whose motor output system remains intact make highly inaccurate movements. Rothwell *et al.* (1982) demonstrated that a patient with peripheral deafferentation was unable to make automatic reflex corrections to movements and was unable to sustain constant levels of muscular contraction or maintain long action sequences in the absence of visual feedback. The lack of a sensation of the current position of the limb is not only a problem for checking the success of movement through feedback. It also creates a problem because the computation by the inverse models of the appropriate movement requires that the starting position of the limb must be known.

Similar problems can occur after brain damage in somatosensory areas as a result of which the patient can no longer experience the limb controlateral to the lesion. Jeannerod *et al.* (1986) describe a patient with hemianaesthesia after damage involving the right inferior parietal lobe. The patient could initiate simple single-component movements, but could not make complex multi-component movements with his left hand in the absence of visual feedback. Wolpert *et al.* (1998b) describe an interesting variant of this phenomenon. Patient PJ had a large cyst in the left parietal lobe and reported the experience of the position and presence of her right arm and leg fading away over seconds if she could not see them. Her experience of a constant tactile stimulus or a weight also faded away, but changes in such sensations could be detected. Slow reaching movements to peripheral targets with the right hand were inaccurate, but reaching movements made at a normal pace were unimpaired. In this case there seemed to be a circumscribed problem with the representation of the current limb position in that it could not be maintained in the absence of changing stimulation.

In all these cases of deafferentation without paralysis, visual signals provide the only sensory information for making accurate movements. They provide information about the position of a limb prior to movement and provide feedback about the accuracy of the movement. As a result the motor control system will learn to ignore somatosensory and proprioceptive signals when predicting the outcome of movements or estimating the current state of the system. It will learn to base such estimates solely on the stream of motor commands and upon visual information. In the absence of visual signals the estimates can not be made and the experience of the limb fades away.

In patients with deafferentation and paralysis no movements can be made and so the system has no chance to learn to attend to one modality of sensation rather than another. The experience of a phantom can therefore be driven by sensations from other limbs that have been remapped into the deafferented cortical region.

10.2.3 Supernumerary limbs

Patients sometimes report experiencing one or more supernumerary limbs in addition to their real limbs (Vuilleumier *et al.*, 1997). For example, a patient described by Hari *et al.* (1998) reports experiencing an additional left arm. The extra arm occupies the position vacated by the real left arm a minute or so previously. The felt position of phantom extra arm mirrors the voluntary (but not passive) movements of the right arm. Experience of the extra arm ceases if the patient moves her left arm or looks at it or has it touched.

This experience can be explained by assuming that the estimated position of a limb is based on integrating information from motor commands and sensory feedback. Failure to integrate these two sources of information could lead to the experience of two limbs rather than one. At the time of initiating an action the patient of Hari *et al.* (1998) has the normal awareness of movement based on the representation of the predicted position of the arm. However, the representation of the estimated actual position of the arm fails to get updated on the basis of the motor commands. This discrepant representation of the estimated position of the arm emerges into awareness some time after the movement has been completed leading to the experience of an extra arm. Correct updating of this representation occurs on the basis of signals from the somatosensory or visual system. However, false updating can also occur based on motor commands controlling the right limb. This false updating must be based on motor commands rather than sensory feedback since passive movements of the right arm do not affect the phantom. Presumably the effect of signals concerning movements of the right limb are normally suppressed when they are discrepant from the motor commands driving the left limb. It is possible that movement of the phantom in this case derives from motor signals relating to the controlateral limb.

10.2.4 Anosognosia

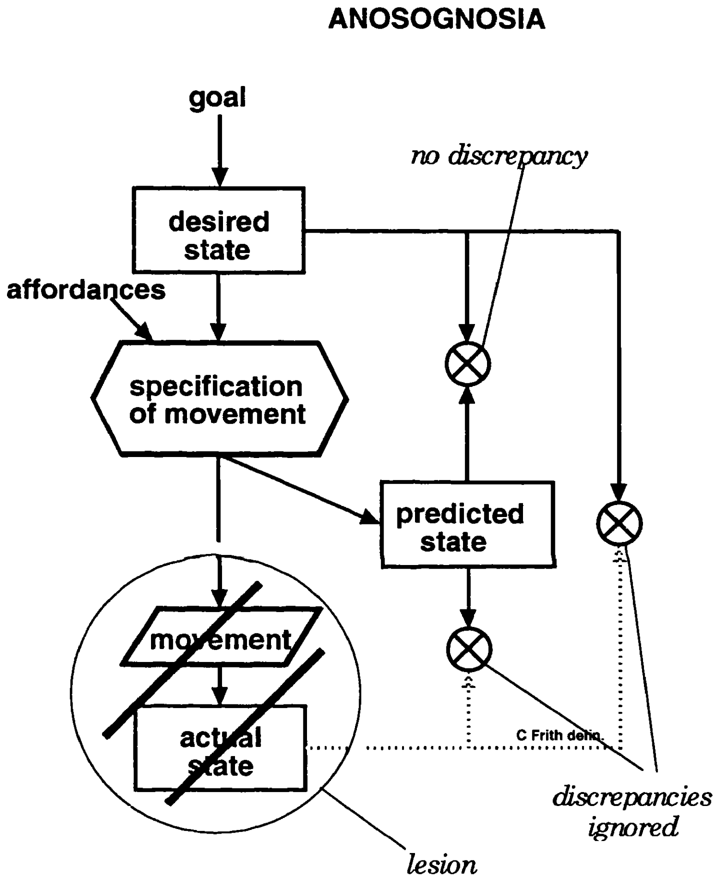
A patient with anosognosia is unaware of some impairment that has resulted from brain damage (Babinsky, 1914). For example, patients with right hemisphere damage leading to paralysis on the left side occasionally develop the false belief that there is nothing wrong with their paralysed limb (e.g. Ramachandran, 1996). In some cases the patient will claim to be able to move their limb even though no movement ever occurs.

This disorder is often associated with unilateral neglect for the left side of space. Geschwind (1965) suggested that anosognosia arises from a disconnection such that sensory feedback (both somatosensory and visual) indicating that the limb is not working is no longer available to a left hemisphere monitoring system. However, making sure that the paralysed left arm can be seen in the right visual field does not alter the denial of impairment. Heilman *et al.* (1998) have proposed a 'feed-forward' theory of anosognosia. According to this account anosognosic patients receive no signals indicating movement failure because the comparator that contrasts intended and actual movements receives no signal that a movement has been intended. Because patients do not try to move the paralysed limb they never discover that it is paralysed. While this account can explain denial of impairment, it is not clear how it can explain cases in which the patient apparently experiences having made a movement when none has actually occurred.

The experience of making a limb movement when none has actually occurred can be explained in terms of internal models. Evidence suggests that awareness of initiating a movement is based on a representation of the predicted consequences of making that movement, rather than its actual consequences (Libet *et al*, 1983; as discussed in the introduction of this thesis). A representation of the predicted consequences of a movement can be formed as long as the inverse models can compute the appropriate motor commands and the forward models can derive from these the expected consequences. Thus, a patient with a paralysed limb would have the normal experience of initiating a movement with that limb as long as the inverse model and forward model were functioning normally. However, to continue to believe that he or she had initiated that movement would require further abnormalities in the system. First, there would have to be a failure to register the discrepancy between the predicted consequences and the actual consequences of the movement that was initiated. Second, there would have to be a failure to update the operations of the forward model. With experience the forward model should learn that the motor commands issued by the inverse model result in minimal movements of the paralysed limb. In the patient with anosognosia this updating apparently does not occur.

Thus the false experience of movement reported by patients with anosognosia might occur because, while representations of the desired and predicted positions of the limb are appropriate, the patient is not aware of the discrepant representation of the actual position of the limb (**Figure 10-1**). The inverse models issue the appropriate motor commands, but, due to paralysis, do not generate a limb movement. However, the forward models have estimated, on the basis of these commands and from past experience prior to brain damage, the new position of the limb. The lack of a discrepancy between intended and predicted positions indicates success. Contrary information derived from sensory feedback concerning actual limb positions is not available, since the relevant brain regions have been damaged, or else this contrary information is neglected. As a result the estimated position of the limb is based on sequences of motor commands and not upon sensory feedback.

Figure 10-1



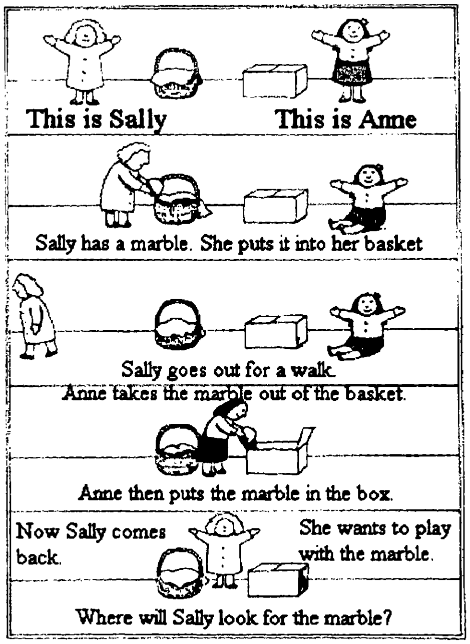
The proposed underlying disorder leading to anosognosia. The patient formulates the action needed to fulfil his intention and is aware that the action initiated is appropriate. No information about the actual position of the limb is available to indicate that no action has actually occurred.

10.3 Forward models and theory of mind

As well as showing deficits in monitoring their own actions, people with schizophrenia also show abnormalities in interpreting other people's actions (Frith, 1992). This is clear in certain schizophrenic symptoms, for example paranoid schizophrenic patients often misinterpret the actions of others as threatening or as aimed towards them. Another schizophrenic symptom is the belief that they can control other people's actions. Understanding other people's actions in terms of their desires, beliefs and intentions is often referred to as plays a 'theory of mind' and plays a central role in social interaction. Having a 'theory of mind' enables us to interpret other people's actions in terms of their goals, desires, intentions and beliefs. For instance, understanding that an action such as lifting a glass can be caused by someone's intentions provides us with useful information about that person's desires (to drink from the glass). It has been found that schizophrenic patients show impairments on theory of mind tasks (Corcoran *et al.*, 1995; Frith & Corcoran, 1996).

Children develop an understanding of other people's desires and beliefs at around the age of four years (Wimmer & Perner, 1983). At this age they are able to pass theory of mind tasks, such as the Sally-Anne false belief task. In this task, children are shown two dolls, Sally and Anne, in a room containing a basket and a box (**Figure 10-2**). Sally has a marble, which she puts in the basket, and then she leaves the room. While Sally is out of the room, Anne removes the marble from the basket and hides it in the box. The children are asked where Sally will look for the marble when she returns. Three year olds fail this task - they say that Sally will look where they know the marble is hidden, in the box. By four or five children give the correct answer (the basket) - by this age they have developed a theory of mind and understand that people can have false beliefs, which differ from their own. Children with autism often have difficulties understanding other people's beliefs and most fail the Sally-Anne test well above age five (Baron-Cohen *et al.*, 1985; Frith & Happe, 1989). Autism is also associated with an inability to interpret people's actions in terms of their goals, desires or intentions. It has been suggested that the trouble autistic children have forming social relationships might be related to their difficulties in understanding other people's desires, intentions and beliefs (Frith, 1992).

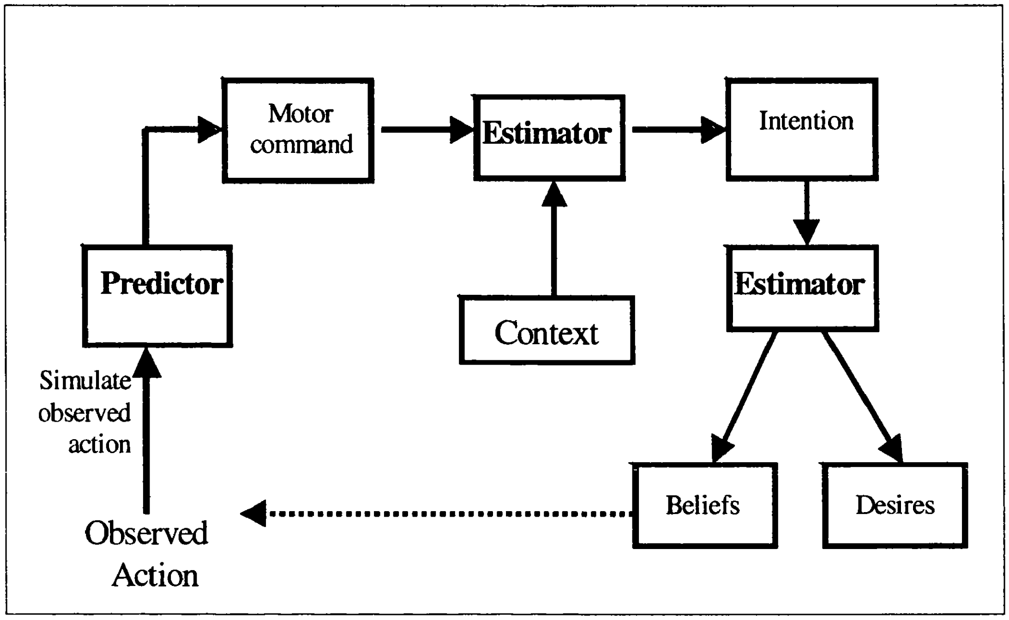
Figure 10-2



The Sally-Anne task – see text for details.

It is possible that internal models play a role in understanding other people's intentions and desires. In order to understand the intention behind an observed action, it is possible that the brain simulates (and prepares to make) the same action. This could be achieved by reversing the normal process of forward model. Normally goals, and desires determine one's intention, which is used to provide the motor commands. The normal forward model estimates the sensory consequences of a movement on the basis of the motor commands. It is possible that the observed sensory consequences of a movement provide information about the motor commands made to produce such a movement, and the estimated motor commands provide information about the person's intentions. It might then be possible to estimate the person's goals, desires and beliefs from the estimated intentions, given the particular context. Using a representation of our own intentions it might be possible to calculate what our own desires and beliefs would be in the same intentional situation within the same context (**Figure 10-3**). So estimating someone's goals, desires and intentions from observing their actions might be possible by simulating the action. This could be done purely automatically at an unconscious level.

Figure 10-3



A model for determining someone's intentions, desires and beliefs from observing the sensory consequences of their actions. This 'reverse' forward model makes predictions of the motor command by simulating the observed action. The predicted motor command can then be used together with the context of the movement, to estimate the person's intentions. The estimation of their intentions can be used to estimate their beliefs and desires. Theses are all based on a simulation of one's own intentions, beliefs and desires given the same motor command.

There is evidence that observing someone making an action activates a component of the brain's motor system. Neurons in the premotor cortex of monkeys discharge when the monkey observes someone grasping an object, without making any movements themselves ('mirror neurons'; Rizzolatti *et al*, 1990). Similarly, when human subjects observe someone making a movement, without making any movements themselves, a component of their brain's motor system is activated (Iacoboni *et al*, 1999). Brain regions activated during motor imagery are a subset of those activated during motor execution (Decety *et al*, 1994; Stephan *et al*, 1995). Jeannerod has proposed that both imagining making a movement and observing someone else making a movement are closely related to motor preparation (Jeannerod, 1994). Since similar brain areas are engaged by motor preparation, motor imagery, and observing movement, it is proposed that they are involved with representations of intended and predicted movements.

Imitation might play a role in understanding other people's intentions and desires from their motor actions. Young babies, even new-borns, naturally imitate other people's gestures, facial expressions and actions, and imitation seems to play an important role in learning about other people (Meltzoff, 1999). Iacoboni *et al* (1999) proposed that the motor plans necessary for imitating an action may be based on a mechanism that directly matches the observed action onto an internal motor representation of that action.

Without this mechanism of calculating an intention from actions, actions might be taken at face value, and be interpreted purely in terms of their mechanics with no reference to why they were made. This is characteristic of people with autism. If desires and intentions can normally be calculated from actions, it is possible that the component of the forward model that calculates intentions from actions is impaired in autism. If forward models are created and stored in the cerebellum, and there is much evidence to support that supposition, then people with autism would be expected to have impaired cerebellar functioning. The cerebellum is no longer thought of as a purely motor structure; there is a wealth of functional neuroimaging evidence suggesting that is involved in cognition. Recent evidence suggests that the cerebellum is involved in theory of mind – it is activated when subjects look at cartoons in involving an understanding of theory of mind compared to cartoons that do not require such an understanding (Fletcher *et al*, 1995; Brunet *et al*, 2000; Gallagher *et al*, 2000). Furthermore, there is a strong, though controversial, argument that the cerebellum is abnormal in autism. This theory has been supported by many recent structural imaging studies (Haas, 1996; Courchesne, 1999; Abell *et al*, 1999; Carper & Courchesne, 2000).

However, there is no evidence that patients with cerebellar lesions show autistic symptoms. Thus, if cerebellar abnormalities do contribute to the aetiology of autism, they must be complicated, and probably involve the cerebellar output to other brain areas. If there are any impairments of forward models in people with autism, they are clearly different from the impairments shown by people with schizophrenia. Autistic people do not experience the same psychotic symptomatology associated with schizophrenia. However, there are many components of the forward model that can be impaired and it is possible that the aspects impaired in schizophrenia are different from those impaired in autism. Furthermore, if the cerebellum is implicated in either disorder, it clearly plays a different role in each. It is possible that the cerebellar output to different parts of the frontal lobes, for example, might be impaired in these two disorders. Theory of mind tasks have been associated with the medial frontal gyrus (pre-cingulate sulcus) in four studies (Goel *et al*, 1995; Fletcher *et al*, 1995; Brunet *et al*, 2000; Gallagher *et al*, 2000). In comparison, the dorsolateral prefrontal cortex (DLPFC) has been associated with willed action (Frith *et al*, 1991; **chapters 3 and 6** of this thesis) and self-monitoring (Fink *et al*, 1999). In Fink's study, when there was a mismatch between motor intention (to move the hand) and sensory experience (proprioception and visual feedback of the moving hand), there was activation in the right DLPFC (BA 9/46). The laterality was independent of the hand attended and suggests that the right DLPFC is involved when actions must be maintained in the face of a conflict between intention and sensory outcome. The ACC has also been associated with distinguishing between self- and externally generated actions (**chapter 6**). The possibility that different cerebellar-cortical pathways are dysfunctional in autism and schizophrenia would be an interesting subject in future investigations.

10.4 Overall conclusions

The experiments in this thesis have added to our understanding of how forward models of the sensorimotor system function, their behavioural and neural characteristics, and the consequences of a breakdown of some component of the forward model. As well as helping to answer some questions the experiments also generate many more questions, giving scope for new experiments and theories about the forward model. The experiments presented in this thesis are in basic sensory and motor modalities. Whether forward models play a role in higher, cognitive functions, such as understanding other people's goals, intentions and desires, is a fascinating possibility and remains to be investigated.

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APPENDIX 9: PATIENT QUESTIONNAIRE

TACTILE EXPERIMENT

General information **Date**

Name of patient Consultant

Ward Keyworker

Date of Birth

Country of origin:

Does the patient speak English?

Clinical information

What is the patient's diagnosis?

What symptoms does the patient currently experience?

Auditory hallucinations?

Thought interference (insertion, withdrawal and broadcast)?

Passivity?

Does he or she have insight into his or her illness?

Is the patient on medication?

Which kind?

How long has the patient been on this medication?

How long has the patient been in hospital?

Background information

What is the patient's education level?

What is the education level of his or her parents?

Is the patient right or left handed?

Does the patient have any know organic brain disorder e.g. Head injury, epilepsy?

Does the patient have any serious medical illness?

Does the patient have a family history of any know organic brain disorder, or mental illness?

Is the patient likely to be distressed by the procedure?

Is the patient a drug or alcohol abuser?

Is the patient violent or suicidal?

Other comments: