

PREDICTIVE ATTENUATION OF TACTILE SENSATION

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ABSTRACT

It has been proposed that, in order to enhance sensitivity to novel information, the brain removes predictable components of sensory input. This thesis describes a series of psychophysical and behavioural studies investigating predictive filtering in the perception of touch. Using a novel force-matching paradigm, we demonstrate that self-generated tactile sensations are perceived as weaker than the same stimuli externally imposed. This attenuation is shown to be temporally tuned to the expected time of contact and modulated by the certainty with which a sensation can be attributed to self-action. We confirm experimentally that this attenuation results from a predictive, rather than postdictive, mechanism. Such a mechanism may predict the sensory consequences of action based on an internal model of the environment and an efference copy of the motor command. We investigate how prediction is acquired in a new environment and the coordinate systems in which the new environment is internally represented. Using a novel protocol of transcranial magnetic stimulation, we find evidence to suggest that the efference copy signal underlying the prediction arises upstream of primary motor cortex. Patients with schizophrenia are found to show less attenuation than healthy controls, consistent with models of the disease that propose an underlying deficit in sensory prediction. These experimental findings are discussed in relation to potential neural mechanisms of sensory filtering, and the many proposed roles for predictive mechanisms in human sensory and motor systems are reviewed.

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CHAPTER 1: INTRODUCTION

1.1 Discriminating between self- and externally-generated sensation

Whenever we move, speak or otherwise perform an action the resulting changes to our body and the environment are detected by our sensory systems. Under normal circumstances we recognise these sensations as the consequences of our actions and are able to distinguish them from similar sensations that are generated externally. We are unlikely to mistake the sound of another person talking for our own voice, and we have no difficulty distinguishing between movements we make ourselves and movements that are passively applied to our body by external forces. This ability to perceive our own actions as distinct from other people's is an important part of our perception of ourselves as a single unified self, capable of willed action, and is probably crucial to our functioning as a social animal. The ability to discriminate between self- and externally-generated sensory input is also thought to play a role in some of the more fundamental functions of our sensory and motor systems.

The earliest evidence for such a role came from the investigation of eye movements. When we move our eye the image of the world on our retina also moves, and yet we do not perceive the world to move. This is not simply because we have an expectation that the world will remain stable: as Descartes observed in his *Treatise of Man* (1664), tapping on the side of the eye with a fingertip generates an illusion of motion in the opposite direction, exactly as one would expect to occur during an eye movement. In

the nineteenth century, inspired by Descartes' observations, Helmholtz (1867) proposed that during normal eye movements the expected shift in the retinal image is compensated for in perception according to the 'effort of will' required to generate the movement. A century later, two separate studies both published in the same year proposed a model for this compensation (Sperry, 1950; von Holst and Mittelstaedt, 1950). According to von Holst's 'principle of reafference', when the motor areas of the brain generate a motor command signal to move the eyes they also send a copy of the command to the visual areas. This 'efference copy' is used to generate a prediction of the change to the visual input that will result from the eye movement (termed the 'corollary discharge' by Sperry). This predicted shift in the visual input is then reversed and applied to the actual visual input at an early stage of processing, cancelling the real shift in the retinal image with the result that a stable percept of the world is maintained.

Experimental studies have supported a role for efference copy in visual perception. The illusory movement observed by Descartes, Helmholtz and others when tapping on the side of the eye has a clear interpretation under von Holst's model: the pressure applied by the finger causes a movement of the eye, but because this movement is not generated by the motor areas controlling the eye muscles an appropriate efference copy is not sent to the visual areas and the resulting retinal shift is not compensated for. As a result the world appears to move in the opposite direction to the applied force.

According to von Holst's model, if the eye muscles were partially paralysed then any attempt to move the eyes would result in a mismatch in size between the predicted

and actual shift of the image on the retina. This would be expected to produce an illusory movement of the visual scene in the direction of the intended eye movement. When this experiment is performed with subjects observing a simple visual scene such as a point light-source an illusory movement is indeed observed (Mach, 1885; Kornmuller, 1930; Stevens et al., 1976). However the illusion disappears if the whole room is visible (Matin et al., 1982), suggesting that the role of efference copy in determining visual perception may be modulated by an expectation that the world as a whole tends to remain stable.

Similarly, an efference copy model predicts that a retinal afterimage viewed in darkness should appear to move in the direction of an eye movement, as the position of the afterimage on the retina remains constant. For small foveal afterimages this is indeed observed (Mack and Bachant, 1969), but an afterimage of a whole visual scene, generated by a brief intense flash of light, does not show this illusory movement (Pelz and Hayhoe, 1995). This finding again suggests that an expectation of global stability may in some cases override the efference copy mechanism. Indeed, the efference copy mechanism alone may be too slow to maintain visual stability during saccadic eye movements: illusory movement of foveal afterimages perceptibly lags the centre of gaze, and the afterimage becomes stationary during rapid back-and-forth saccades (Grusser et al., 1987). Visual stability may owe more to a failure to accurately compare object locations before and after saccades: Bridgeman et al. (1975) found that saccade targets could be displaced substantially during a saccade without subjects' awareness.

Despite uncertainty over the importance of efference copy in maintaining visual stability, the principle proposed by von Holst and Sperry of predicting the sensory consequences of action has been highly influential. In recent years this principle has come to be seen as part of a broader theory of how the brain maintains and updates its internal representations of the body and the environment—the theory of ‘internal models’.

1.2 Internal models and the sensorimotor loop

Human behaviour can be viewed in terms of the ‘sensorimotor loop’ (Figure 1-1 A). The motor systems of the central nervous system (CNS) compute a motor command signal on the basis of desired goals, the environmental context, and the current state of the body. This motor command signal is sent to the muscles which produce a change in the state of the body and in some cases the environment. These changes are detected by the sensory systems of the CNS, and this sensory feedback is used in computing the next motor command, closing the loop.

Although the sensorimotor loop describes how the CNS interacts with the external world, it has been proposed that the brain also internally represents each of the stages of the sensorimotor loop in the form of ‘internal models’ (Figure 1-1 B). These internal models mimic the behaviour of the body and the environment (Ito, 1970; Jordan and Rumelhart, 1992; Wolpert et al., 1995). The ‘inverse model’ is a form of controller which takes as input the desired state and outputs the motor command required to achieve it. The ‘forward model’ works in the opposite direction, taking as

input a copy of the motor command and generating a prediction of how it will affect the body and environment. The forward model can be separated into two components: the 'forward dynamic model' maps a given motor command onto the predicted change it will make to the state, and the 'forward sensory model' predicts what sensory feedback will be produced by this change to the state.

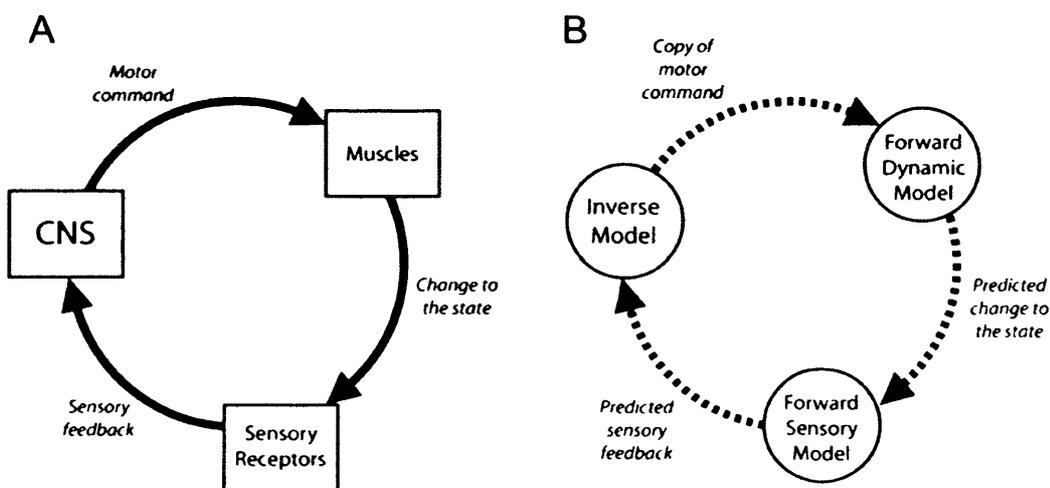


Figure 1-1 (A) The sensorimotor loop. The CNS generates motor command signals which cause muscle activations resulting in changes to the state of the body. These changes to the state are signalled to the CNS as sensory feedback. (B) A corresponding internal loop may exist within the CNS. Motor commands are generated by the inverse model and a copy sent to the forward dynamic model. The forward dynamic model predicts what change to the state the motor command will produce, and the forward sensory model predicts what sensory feedback will result.

1.2.1 Inverse models

A number of theories have been proposed to explain how the CNS computes the motor command signal required to achieve a planned movement. One of the earliest proposals was that the CNS makes use of the elastic properties of the muscles and the spinal cord reflex loops to move the body through a series of 'equilibrium points' to the desired endpoint (Feldman, 1966; Bizzi et al., 1984; Hogan, 1984; Flash, 1987).

Taking the arm as an example, any given constant activation of the muscles in the arm defines an equilibrium position at which the torques generated by the muscles cancel each other out and the arm is stable. By generating a motor command corresponding to a sequence of these equilibrium points the CNS could guide the hand along a planned trajectory to a desired location. This is an appealing proposal as it vastly simplifies the computation necessary for movement control; however it has two major disadvantages. Firstly, in order to prevent large deviations from the desired trajectory it requires the muscles and reflex loops to be maintained at a high level of stiffness, which is energetically inefficient. Studies that have measured the stiffness of the arm during movement have concluded that the stiffness is too low for the arm to be moving under equilibrium point control alone (Gomi and Kawato, 1996; Hodgson and Hogan, 2000). Secondly, if the dynamics of a limb change (for instance if one picks up a heavy object) then the equilibrium points change also, so if accurate movements are still to be achieved the controller must rapidly learn the new equilibrium points. The complexity of this learning problem negates the computational simplicity which was the main argument in favour of equilibrium point control.

As an alternative to equilibrium point control, the inverse model hypothesis holds that the CNS explicitly models the dynamics of the body so as to compute what motor command signal is required to produce any desired movement trajectory (Kawato et al., 1987; Wada and Kawato, 1993; Jordan, 1995). A motor control system based on an inverse model has the advantages that it can operate at low stiffness and that it is able to adapt to changes in the dynamics of the body.

1.2.2 Evidence for an inverse model in the human motor system

The strongest evidence in support of the inverse model hypothesis comes from studies which demonstrate the ability of the human motor system to adapt rapidly to novel dynamics. In a classic study by Shadmehr and Mussa-Ivaldi (1994) subjects grasped the handle of a computer-controlled manipulandum with their right hand and were instructed to move their hand to a series of targets displayed on a monitor. Following an initial training period, the manipulandum began imposing forces on the hand. The direction and magnitude of the force varied as a function of the instantaneous velocity of the hand.

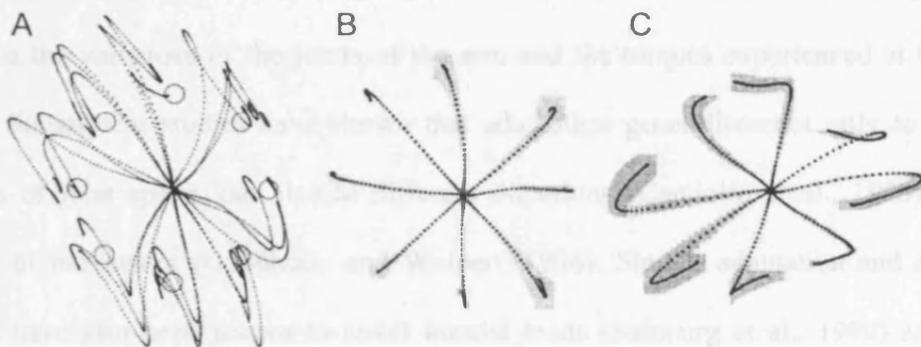


Figure 1-2 (A) Hand paths on first exposure to a force field. (B) Average hand paths after 750 movements in the force field. (C) Average hand paths on catch trials after 750 movements in the force field. (Adapted from Shadmehr and Mussa-Ivaldi, 1994.)

On initial exposure this force field caused large deviations in the subject's hand path and a corrective movement was required to reach the target (Figure 1-2 A). However, as the subject continued to make movements in the force field, hand paths gradually became straighter and approached the pre-exposure trajectory (Figure 1-2 B). At this point, if the force was unexpectedly absent on a movement (referred to as a 'catch

trial') a large deviation of the hand path was observed in the opposite direction to the earlier errors (Figure 1-2 C). The presence of these 'after-effects' implies that the subject's motor control system had composed a model of the expected forces during a movement and was actively generating opposing forces to compensate.

Next, the subject was moved so that the configuration of the arm in the workspace was changed and instructed to continue moving to the targets. Even though forces had not been experienced in these new joint positions, after-effects were again observed, implying that the motor system had generalised the adaptation beyond the trained workspace. The pattern of generalisation of expected forces to the new arm configuration implied that the motor system had modelled the forces as a mapping between the velocities of the joints of the arm and the torques experienced at those joints. Subsequent studies have shown that adaptation generalises not only to new regions of joint space, but also to different directions (Gandolfo et al., 1996) and speeds of movement (Goodbody and Wolpert, 1998). Similar adaptation and after-effects have also been shown to novel inertial loads (Sainburg et al., 1999) and to force fields determined by the position of the hand (Flash and Gurevich, 1997).

Lackner and Dizio (1994; 1998) have used a rotating room to investigate how the human motor system adapts to Coriolis force. Coriolis force is a fictitious force produced when the normal effects of inertia are experienced in a rotating reference frame; it is felt as a velocity-dependent force acting at 90° to the direction of motion. When subjects made movements under Coriolis force in darkness to targets that were extinguished at movement onset, they initially made errors in both the trajectory and the endpoint of the movement (Lackner and Dizio, 1994). As with a mechanically-

imposed force field, these errors diminished with practice, and after-effects were observed if the rotation was stopped. The initial errors observed in the movement endpoint are particularly troublesome for the equilibrium point control hypothesis: as no Coriolis force acts on the arm once it has stopped moving, a controller that uses muscle stiffness to determine position should end up at the intended location. In contrast, these errors are predicted by the inverse model hypothesis: an inverse model generates an appropriate motor command based on an internal representation of the current dynamics, and so if the actual dynamics differ greatly from those represented by the model the movement will miss the target.

Although a controller based on equilibrium points alone cannot account for all the results from adaptation studies, the modulation of muscle stiffness may still play a role in movement control. An inverse model minimises movement errors by adapting to new dynamics, but this requires a certain amount of experience in the new environment. During the first movements in a novel force field, opponent muscles are co-activated, increasing the stiffness of the arm and so reducing the movement errors caused by the external force. With continued practice, the inverse model adapts to compensate for the novel dynamics and this 'co-contraction' decreases (Milner and Cloutier, 1993; Thoroughman and Shadmehr, 1999). Control of muscle stiffness is also used to minimise errors when the dynamic environment is unstable, and so cannot be predicted by an internal model. When the instability only affects movement in a particular direction, the motor system selectively activates muscles so as to maximise stiffness in that direction (Burdet et al., 2001).

1.2.3 Forward models

It is clear that a motor system requires some kind of controller, such as an inverse model, in order to generate appropriate motor output to achieve the system's goals. It is not immediately obvious why a motor system should have a use for forward models, which model the opposite transformation. Forward models act as predictors, modelling what change a given motor output will make to the body and the environment and how this change will in turn affect sensory input (Jordan and Rumelhart, 1992; Miall and Wolpert, 1996). In theory a motor system does not need to make these predictions as it can rely purely on sensory input to estimate the current state of the world. However, the use of forward models confers a number of theoretical advantages.

1.2.3.1 Compensating for inaccuracies in sensory feedback

One problem that the human motor system faces is that of inaccuracies in sensory feedback. Sensory transduction and neural transmission are imperfect biological processes which contaminate the sensory signal with noise. Further, a combination of transduction, transmission and processing time means that the sensory information available to the motor system is often substantially delayed. An estimate of the current state of the body and environment based on this delayed, noisy feedback is inevitably inaccurate, which will make subsequent movements inaccurate also. In contrast, an estimate of the current state generated by a forward model is available without significant noise or delay (Miall et al., 1993). A system which combines these two sources of information to provide an improved estimate of the state is known as an 'observer'. For a linear system, the observer which produces an optimal estimate of the current state is known as a 'Kalman filter' (Kalman and Bucy, 1961; Goodwin and

Sin, 1984). A Kalman filter uses a forward dynamic model to transform the combination of an estimate of the previous state and an efference copy of the motor command into a prediction of the current state. A forward sensory model transforms this prediction into an estimate of the expected sensory feedback. The difference between the output of this forward sensory model and the actual sensory feedback is used to estimate the error in the state. This error estimate is combined with the output of the forward dynamic model to obtain the optimal estimate of the current state. A number of experimental studies have supported the presence of a mechanism similar to the Kalman filter in the human motor system (Kuo, 1995; Wolpert et al., 1995; Merfeld et al., 1999; van Beers et al., 1999).

1.2.3.2 Mental simulation

As described earlier, forward dynamic and sensory models can be used in conjunction with an inverse model to complete an internal representation of the sensorimotor loop (Figure 1-1). If the output of the inverse model to the motor effectors is blocked, a recursive use of this internal loop could allow intended movements to be mentally simulated. Such mental simulation could be used to fine-tune a motor plan prior to execution, or choose between alternative motor plans. This ability could be particularly useful in situations where a complicated sequence of movements must be combined, or where any error in the movement is likely to be costly. Mental practice has been shown to improve performance in a range of motor tasks (Hall et al., 1992), increasing speed, strength and temporal consistency (Yue and Cole, 1992; Pascual-Leone et al., 1995; Vogt, 1995). The durations of imagined movements are closely matched to the actual movement times (Decety and Michel, 1989), and show the same trade-off between speed and accuracy (Sirigu et al., 1996), supporting the hypothesis

that mental simulation and actual movement generation involve the same internal representations.

1.2.3.3 Object manipulation

The ability of forward dynamic models to predict the effect of our actions on the environment may play a fundamental role in our ability to manipulate objects. For example, when holding an object between finger and thumb an upward force (the 'load force') must be generated by the hand to counteract the object's weight. In order to transmit this load force to the object, an inward force ('grip force') must also be generated: if insufficient grip force is applied the object will slip. If the hand is moved then a change to the load force is required to counteract the inertia of the object. Experiments have shown that in this situation subjects correctly modify their grip force in parallel with the load force in order to prevent the object from slipping (Johansson and Westling, 1984; Johansson and Cole, 1992; Flanagan and Wing, 1993, 1995). The absence of any significant delay implies that the motor system is not relying on sensory feedback, but must instead be predicting the required grip force on the basis of a forward model of the dynamics of the system (Flanagan and Wing, 1997; Kawato, 1999; Flanagan et al., 2003). In support of this, when a gripped object is moved by external forces the modulation of grip force is no longer anticipatory, lagging the onset of the external force by at least 80 ms (Johansson et al., 1992a; Johansson et al., 1992b).

1.2.3.4 Context estimation

In order to choose an appropriate motor output, the CNS must identify the current context in which a movement is occurring. For example, the appropriate grip force required when lifting an object depends not only on the acceleration of the hand but also on the mass of the object. Although an object's size and appearance can be used to estimate its mass before lifting it, appropriate scaling of grip force is observed after a few lifts even when these visual cues are absent or misleading (Gordon et al., 1993). This suggests that the motor system is able to infer the mass of an object from the sensory feedback received during handling it. This could be achieved by the use of multiple forward models (Wolpert and Kawato, 1998). According to this proposal, each forward model learns to map motor commands into expected sensory feedback for a single sensorimotor context. The current context can then be estimated by finding the forward model which is most accurate in estimating the current sensory feedback.

In the MOSAIC model (Haruno et al., 2001), this architecture is extended by pairing each forward model with an inverse model that is tuned to generate motor commands appropriate for the same context. The actual motor command output is a weighted sum of the output of the inverse models. The weights are determined by the probability of each context, obtained by comparing the output of each forward model with the sensory input. This architecture is therefore able to estimate the current context and use this information to choose the appropriate motor command to achieve the motor system's goals.

1.2.3.5 *Inverse model learning*

Earlier in this chapter, evidence was presented of the ability of the inverse model to rapidly adapt to novel dynamics. This ability is necessary because the dynamics of the sensorimotor system can change both in the short-term, due to interactions with the environment, and on longer time scales, due to growth in the muscles and bones. However, adapting the inverse model is a computationally difficult problem because the motor system does not have access to the error in its output (the motor command error) but only to the sensory consequences of that error. It has been proposed that the forward model may provide a solution to this ‘distal learning’ problem.

Training the forward model is a classical ‘supervised learning’ problem: given a copy of the motor command, the forward model generates an estimate of the expected sensory feedback; the difference between the estimated and actual sensory feedback provides a sensory error signal which can be used to update the forward model. Because the error signal is in the same coordinate system as the output, the update process is computationally straightforward: several learning algorithms have been proposed as models of this process, the most common being back-propagation (Rumelhart et al., 1986). As a solution to the distal learning problem, Jordan and Rumelhart (1992) proposed combining the inverse and forward models in series to produce a composite system which predicts the sensory consequences of any given input to the inverse model. Because the output is in sensory coordinates, this system can be trained with the sensory error signal. If the forward model is held fixed during the update process, this provides a means of adapting the inverse model.

An alternative solution to the distal learning problem has also been proposed. In the feedback error-learning model (Kawato et al., 1987), a simple hard-wired feedback controller works in parallel with the inverse model, generating motor commands in response to sensory feedback to correct for discrepancies between the current and desired state of the body. The output of this feedback controller provides an error signal in motor coordinates that can be used to train the inverse model.

1.2.3.6 Identifying one's own actions

As noted at the start of this chapter, we are readily able to discriminate between those changes in our body and environment that result from our own actions and those that have an external cause. Internal models provide a simple framework for making this distinction (Figure 1-3). Given the current state and an efference copy of the motor command, the forward model will output a prediction of the expected sensory input. When no external influence is acting, this prediction will closely match the actual sensory feedback. However, changes to the body or environment that have an external cause cannot be predicted by the forward dynamic model and so will produce a discrepancy between the predicted and actual sensory input. A decision mechanism based on these principles would identify a change to the body or environment as self-generated if the sensory discrepancy associated with it remains below a certain threshold (thereby allowing for small errors in prediction). If the discrepancy exceeds that threshold the change is identified as having an external cause.

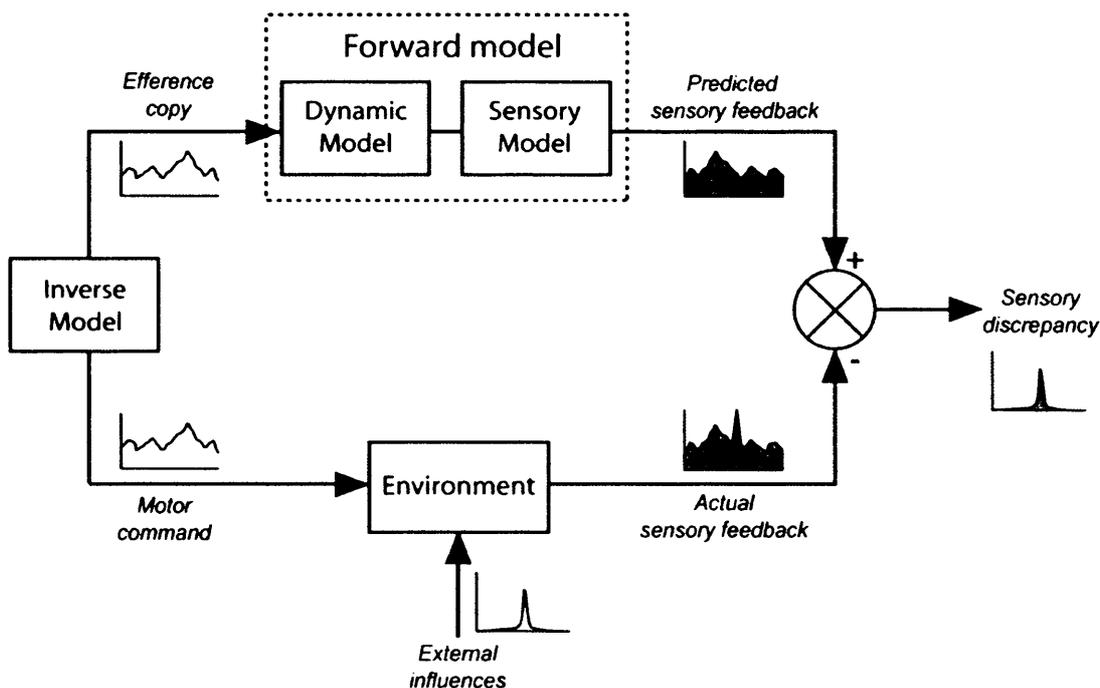


Figure 1-3 Distinguishing between one's own actions and external events. On the basis of efference copy, a forward model predicts the sensory feedback that will result from a planned action. The actual sensory feedback will reflect the sum of self- and externally-generated changes to the environment. Subtracting the predicted from the actual sensory input reveals an estimate of the sensory feedback due to external influences.

This ability to attribute agency to sensory events permits differential processing of self- and externally-generated sensations. An example of this is seen in the perceived timing of sensory events. Haggard et al. (2002) asked subjects to report the perceived times of a voluntary button press and a consequent auditory stimulus. The time at which subjects perceived they had made the action was found to be shifted forwards towards the time of the auditory event it triggered, and the perceived time of the auditory stimulus was shifted backwards towards the time of the voluntary action. This 'intentional binding' is reversed if the button press is passively generated (Tsakiris and Haggard, 2003), suggesting that it reflects an attribution of agency based on efference copy.

1.2.3.7 Sensory filtering

Our sensory systems are highly tuned to detect unexpected changes in our environment, and as such it may often be advantageous to discount changes to the sensory input that result solely from our own actions. The stability of visual perception during eye movements described earlier in this chapter provides one example of this. In order for the effect of an eye movement on the visual percept to be discounted, an efference copy of the motor command signal is transformed into the expected shift in the retinal image (the corollary discharge). This transformation is the proposed role of the forward model. The predicted retinal shift is then used to modulate the actual sensory input to maintain a stable visual percept of the world. Similar mechanisms may maintain stability in other sensory modalities: for instance, when one moves a finger over a surface it does not produce the perception that the surface is moving (Gibson, 1962).

As well as maintaining perceptual stability, it has been proposed that predictive mechanisms could enhance the salience of unexpected external events by attenuating self-generated sensory input. During active movement of a digit or limb, the ability to detect small cutaneous stimuli is reduced in the moving body part (Angel and Malenka, 1982; Chapman et al., 1987) as is the perceived intensity of suprathreshold stimuli (Milne et al., 1988). This suppression or 'gating' of tactile input begins prior to movement onset and indeed prior to muscle activation as measured by EMG (Williams et al., 1998), suggesting a mechanism based on efference copy. However, a similar magnitude and time-course of gating is also seen when the body part is unexpectedly moved by an external force (Williams and Chapman, 2002), suggesting that the increase in detection thresholds may be better explained by 'backward

masking' (Spencer and Shuntich, 1970; Scheerer, 1973; Laskin and Spencer, 1979) of the stimulus by tactile and proprioceptive sensory signals generated during the movement. In apparent contradiction to this, similar increases in detection threshold are also observed during isometric muscle activation, which is assumed to generate substantially less peripheral sensory input than active movement. These findings suggest the possibility that movement-related tactile gating is the result of a combination of predictive and masking mechanisms.

Predictive filtering has been more clearly implicated in the perception of tickle. It is a common experience that it is hard to tickle oneself, and empirical studies have confirmed that a self-generated tickle is perceived as less intense than an identical stimulus externally imposed (Weiskrantz et al., 1971; Claxton, 1975; Blakemore et al., 1998a). Blakemore et al. (1999a) used a pair of robotic arms to simulate a self-generated tickle. When subjects moved one robot with their left hand, a second robot moved a tactile stimulus across the palm of their right hand in unison. When subjects were instructed to move their left hand sinusoidally back and forth they consistently rated the stimulus in the right hand as less tickly, intense, and pleasant than if the same stimulus was delivered with the left hand still. A discrepancy was then introduced between the subject's movement and the movement of the tactile stimulus, either by introducing a time delay between the movement of the hand and the stimulus, or by rotating the direction of movement of the stimulus relative to the hand. The subject's rating of the ticklishness of the stimulus increased with increasing delay or rotation. This result is consistent with the involvement of a predictive mechanism such as a forward model. A prediction of the expected sensory input to the right hand could be computed by such a mechanism on the basis of an efference copy of the

motor command signal sent to the left hand. Subtracting a proportion of this predicted input from the actual input at an early stage of processing would attenuate the self-generated sensory input, reducing the perceived intensity of the tickle. According to this model, when a small temporal or spatial discrepancy is introduced between the hands it creates a mismatch between predicted and actual sensory input such that the amount of attenuation is reduced.

The ability to accentuate biologically-relevant external events by discounting the effects of self-action could have strong adaptive value. If so, the kind of predictive sensory filtering proposed for tickle may have broad application in the sensory system. The main focus of this thesis will be the experimental investigation of predictive attenuation in the sensation of touch.

1.3 Self-monitoring in schizophrenia

An understanding of the role of internal models in the human sensory system may be useful in explaining some of the symptoms of schizophrenia. Schizophrenia is in part characterised by a failure to distinguish between self-generated and external sensation, a discrimination which, as described earlier, may depend on the forward model.

1.3.1 Background

Schizophrenia is a category of psychiatric disorder diagnosed on the basis of psychotic symptoms such as delusions, hallucinations and disorganisations of speech

and behaviour. First defined by Eugen Bleuler (1911) as a 'loosening of associations' between different mental functions, historical disagreements and uncertainties over the best way to define the disorder have led to substantial variation in the symptomatology it covers. Nonetheless a set of core symptoms can be identified, and can be divided into three categories or syndromes (Liddle, 1987). Firstly, patients generally exhibit 'disorganisation': disordered and inappropriate thoughts, speech and emotional responses. Secondly, patients display 'psychomotor poverty': lack of speech, decreased spontaneous movement, lack of emotional response, and apathy. These 'negative' symptoms tend to become more dominant over time, and characterise the chronic phase of schizophrenia. Thirdly, patients suffer from 'reality disorder' in the form of delusions and hallucinations. These 'positive' symptoms are most prominent in the acute phase of the illness, and it is these symptoms that may best be explained by a breakdown in self-monitoring.

1.3.2 Positive symptoms explained as a failure of self-monitoring

The delusions suffered by patients with schizophrenia vary widely: they may have paranoid delusions, or believe they have supernatural abilities, or that everyday things or events have specific relevance to them. However, one set of delusions that is particularly characteristic of schizophrenia is that of 'passivity phenomena', in which the patient feels that he is no longer in control of his own thoughts or feelings and that his actions are being controlled by a mysterious outside force (Schneider, 1959). In fact, the actions that patients identify as externally controlled are mostly consistent with their intentions.

Frith (1987; 1992), expanding on a suggestion originally made by Feinberg (1978), has proposed that these 'delusions of control' may be explained by a defect in a central self-monitoring mechanism, resulting in a failure to identify one's actions as one's own. In the internal model framework described earlier in this chapter, changes to the body that are imposed by external forces are identified by a discrepancy between the actual sensory feedback from the movement and the feedback predicted by a forward model. A breakdown in the forward model or comparison mechanism would result in the incorrect identification of one's own actions as externally generated (Frith et al., 2000). Consistent with this, Blakemore et al. (2000) showed that patients with positive symptoms do not rate a self-generated tickle as less intense than a tickle applied by the experimenter, unlike healthy controls and patients without positive symptoms. Patients with schizophrenia also find it difficult to distinguish between vision of their own hand and vision of another hand making a similar movement (Daprati et al., 1997).

A breakdown in self-monitoring has also been proposed as an explanation for the hallucinations experienced in schizophrenia. Patients with schizophrenia may experience hallucinations involving any of the five senses, however by far the most common are auditory hallucinations in the form of voices, and patients who do not hear voices generally do not suffer from hallucinations at all (Johnstone et al., 1986). There is evidence that these auditory hallucinations may be caused by a misidentification of the patient's inner speech as externally generated. Case studies in which the subvocal activity of hallucinating patients was picked up by a microphone have found that these whispers correspond to the patient's subsequent report of what the hallucinated voices said (Gould, 1949; Green and Preston, 1981). Suppressing this

subvocal activity by holding a patient's mouth wide open can substantially reduce the number of auditory hallucinations (Bick and Kinsbourne, 1987). Also Dierks et al. (1999) have shown in a functional imaging (fMRI) study of patients with schizophrenia that activity in the frontal operculum, an area normally associated with the generation of speech, is increased during auditory hallucinations.

In summary, a number of the most prominent symptoms of schizophrenia can be explained as a misidentification of one's own actions as externally generated. This could result from a mismatch between the predicted sensory consequences of one's actions and the actual sensory input. Patients with schizophrenia do not exhibit obvious abnormalities in their motor control, and show normal scaling of grip force when lifting objects (Delevoeye-Turrell et al., 2003). This suggests that these patients are able to predict changes to the state of the body and environment on the basis of planned movements (the role proposed for the forward dynamic model). Any impairment is therefore likely to be either in the transformation from the predicted outcome of an action to the predicted sensory feedback (the role of the forward sensory model), or in the mechanism that compares this prediction with the actual sensory input.

1.4 An overview of the human tactile sensory system

The main focus of the experimental chapters of this thesis will be the perception of tactile stimuli delivered to the fingertip. The human somatosensory system consists of distinct sensory receptors and pathways which extract and transmit sensory

information in four principal modalities: touch, proprioception, nociception, and temperature sense. The sense of touch is mediated by ‘mechanoreceptors’: specialised nerve endings which are excited by indentation of the skin or motion across its surface. The greatest density of mechanoreceptors is found on the skin of the fingers, the palm of the hand, the sole of the foot, and the lips, and therefore these areas have the greatest tactile sensitivity. The fingertips are the most highly innervated, receiving approximately 250 mechanoreceptor nerve fibres per square centimetre (Vallbo and Johansson, 1978).

Each mechanoreceptive ending is encapsulated in a specialised end organ. The morphology of this capsule, together with its location within the skin, determines how the skin must be deformed to excite the receptor. In the fingertip, the main area of interest in this thesis, there are four principal types of receptor, each adapted to extract a particular type of information from a tactile stimulus. FAI receptors (Meissner’s corpuscles) are located in the superficial layers of the skin and have small receptive fields; they are rapidly adapting, generating short bursts of action potentials to signal the onset and offset of skin contact. Also sited in the superficial layers, SAI receptors (Merkel disks) are slowly adapting: they fire in response to sustained pressure on the skin, with a firing rate that increases with the applied force (Goodwin et al., 1995). Mechanoreceptors in the deep subcutaneous tissue can also be separated into two principal types. FAII (Pacinian corpuscle) receptors are fast-adapting with large receptive fields; they respond strongly to vibration, particularly at high frequencies (Mountcastle et al., 1972), and also to movement of the finger across a surface. SAII receptors (Ruffini endings) are slowly adapting and signal large-scale stretching of the skin.

Action potentials generated by mechanoreceptive endings in the fingertip are transmitted via the neuronal axon (the 'primary sensory afferent') to the medulla. Second- and third-order sensory neurons carry this signal to the thalamus and on to primary somatosensory cortex (SI). The primary sensory afferents are large, myelinated fibres with high conduction rates: the interval between onset of a tactile stimulus in the fingertip and activation of SI is approximately 25 ms (Romo et al., 1996).

Primary somatosensory cortex is organised somatotopically, and at this stage there are extensive interconnections between neurons with inputs originating from the same area of the body. Here, information from the many varieties of receptors is integrated to identify higher-order features of stimuli such as the texture of surfaces, the location and orientation of edges, and direction of motion across the skin. Projections from SI transmit this information via secondary somatosensory cortex (SII) to the memory systems in the temporal lobe, and to posterior parietal cortex where tactile information is integrated with proprioceptive and visual input to build up an overall picture of the body and its immediate environment. Further connections to motor areas in the frontal lobe support the integration of this information into motor planning in order to generate motor commands that are appropriate for the current state of the body and environmental context.

1.5 Experiments in this thesis

This thesis will describe a series of experiments that investigate the proposed role of efference copy and internal models in predicting and attenuating the sensory consequences of action.

Chapter 3 describes a novel force-matching paradigm, in which subjects reproduce forces applied to the fingertip. The results of this study demonstrate that constant forces are perceived as weaker when they are self-generated, and that this attenuation of tactile sensation may play a role in the escalation of physical conflicts.

Chapter 4 extends the force-matching paradigm to investigate some of the factors that influence tactile attenuation. A virtual link between two torque motors is used to introduce discrepancies in spatial alignment and gain between the force applied by one finger and the force felt in another. Tactile attenuation is found to be reduced by a spatial misalignment but not by a discrepancy in magnitude between force input and output.

Chapter 5 describes a study designed to investigate the time course of tactile attenuation. The perception of force is assessed when subjects tap with one finger on another through a virtual object created by two torque motors. By introducing varying time intervals between the action and the resulting sensation, we reveal a relatively broad window of attenuation centred on the expected time of contact.

The study described in Chapter 6 tests the hypothesis that tactile attenuation results from a predictive mechanism, rather than a postdictive or masking mechanism. Attenuation is shown to occur at the time of an expected contact between the fingers even if the contact does not in fact occur. Movement alone is found to be insufficient to produce attenuation. These results are consistent with a mechanism that predictively attenuates incoming sensory signals on the basis of efference copy.

Chapter 7 investigates the acquisition of prediction when subjects are exposed to a novel relationship between the motion of one hand and force applied to the other. Subjects learn to maintain postural stability by actively opposing the predicted forces. From the patterns of generalisation to new postures we discover that the motion and the resulting force are represented in different coordinate frames by the motor system.

The study in Chapter 8 investigates tactile attenuation in patients with schizophrenia, and demonstrates that these patients show less attenuation of self-generated sensation than healthy controls. This finding is consistent with previous self-monitoring theories of schizophrenia, and suggests that the illness may be characterised by a deficit in the sensory component of the forward model.

Chapter 9 investigates the neural basis of the efference copy signal. Transcranial magnetic stimulation is used to modulate the excitability of motor cortex. Tactile attenuation is found to be reduced by a decrease in excitability of motor cortex contralateral to the active hand. This is shown to be consistent with a model of predictive attenuation in which efference copy signals are generated upstream of primary motor cortex.

CHAPTER 2: METHODS

2.1 Tactile force-generating apparatus

This thesis investigates predictive attenuation in the perception of self-generated tactile stimuli. Previous experimental studies that have explored this issue have concentrated on the perception of tickle, as the difference between the experiences of tickling oneself and being tickled by someone else is widely recognised. However, only a tiny fraction of the tactile stimuli we encounter each day are ticklish, and the behavioural relevance of ticklishness is far from understood. For the experiments described in this thesis I chose to concentrate on a much more common form of tactile sensation: the perception of abrupt and constant forces normal to the fingertip. Forces of this kind are experienced during tactile exploration, and whenever we use our hands to manipulate objects. In order to facilitate their investigation, a computer-controlled apparatus was designed which could apply forces to the tip of a subject's finger.

The basic tactile apparatus, illustrated in Figure 2-1, consisted of a light-weight aluminium lever attached at one end to the axis of a torque motor, which was fitted with a rotary optical encoder. A force sensor was mounted on the other end of the lever, and a subject rested his or her index finger in a moulded support beneath the force sensor.

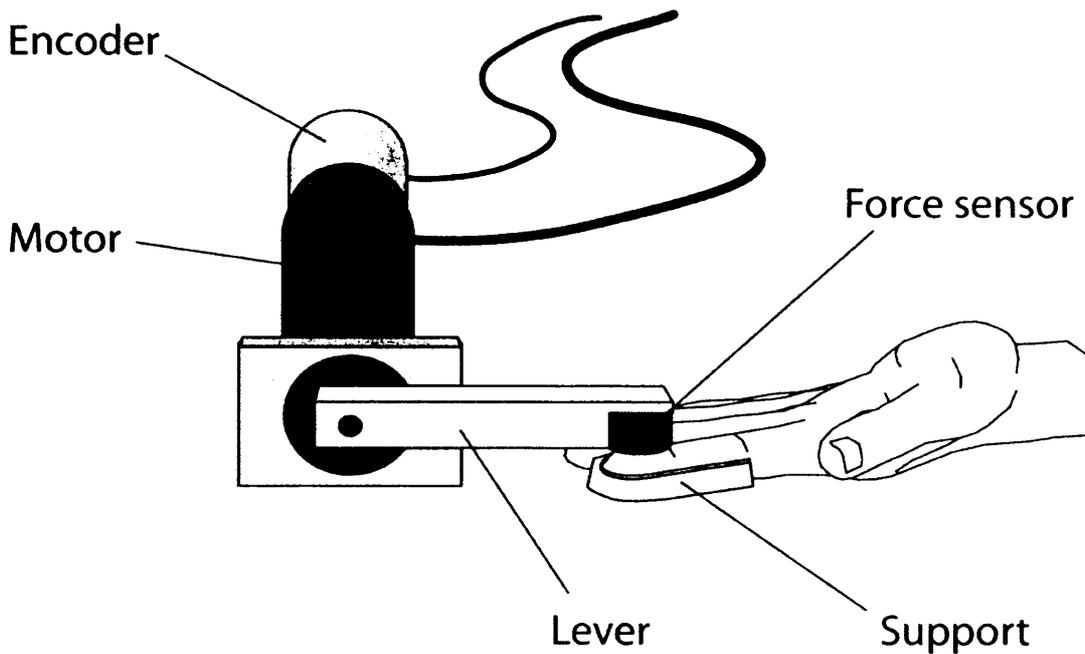


Figure 2-1 Design of the basic tactile force-generating apparatus.

Torques generated by the motor were transmitted to the fingertip as normal forces through the lower surface of the force sensor, according to the equation,

$$F = \frac{\tau}{l}$$

where F is the force applied to the fingertip, τ is the torque generated by the motor, and l is the distance along the lever from the fingertip to the axis of rotation. The subject could also apply forces to the fingertip with a finger of the other hand, by pressing on the upper surface of the lever directly above the force sensor. In either case, all forces transmitted to the fingertip were recorded by the force sensor. Because the surface of the fingertip yields under pressure, applying a force led to a small downward deflection of the lever which was recorded by the rotary encoder.

The tactile apparatus was controlled by a Pentium PC fitted with an analogue-digital I/O card (Sensoray Company Ltd, Model 626). The desired torque output, updated at

1000 Hz, was signalled as a voltage output from the I/O card to a servoamplifier (Maxon Motors UK, Model ADS 50/10) housed in a purpose-built controller unit. The servoamplifier converted the voltage input into a pulse-width-modulated current output to drive the torque motor. The force sensor and rotary encoder outputs were channelled via the controller unit to the I/O card and recorded by the PC at 1000 Hz. The controller unit contained two amplifiers and associated circuitry so that two of the tactile set-ups described above could be operated in parallel.

Two separate versions of this basic experimental apparatus were built according to the design described above. The original version of the apparatus was built with the following components: Maxon Motors RE35 torque motors, Dynamics Research Corporation T23BA encoders, and Entran 25N load cells. This version of the apparatus was designed for the study described in Chapter 3, and was subsequently used for the patient study described in Chapter 8. A second apparatus was built for the study described in Chapter 4; these experiments required a larger range of forces from the motor, so geared torque motors were used (Maxon Motors RE35; gearing ratio 1:4.8). The other components were also upgraded from the original specification: ATI Nano-17 6-axis force/torque sensors, and IED Model SA40 incremental encoders were used. This second version of the apparatus was subsequently used, with various modifications, in Chapters 5, 6 and 9; full details are given in each chapter.

The mechanical bandwidth of the tactile apparatus was assessed by recording the actual force output for sinusoidal inputs varying in frequency between 1 and 100 Hz, with a desired force amplitude of 1.5 N. The gain and phase lag as a function of frequency is shown in Figure 2-2. The mechanical bandwidth, defined as the

frequency at which the gain falls to $1/\sqrt{2}$, was estimated at 87 Hz (by linear interpolation between the two nearest frequencies tested). This assessment was conducted on the geared motor system used in Chapters 4, 5, 6, and 9. In general, gearing decreases the mechanical bandwidth, so this value may underestimate the bandwidth of the original ungeared apparatus used in Chapters 2 and 8.

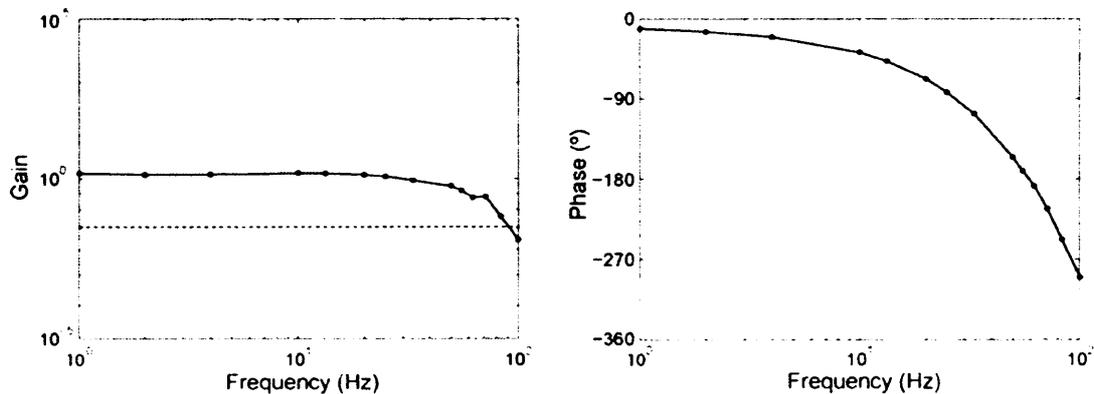


Figure 2-2 Bode plot displaying the frequency response of the tactile apparatus. The dotted line indicates a gain of $1/\sqrt{2}$.

2.2 vBOT robotic manipulandum

The experiment described in Chapter 7 investigates the development of predictive control when forces on one hand are determined by movements of the other hand in a novel way. Two force-generating robotic manipulanda ('vBOTS') were used, one for each hand (Figure 2-3). These robots were similar in design to the single manipulandum used in Shadmehr and Mussa-Ivaldi's study, described in the first chapter.

The vBOT consisted of a handle at the end of a carbon-fibre parallelogram arm, which was driven by two torque motors via low-friction timing belts. The motors were fitted with high-resolution rotary encoders (30,000 counts per revolution). The system was controlled by a PC via a controller unit and I/O card of the same specification as those used with the tactile apparatus. A subject sat gripping the robot handles, with his or her upper arms supported in the horizontal plane by slings.

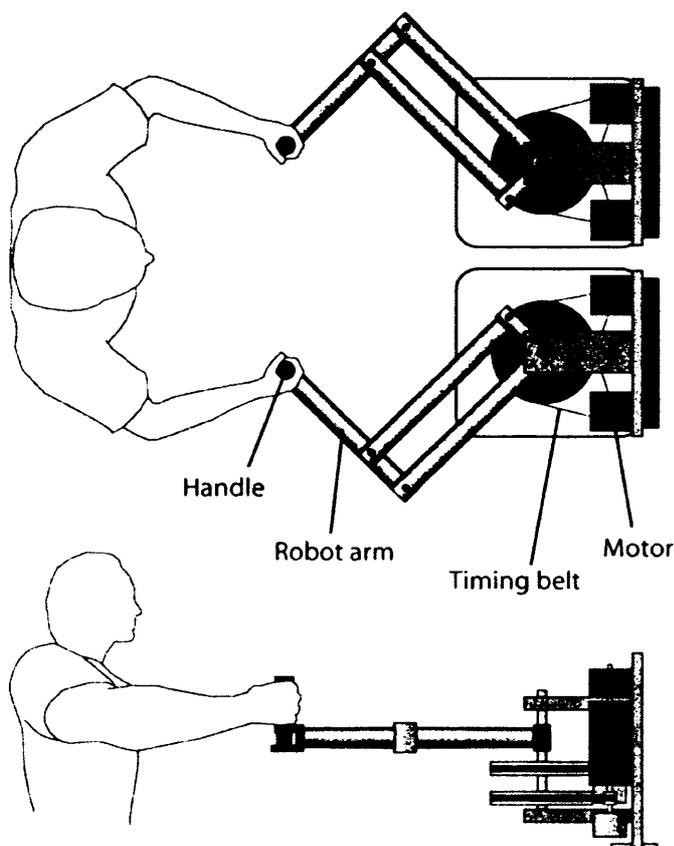


Figure 2-3 The vBOT robotic manipulanda.

The vBOT was designed to have low inertia and high back-drivability, so the subject was able to move the handle of each robot throughout the workspace with minimal resistance. The positions of the handles were calculated online at 1000 Hz from the encoder output according to the kinematic equations of the robot arm,

$$\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} l_1 \cos(\theta_1) + l_2 \cos(\theta_1 + \theta_2) \\ l_1 \sin(\theta_1) + l_2 \sin(\theta_1 + \theta_2) \end{bmatrix}$$

where x_1 and x_2 are the Cartesian co-ordinates of the position of the handle, l_1 and l_2 are the lengths of the two links of the robot arm, and θ_1 and θ_2 are the angles at the two joints. The velocity and acceleration of the handle were estimated online by finding a least-squares fit, over a 30 ms moving time-window, to the linear equation of motion,

$$\Delta x = v_f \Delta t - \frac{1}{2} a \Delta t^2$$

where Δx is the change in position over the time window, v_f is the final velocity, a is the acceleration, and Δt is the duration of the time window. The handle positions, and other targets and symbols specific to the experiment, were displayed on a rear-projection screen. The subject viewed the reflection of the screen in a mirror, positioned so that the handle positions and targets appeared in the plane of the robot arm.

Forces to be applied to the hands were calculated as a function of the positions and velocities of the handles (see Chapter 7 for full details). The torques from the motors required to produce the desired force were calculated online according to the equation,

$$\tau = \left(\frac{\partial x}{\partial \theta} \right)^T F$$

where τ is a 2x1 vector of torques generated by the motors, F is a 2x1 vector of forces applied at the hand, and $\partial x / \partial \theta$ is the 2x2 Jacobian matrix, which describes how

changes to the joint angles of the robot arm (θ) are reflected in changes to the position of the handle (x).

2.3 Theta-burst transcranial magnetic stimulation

Chapter 9 describes an experiment which assessed the effect of modulating the excitability of motor cortex on tactile attenuation. This modulation was achieved using the technique of transcranial magnetic stimulation (TMS).

In TMS, a current pulse is generated in a stimulating coil held over a subject's head. This current pulse, typically lasting only 100 μ s, generates a rapidly-changing magnetic field, which induces secondary currents in the neural tissue underneath the coil in accordance with Faraday's principles of electromagnetic induction (Faraday, 1831). These induced currents can cause neurons to depolarise, in a similar way to the action of a conventional electrical stimulator on peripheral nerves. The effect of this stimulation depends on the area of the brain to which it is applied: for instance, single TMS pulses over visual cortex cause subjects to observe phosphenes (Marg and Rudiak, 1994). TMS pulses over motor cortex result in muscle activations ('motor evoked potentials' or MEPs) on the contralateral side of the body (Day et al., 1989) which can be measured with electromyography (EMG). This single-pulse technique has been used extensively to study central motor pathways (Rothwell et al., 1991).

As well as these direct effects, the synchronous excitation of a large population of neurons induced by a TMS pulse can temporarily disrupt whatever processing is

taking place in the affected brain region. This may result in changes to behaviour or task performance, providing an indication of the functional role of the targeted area of cortex. Unlike functional neuroimaging, this ‘virtual lesion’ technique (Pascual-Leone et al., 1999; Pascual-Leone et al., 2000) makes it possible to establish a clear causal link between activity in a given cortical area and behaviour. While a single pulse of TMS can cause a very brief disruption in function, longer-lasting effects can be produced with trains of TMS pulses delivered at rates up to 50 Hz. This ‘repetitive’ TMS (or rTMS) can have effects that extend 30 minutes or more beyond the period of stimulation (Chen et al., 1997; Pascual-Leone et al., 1998). By comparing task performance before and shortly after rTMS, the functional effects of stimulation can be evaluated without contamination from non-specific effects of the noise, discomfort and muscle twitches produced during stimulation.

In the experiment described in Chapter 9, a recently-developed form of rTMS was used to selectively alter the functioning of motor cortex. The ‘theta burst’ protocol (Huang and Rothwell, 2004; Huang et al., 2005) is based on patterns of stimulation originally developed for direct electrical stimulation in cortical slice preparations and in vivo animal studies. It consists of bursts of three TMS pulses (separated by 20 ms) repeated at 200 ms intervals. In continuous theta burst stimulation (cTBS) an uninterrupted train of pulses is delivered in this pattern for up to a minute (Figure 2-4 A). Patterns of electrical stimulation similar to this have been shown to produce long term depression (LTD) of synaptic excitability in animal preparations (Heusler et al., 2000). Applied over motor cortex, cTBS suppresses the excitability of motor cortex for up to 40 minutes, observed as a reduction in the amplitude of MEPs elicited by single TMS pulses (Figure 2-4 B). In contrast, intermittent theta burst stimulation

(iTBS), consisting of a series of 2 s trains of TBS repeated every 10 s, produces a long-lasting increase in excitability of motor cortex (Figure 2-4 A&B). Analogously, similar patterns of direct electrical stimulation have been shown to produce long term potentiation (LTP) of synaptic excitability (Capocchi et al., 1992).

In chapter 9, the perceived intensity of self-generated tactile stimuli is assessed prior to and following cTBS and iTBS, in order to investigate the effect on tactile attenuation of enhancing or suppressing motor output at the level of primary motor cortex.

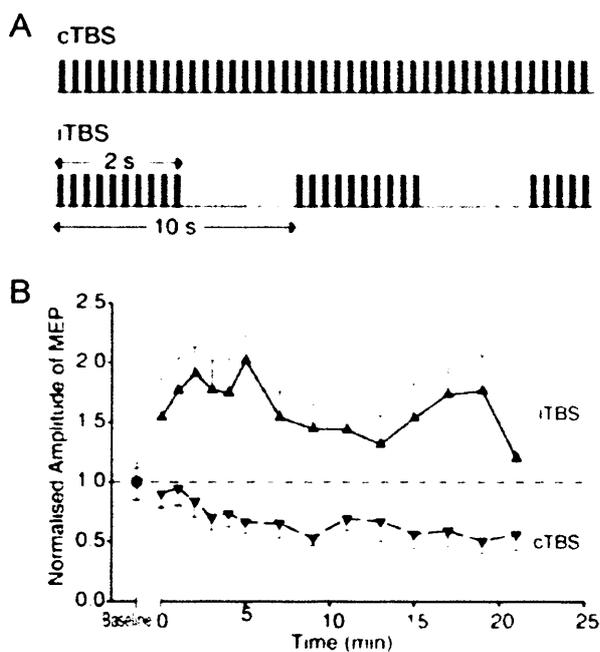


Figure 2-4 Paradigms of theta burst stimulation and their effects on motor evoked potentials. (A) Illustration of cTBS and iTBS stimulation protocols. In cTBS, 600 TMS pulses are delivered in an uninterrupted theta-burst pattern for 40 s. In iTBS, the same number of pulses is delivered in 2 s trains over 190 s. (B) Time course of changes in MEP amplitude following conditioning with cTBS (down triangle) or iTBS (up triangle). Adapted from Huang et al.(2005).

CHAPTER 3: FORCE ESCALATION AS A CONSEQUENCE OF SENSORY ATTENUATION

3.1 Introduction

Physical conflicts tend to escalate. Two children involved in a tit-for-tat exchange of blows, for example, will often both claim that the other hit them harder. In this study, similar escalation of force is demonstrated in a controlled experimental setting when subjects are given instructions designed to maintain parity. A second experiment shows that this force escalation results from a reduction in the perceived intensity of self-generated forces. This could arise from a predictive filtering process (Sperry, 1950; von Holst and Mittelstaedt, 1950; von Holst, 1954) in which the sensory consequences of a movement are anticipated and used to attenuate the incoming sensory input. These results suggest that the squabbling children may both be reporting their true percept, and that escalation of physical conflict may be a natural by-product of sensory attenuation during neural processing.

3.2 Experiment 1

3.2.1 Methods

After providing written informed consent, six pairs of right-handed subjects took part in experiment 1. Each member of a pair rested his or her left index finger in a moulded support beneath a force sensor (25 N load cell, Entran Ltd.) at the end of a

lever attached to a torque motor (RE35, Maxon Motors UK). The torque motors were fitted with optical encoders (T23BA, Dynamics Research Corporation). The apparatus and task are illustrated in Figure 3-1 A (see Chapter 2 for full details of the force-generating apparatus). A trial was started by one torque motor producing a 0.25 N force on one subject's finger. Subjects then took turns to press down with their right index finger for 3 seconds on the other subject's left index finger through the force sensor. Subjects were instructed to apply the same force on the other subject as had just been exerted on them. Each subject was unaware of the instructions given to the other. The trial was continued until each subject had pressed four times. Each pair of subjects completed four trials.

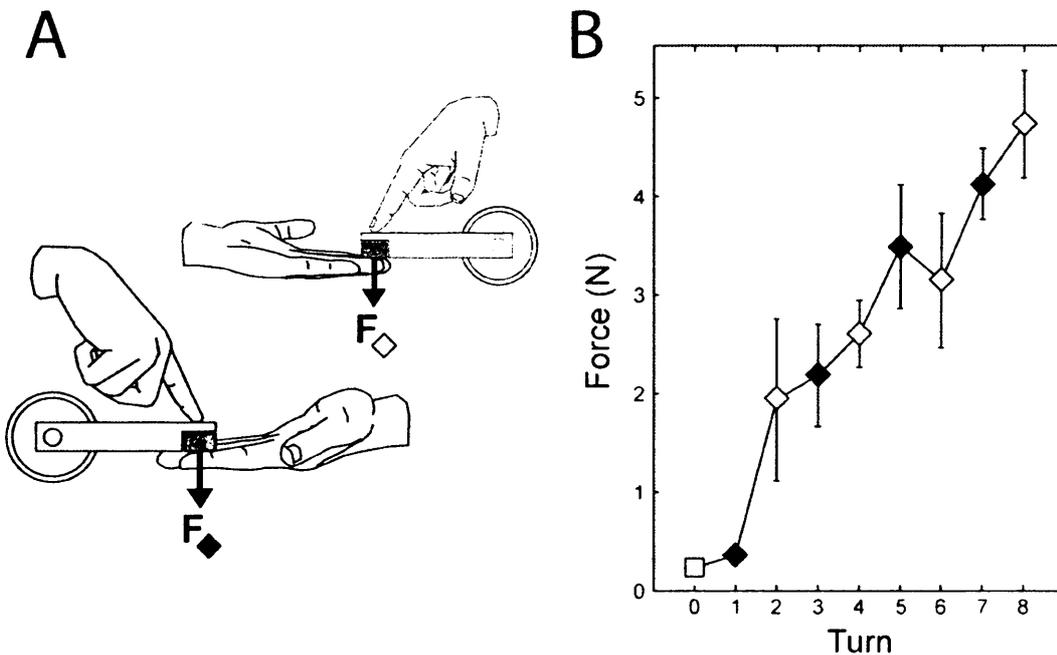


Figure 3-1 Task and results of Experiment 1. (A) Schematic of the experimental set-up and task. (B) Force escalation in a typical pair of subjects (subject 1 filled diamonds and subject 2 empty diamonds, mean \pm S.E. across trials). The initial force (empty square) was generated on subject 1 by the torque motor.

3.2.2 Results

In all cases the forces escalated rapidly (example shown in Figure 3-1 B). Across the 6 pairs there was a significant ($F_{1,5} = 12.1$, $p < 0.05$) average increase of 3.2 N over the 8 turns corresponding to a 38% mean escalation on each turn. The increase was also significant ($p < 0.05$) within every pair of subjects. Force escalation thus occurs rapidly even under instructions designed to achieve parity.

3.3 Experiment 2

3.3.1 Methods

To investigate the basis of the escalation process, we examined the perception of force in an additional twelve right-handed subjects tested individually. Each subject rested his or her index finger in a moulded support beneath the lever of the torque motor, as in experiment 1. Subjects completed two blocks of 40 trials in a counterbalanced order. To start each trial a torque motor applied a constant target force to the tip of the subject's left index finger for 3 s (force profile illustrated by dashed line in Figure 3-2 C). Following an auditory go-signal, subjects were then required to reproduce the force they had just felt. In the 'direct' block, subjects reproduced the force by pressing with their right index finger on their left index finger through the force sensor (Figure 3-2 A). In the 'indirect' block, subjects reproduced the experienced force by adjusting the position of a joystick with their right index finger (Figure 3-2 B). The joystick output voltage was scaled and transmitted to the torque motor controller, so that by moving the joystick the subject could adjust the force applied to the left index finger in the range 0 to 5 N. After 3 s an auditory stop-signal was given to end the trial. A single value for the matching force was obtained for each trial by calculating the mean

force recorded by the force sensor in the interval 2 to 2.5 s after the go-signal (grey area, Figure 3-2 C).

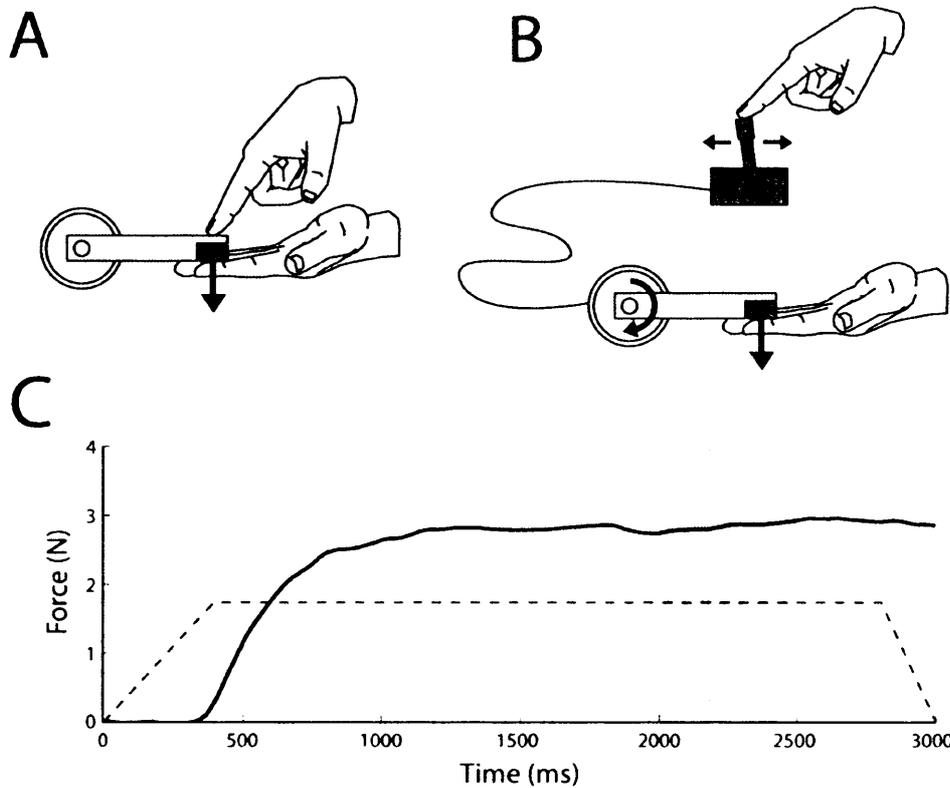


Figure 3-2 Apparatus and task from the resting condition in Experiment 2. (A) In the ‘direct’ condition, subjects reproduced a target force on the passive left index finger by pressing with the index finger of the other hand. (B) In the ‘indirect’ condition, subjects controlled the torque motor output via a joystick. (C) Time course of forces generated by the torque motor (dashed line), and then by the subject (solid line) during a typical direct condition trial with a target force of 1.75 N. The grey area indicates the interval over which the mean subject-generated force was calculated.

Each block consisted of 40 trials, 4 trials each of 10 target forces in the range 0.5 to 2.75 N. The ‘direct’ and ‘indirect’ blocks were repeated in a second condition in which subjects were required to keep their left finger flexed throughout force presentation and matching.

3.3.2 Results

When subjects were required to match a target force delivered to their passive left index finger by pushing through the force sensor, they consistently overestimated the force required (Figure 3-3 A, filled circles). When the force was generated via the joystick the reproduced force matched the original force much more accurately (Figure 3-3 A, empty circles). A regression analysis showed a significant increase in both the intercept ($F_{1,11} = 18.1$, $p < 0.01$) and slope ($F_{1,11} = 25.7$, $p < 0.001$) when the force was applied directly compared to via the joystick. The mean increase across the 12 subjects was 0.53 N (S.E. 0.12 N) for the intercept and 49% (S.E. 9%) for the slope.

Very similar results were obtained when the experiment was repeated with the left index finger flexed (Figure 3-3 B). The matching forces generated in this flexed condition did not differ significantly from the resting condition in either 'direct' or 'indirect' blocks ($F_{1,11} < 0.13$, $p > 0.73$). Significant increases were again seen in both intercept and slope when the force was applied directly compared to via the joystick ($F_{1,11} > 20.9$, $p < 0.001$).

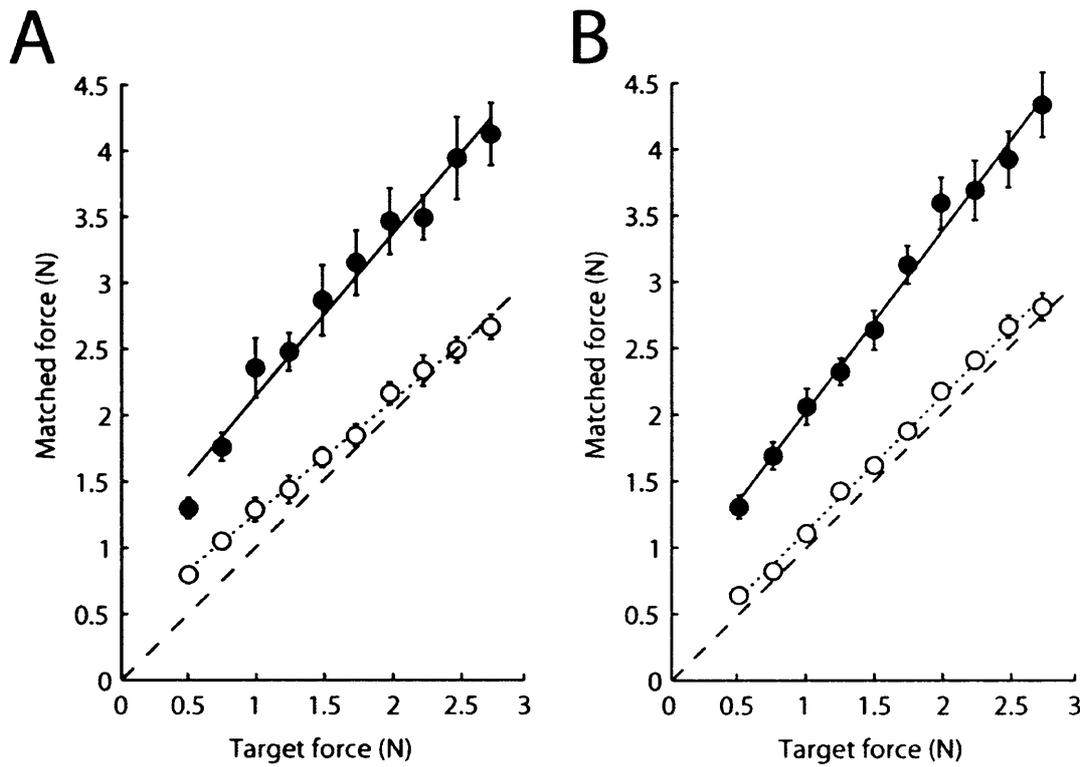


Figure 3-3 Results from Experiment 2 with left finger passive (A) and flexed (B). Matching force generated in the ‘direct’ condition (filled circles, solid line) and ‘indirect’ condition (empty circles, dotted line) as a function of the externally-generated target force (mean \pm S.E. across subjects, regression lines are derived from mean regression parameters across subjects in each condition). Perfect performance is shown by the dashed line.

3.4 Discussion

In the first experiment in this study, pairs of subjects exchanged presses on each other’s fingers. Despite both being instructed simply to reproduce the force applied by the other subject, the forces produced escalated rapidly. This may be a model for the way in which real physical conflicts escalate.

The second experiment sought to investigate the basis of the escalation process. When subjects were required to reproduce a force applied to their fingertip by pressing with a finger of the other hand, they consistently overestimated the force required. This observation suggests that self-generated forces are perceived as weaker than externally-generated forces of the same magnitude. This may arise from a process in which the sensory consequences of an action are predicted on the basis of an efference copy of the motor command. Subtracting a proportion of the predicted sensory input from the actual input at an early stage of processing would attenuate the perceived intensity of self-generated sensations (Sperry, 1950; von Holst and Mittelstaedt, 1950; von Holst, 1954; Miall and Wolpert, 1996). Such a mechanism may have evolved in order to enhance the salience of sensations that have an external cause. This kind of predictive attenuation has previously been proposed as an explanation of why it is difficult to tickle oneself (Weiskrantz et al., 1971; Claxton, 1975; Blakemore et al., 1998a).

The overestimation of force is specific to self-generated forces and not simply due to a failure of memory: the same subjects were able to accurately reproduce the target force when they controlled the torque motor output with a joystick. In this situation the active hand is not generating the force directly, but instead the movement of the hand is translated into a force via the torque motor. A study investigating the control of grip force (Blakemore et al., 1998b) has shown that in this unusual situation predictive mechanisms are not employed. When one hand pushes on an object gripped in the other hand a precise anticipatory modulation of grip force is seen. However, when the force on the gripped object is instead controlled indirectly via a joystick, grip force modulation ceases to be predictive. In the current study, the absence of

attenuation when subjects reproduced the target force via the joystick is consistent with a similar failure of prediction.

When a force is applied to the relaxed finger, the perception of force is mediated through the mechanoreceptors in the fingertip. We also examined a condition in which subjects were required to keep their finger flexed during force presentation and matching. In this condition afferents from the muscles and joints could also contribute to the perception of force. The attenuation observed in this flexed condition was not significantly different from that seen in the resting condition. This suggests that sensory input from the muscles and joints may be attenuated by the same mechanism that attenuates tactile inputs. Alternatively, these secondary sources of sensory input may simply not have any substantial influence on force perception.

The attenuation of self-generated forces observed in this study occurred even though accurate perception of force was the primary requirement of the task, suggesting that it is unlikely to be mediated via attentional mechanisms. Previous studies have shown that tactile perception is attenuated in a moving arm or finger (Angel and Malenka, 1982; Chapman et al., 1987; Milne et al., 1988), but in this study we have shown substantial attenuation of self-generated tactile stimuli in the absence of movement. We can conclude that a self-generated force is perceived as substantially weaker than the same force externally imposed. Force escalation can be seen as a natural by-product of this sensory attenuation.

CHAPTER 4: SPATIAL AND GAIN INFLUENCES ON THE ATTENUATION OF SELF-GENERATED TACTILE SENSATION

4.1 Introduction

The study described in the previous chapter investigated sensory attenuation in the perception of self-generated constant forces. Subjects were required to reproduce a target force applied to their finger, either directly by pressing with a finger of the other hand, or indirectly by controlling the force on the finger with a joystick. Subjects accurately reproduced the force when they used the joystick, but substantially overestimated the force required when they generated it directly. This result implies that a self-generated force is perceived as weaker than the same force externally imposed. This sensory attenuation may result from a mechanism that uses a prediction of the sensory consequences of action to filter sensory input. In this chapter we extend the force-matching paradigm to investigate some of the factors that may influence the action of this predictive mechanism.

A previous study of predictive motor control has shown that accurate prediction requires a natural correspondence between actions and their sensory consequences (Blakemore et al., 1998b). Two robot arms were used to simulate holding an object between the hands. When one hand was moved, causing an increase in the load force

on the other, an anticipatory grip force response was observed in the other hand. However, if the force feedback applied to the active hand was inconsistent with a real object, the anticipatory response was diminished. Similarly, predictive tactile attenuation may require the relationship between force-generation and sensation to be consistent with a realisable context. In this study subjects reproduce target forces applied to their finger by pressing through a virtual object, simulated by two torque motors. This allows the force generated by the active right finger to be dissociated from the force delivered to the passive left finger. We use this dissociation to investigate firstly whether predictive attenuation requires a spatial co-alignment between active and passive fingers, and secondly whether it requires equivalence between the force generated by the active finger and the force experienced in the passive finger.

4.2 Methods

After providing written informed consent 16 right-handed subjects (9 male, 7 female, aged 18-40) participated in the experiment. The experimental protocol was approved by a local ethics committee. Each subject rested his or her left index finger in a moulded support. A force sensor (Nano-17 6-axis F/T sensor, ATI Inc.) rested on the tip of the finger at the end of a lever attached to a torque motor (Maxon Motors UK, Model RE35; geared in ratio 1:4.8). The motor was fitted with a rotary optical encoder (Incremental Encoders Direct Ltd, Model SA40). To start each trial the torque motor applied a constant target force to the tip of the subject's index finger for 3 s. Following an auditory go-signal, subjects were then required to reproduce the

force they had just felt. After 3 s an auditory stop-signal was given to end the trial. Each subject completed six consecutive experimental conditions in a pseudorandom order, each consisting of fifty trials: ten trials each of five target forces in the range 1 N to 3 N. In condition 1, subjects reproduced the force by pressing with their right index finger on the lever directly above their left index finger, as in Experiment 2 of the previous chapter.

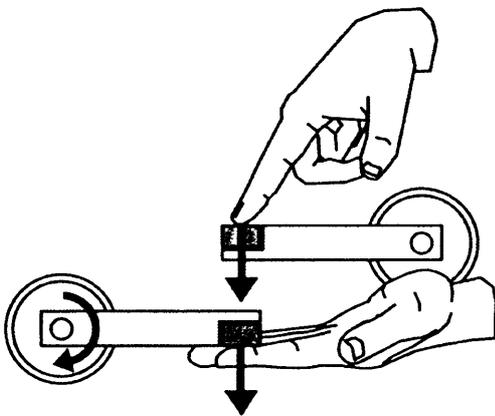


Figure 4-1 Schematic of the experimental apparatus. Forces applied to the upper force sensor were transmitted with a variable gain to the left index finger via the lower torque motor. The upper torque motor could be moved in a direction lateral to the subject to introduce a spatial separation between the active and passive fingers.

In the remaining five conditions subjects generated the matching force on their left index finger indirectly, via a virtual link between two torque motors. Condition 2 was designed to simulate the direct generation of force as closely as possible. In order to produce the matching force, subjects pressed with their right index finger on a second force sensor situated directly above the first (Figure 4-1). This force (recorded online at 1000 Hz and smoothed with a 15 point mean filter) was transmitted to the left index finger by the lower torque motor. Because the surface of the fingertip yields under pressure, applying a force led to a small downward deflection of the lower lever, which was recorded by the rotary encoder fitted to the lower torque motor. In order to maintain an accurate simulation of a virtual object between the fingers, the upper torque motor adjusted the position of the upper force sensor online so as to maintain a

constant vertical distance between the force sensors. It was previously explained to subjects that there would be no physical object between the fingers but that forces they produced would be transmitted to the other finger via the computer.

Conditions 3 and 4 were identical to condition 2 except that the upper torque motor was re-positioned so that during force generation the left and right fingertips were separated laterally by a distance of 10 cm (condition 3) or 30 cm (condition 4). Conditions 5 and 6 were again identical to condition 2 except that now we adjusted the gain relationship between the fingers, such that a 1 N force applied by the right finger resulted in a 0.5 N (condition 5) or a 2 N (condition 6) force on the left finger.

The matching force level generated on the passive finger was calculated for each trial by taking the mean force recorded by the lower force sensor between 2000 and 2500 ms after the go-signal. The attenuation on each trial was then calculated as the fraction of the matching force level by which it exceeded the target force level, and this measure was averaged across trials to give the mean attenuation for each subject and condition. Between-condition comparisons were made using paired t-tests unless otherwise stated

4.3 Results

In order to investigate some of the parameters that might affect sensory attenuation, in this experiment we created a dissociation between force input and output (Figure 4-1). The control condition (condition 2) simulated as closely as possible direct force-generation by the right index finger on the left, as in experiment 2 in the previous

chapter. As in the previous study, subjects applied substantially more force than was required to reproduce the target force (Figure 4-2 A, empty circles). This greater matching force was perceived by subjects as equal to the target force because a proportion of the self-generated sensation was attenuated. The level of attenuation can be inferred by calculating the proportion of the matching force by which it exceeded the target force.

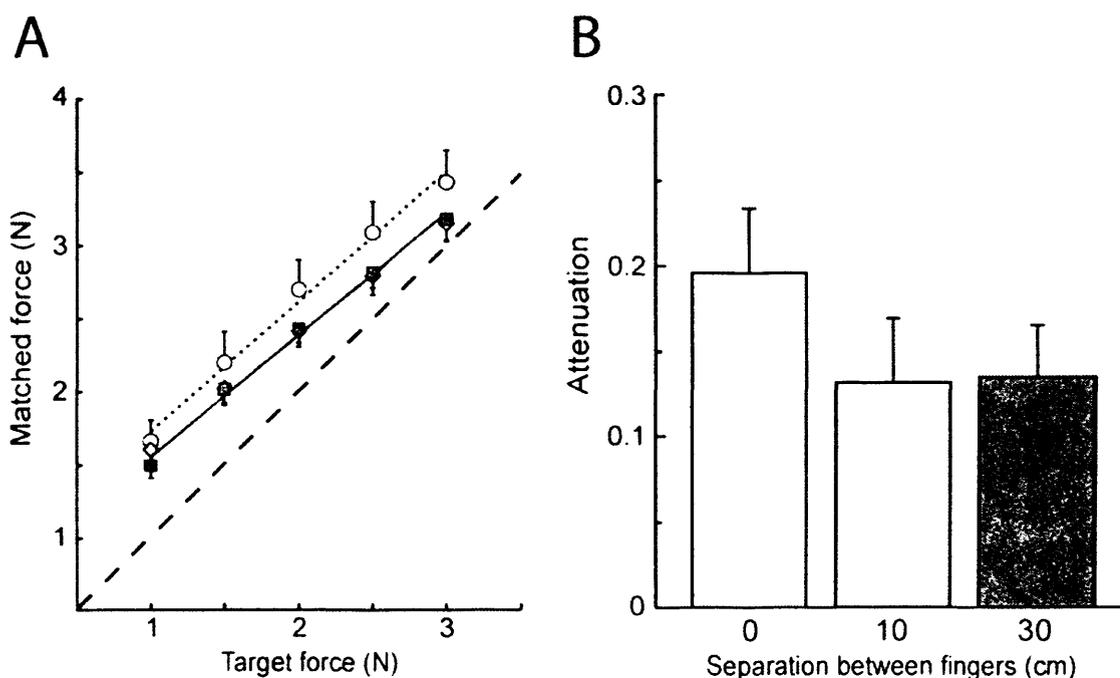


Figure 4-2 Effect of spatial separation on tactile attenuation. Error bars indicate ± 1 SE across subjects. (A) Mean matching force generated by subjects as a function of target force, for lateral separations between active and passive fingers of 0 cm (empty circles), 10 cm (diamonds) and 30 cm (squares). Dashed line represents perfect performance. (B) Attenuation as a function of lateral separation between the fingers.

The mean level of attenuation in this control condition (20%) did not differ significantly ($F_{1,15} = 2.30$; $p = 0.15$) from a condition in which the matching force was

generated directly (23%), implying that the simulation of direct force-generation was sufficiently accurate to have little or no effect on sensory attenuation.

Having created a dissociation between force input and output we were able to investigate the effect of spatial separation on attenuation. Introducing a 10 or 30 cm lateral separation between the active right and passive left fingers resulted in a significant ($F_{1,15} > 5.62$; $p < 0.04$) reduction in the level of attenuation compared to the control condition (Figure 4-2 A&B). However attenuation was not abolished in either of these conditions ($F_{1,15} > 12.3$; $p < 0.004$). The level of attenuation (13%) did not significantly differ between the 10 and 30 cm separations ($F_{1,15} = 0.03$; $p = 0.87$).

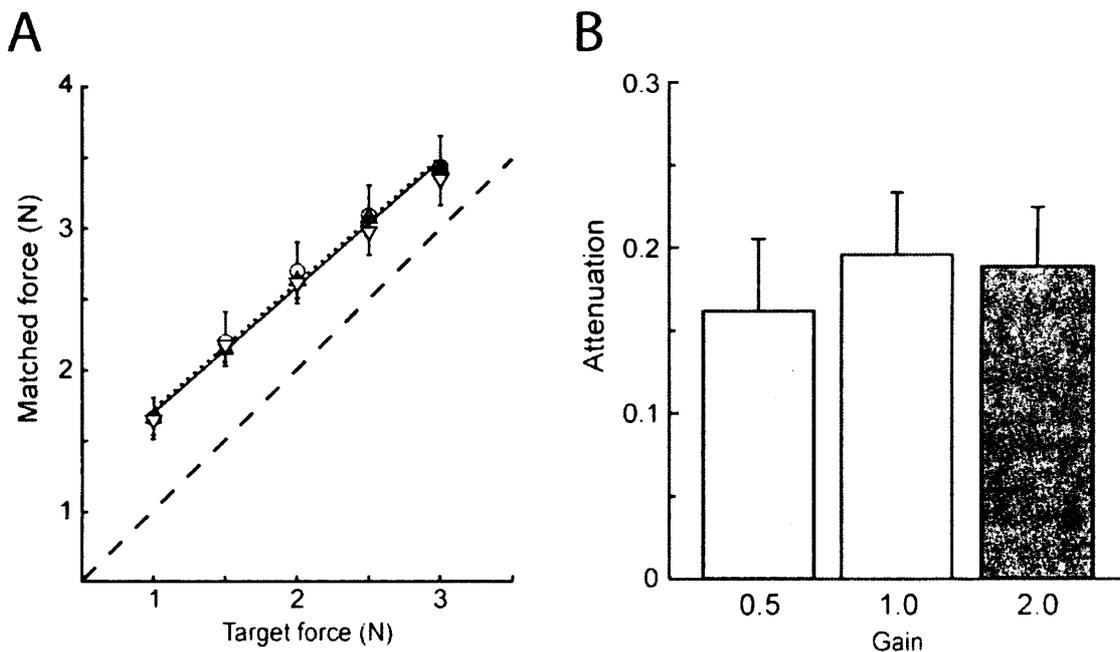


Figure 4-3 Effect of gain on tactile attenuation. Error bars indicate ± 1 SE across subjects. (A) Mean matching force generated by subjects as a function of target force, for gains of 0.5 (downward triangles), 1.0 (empty circles), and 2.0 (upward triangles). Dashed line represents perfect performance. (B) Attenuation as a function of lateral separation between the fingers.

The effect on attenuation of varying the gain relationship between the fingers is shown in Figure 4-3. In three conditions the gain was adjusted such that each newton of force applied by the right finger resulted in a 0.5 N, 1 N, or 2 N force on the left finger. No significant differences in attenuation were observed between these three conditions ($F_{1,15} < 1.48$; $p > 0.24$).

4.4 Discussion

In this study we have confirmed the finding of the previous chapter that the sensation of force in a passive digit is attenuated when the force is self-generated. It has been proposed that the attenuation of self-generated sensation observed here and in previous studies may have evolved in order to increase the salience of externally-generated sensations. To be effective therefore the underlying mechanism must be able to correctly identify when two parts of the body are interacting and apply attenuation only in such situations. This judgement is likely to be based on a range of factors, some of which we have attempted to identify in this study. In order to do this we simulated normal force-generation using a virtual link between two torque motors. This manipulation did not have any substantial effect on attenuation even though subjects were made aware that there was no physical object between the fingers. However, when we introduced a lateral spatial separation between the fingers, the level of sensory attenuation was reduced. This suggests that a spatial co-alignment between force production and sensation may be one of the factors by which sensations are identified as self-generated. When force production and sensation are not aligned it reduces the confidence with which the sensation can be identified as self- rather than externally-generated and so less attenuation is applied. Although infrequent,

spatial misalignments in force of the size examined in this study can occur during manipulation of large objects, and this may explain why the attenuation is reduced but not abolished.

Probably the clearest evidence that two parts of the body are interacting is a precise correspondence between the force generated by one body-part and the force felt in the other at the same moment. Consistent with this, it has been shown that introducing a temporal asynchrony between activity and tactile sensation reduces sensory attenuation (Blakemore et al., 1999a). However, in this study we have demonstrated that altering the gain relationship between the fingers does not affect the level of attenuation. Specifically, doubling or halving the force transmitted from the active finger to the passive finger did not alter the extent to which sensation in the passive finger was attenuated. This result suggests that while temporal correlation between force-generation and sensation may be required to elicit sensory attenuation, an equal magnitude of force does not appear to be important. This is perhaps to be expected: when one digit applies a force on another through an object, the relationship between the force applied and the resulting sensory input can vary substantially depending on the shape and consistency of the object, the surface area in contact with the passive digit, and the angle at which the active digit meets the surface.

The amount by which sensation in the passive finger was attenuated did not vary between the different gain conditions despite substantial differences in the force generated by the active finger. It has been proposed that sensory attenuation may result from a cancellation process, in which a proportion of the predicted sensory input is removed from the actual input. If this is the case, the current finding suggests

that the predictive mechanism must be capable of rapidly adapting to new gain relationships between motor output and sensory input in order to continue generating an accurate prediction. Alternatively it may be that sensory attenuation results from a gating process, in which sensory sites receiving self-generated input are identified and a fixed attenuation is applied to all sensory input from those sites. This issue will be returned to later in the thesis.

CHAPTER 5: PERCEPTION OF THE CONSEQUENCES OF SELF-ACTION IS TEMPORALLY TUNED AND EVENT-DRIVEN

5.1 Introduction

The experiments described in the previous two chapters have shown that a self-generated constant force is perceived as less intense than the same stimulus externally imposed. In this chapter, we investigate the temporal tuning of this tactile attenuation. A previous study (Blakemore et al., 1999a) has addressed a similar issue in the perception of tickle. As discussed in Chapter 1, self-generated tactile stimulation is perceived as less ticklish than external stimulation. Blakemore et al. used a pair of robotic arms to simulate a self-generated tickle, and then introduced a time delay between the subject's active movement and the movement of the ticklish stimulus. They found that a delay of 300 ms was sufficient to abolish the normal attenuation of the self-generated tickle and that smaller delays produced a partial reduction in attenuation. This suggests that the reduction in the perception of self-generated tickle is not the result of a general suppression of sensation from an affected body part, but instead involves a temporally precise modulation of the sensory input.

In this chapter, we use brief force pulses as probes to investigate in detail the time-course of tactile attenuation. Subjects tap with one finger on a finger of the other hand

through a virtual object, simulated by a force sensor and torque motor. Based on our previous results, we predict that the sensation of the tap in the passive finger will be attenuated compared to an externally generated tap of the same magnitude. As in Chapter 4, the virtual object allows the force generated by the active finger to be dissociated from the force delivered to the passive finger. By delaying or advancing the transmission of the tap to the passive finger, and assessing the perceived intensity of the resulting sensation, we are able to map the time-course of attenuation.

5.2 Methods

After providing written informed consent, 30 right-handed subjects (20 men and 10 women) aged 18-40 participated in this experiment: 12 in group A, 10 in group B and 8 in group C. A local ethics committee approved the experimental protocols. Each subject rested his or her left index finger in a moulded support beneath a lever attached to a torque motor (Maxon Motors UK, Model RE35; geared in ratio 1:4.8). To start each trial, subjects depressed and held a start-button with their right index finger (Figure 5-1 A).

For group A, there were 8 different trial types each occurring once every 8 trials in a pseudorandom order. The 8 trial types included 1 no-movement trial and 7 movement trials. On no-movement trials subjects continued to hold down the start-button while two taps were sequentially delivered (test tap followed by comparison tap) to their left index finger by the torque motor separated by an interval of 800–1500 ms. Subjects then indicated which of the two taps they perceived as harder by pressing one of two

response buttons. The peak force amplitude of the second comparison tap was varied across trials according to a maximum-likelihood procedure (see below) so as to find the amplitude at which it was perceived as equal to the first test tap, which always had a fixed amplitude of 2.7 N. Both taps had a fixed duration of 80 ms.

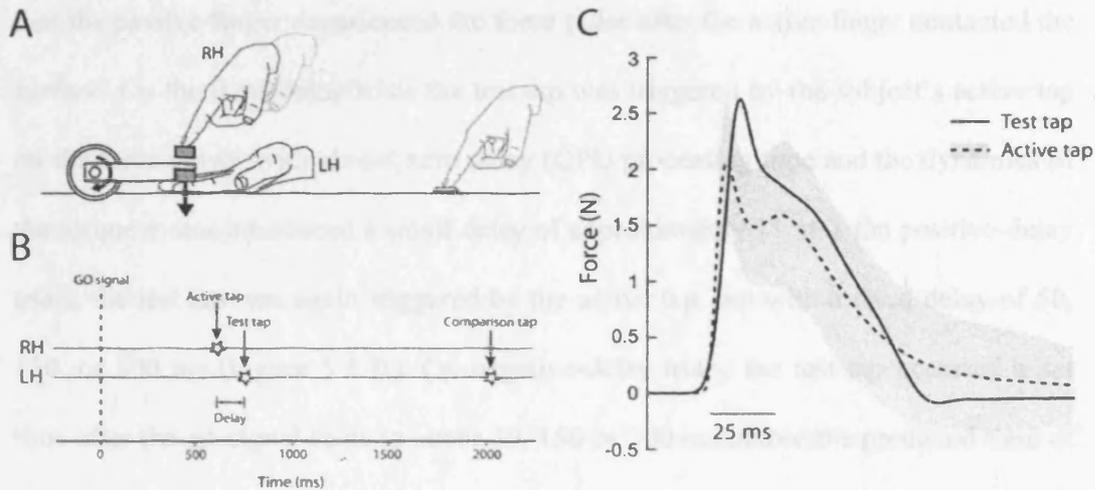


Figure 5-1 Apparatus and procedures. (A) Schematic of the apparatus and task. To begin each trial, subjects depressed a button with their right index finger while resting their left index finger beneath a force sensor fixed to the lever of a torque motor. On movement trials, in response to an auditory go-signal, subjects released the button and made a speeded movement to produce a brief force pulse (active tap) with their right index finger on a second force sensor fixed above their left index finger. A similar force pulse (test tap) was delivered with a variable delay to the left index finger by the torque motor. (B) Time-course of events experienced by the right and left hands (RH and LH) in an example movement trial with a +150 ms delay. The test tap was followed after a short interval by a comparison tap of variable amplitude, and subjects then indicated which of the two taps they perceived as harder. (C) Mean force profiles of the test tap (solid line) and active tap (dashed line, grey area represents ± 1 S.D.) on zero-delay trials. The force profiles have been aligned to force onset for ease of comparison; processing time introduced an 11 ms delay to the test tap not shown here.

On movement trials, after an auditory go-signal subjects released the start-button and made a speeded movement (amplitude 14 cm) to tap with their right index finger on a

force sensor (Nano-17 6-axis F/T sensor, ATI Inc.) fixed above, but not in contact with, their left index finger (active tap, Figure 5-1 A). As in the no-movement trials, two taps were delivered to the left index finger and subjects indicated which they perceived as harder. The test tap came at one of 7 different delays compared to the active tap: -300, -150, -50, 0, +50, +150 and +300 ms, with a positive delay indicating that the passive finger experienced the force pulse after the active finger contacted the surface. On the 0 ms delay trials the test tap was triggered by the subject's active tap on the force sensor with almost zero delay (CPU processing time and the dynamics of the torque motor introduced a small delay of approximately 11 ms). On positive-delay trials, the test tap was again triggered by the active tap, but with a fixed delay of 50, 150, or 300 ms (Figure 5-1 B). On negative-delay trials, the test tap occurred a set time after the go-signal so as to occur 50, 150 or 300 ms before the predicted time of the active tap (based on the median interval between the go-signal and active tap on previous trials). The mean interval between go-signal and active tap during the experimental session was 651 ms. Subjects in group A completed a total of 400 trials. Subjects in group B participated in an identical experimental protocol, but with only three trial types consisting of delays of 0, +100, and +300 ms. Subjects in this group completed a total of 300 trials, 100 in each condition.

To ensure that the test tap was similar in size to the active tap even when it came in advance, we fixed the amplitude of the test pulse at 2.7 N and trained subjects in an earlier practice session to produce an active tap with a similar force amplitude. During the experimental session, any trial in which the amplitude of the subject's active tap fell outside the range of 1.75-3.50 N was rejected and the trial was repeated. During

the experimental session the active tap had mean amplitude 2.40 ± 0.35 N (Figure 5-1 C; forces sampled online at 1000 Hz).

Subjects in group C completed five consecutive experimental conditions in a pseudorandom order (illustrated in Figure 5-2 B). The position of the tip of each subject's right index finger was recorded online with an Optotrak 3020 motion-analysis system (Northern Digital, Waterloo, Ontario) at 150 Hz. Condition 1 consisted of 50 no-movement trials identical to those described above for group A. Condition 2 was identical to condition 1 except that the subject's right index finger was held above and in contact with the upper force sensor in a moulded support and an upwards force pulse (2.4 N, 80 ms) was delivered to the right index finger synchronous with the test tap on the left. Condition 3 consisted of 50 trials identical to the 0 ms delay trials in group A, i.e. the test tap was triggered by the right index finger tapping on the force sensor. Condition 4 was identical to condition 3 except that subjects responded to the go-signal by making a right finger movement that stopped just above the force sensor; the test tap was triggered when the downward speed of the finger fell to zero. In condition 5 at the go-signal subjects made a tapping movement 4 cm in front of the force sensor but did not make contact; the test tap was triggered when the fingertip passed through the horizontal plane coincident with the top surface of the force sensor.

A maximum-likelihood procedure was used to determine the peak force amplitude of the second comparison tap for a given trial. At the end of each trial, the comparison tap amplitude and the subject's response on that trial were pooled with the data from all previous trials of the same type. For group A, the negative-delay trials were each

pooled into one of three bins according to the actual interval between test tap and active tap: 0-100, 100-200 and 200-400 ms. Negative-delay trials with intervals outside of the range 0 to 400 ms were rejected from further analysis. The data from each trial type were fitted with a logistic function according to a maximum-likelihood procedure and the response threshold was calculated to estimate the comparison tap amplitude that would make the test and comparison taps perceptually equal. A force amplitude was chosen from a uniform random distribution bounded by the 1% and 99% points on the fitted psychometric logistic curve and this amplitude was used for the comparison tap on the next trial of the same type. In subsequent analysis, the response threshold was calculated over all responses for each subject and trial type (or bin in the case of negative-delay trials). Within-subject and between-subject comparisons among trial types were made using paired and unpaired t-tests respectively.

5.3 Results

Subjects were required to judge the relative magnitude of two taps experienced sequentially on the left index finger. The first tap (test tap) was of fixed magnitude (2.7 N) whereas the second tap (comparison tap) was varied using a two-alternative forced choice paradigm to determine the point at which it was perceived as equal to the test tap. In a control condition both taps were delivered while the hands were at rest. At the point of perceptual equality, the comparison tap was not significantly different from the test tap ($M = 94\%$ of test tap, $SE = 6\%$, $F_{1,11} = 1.0$; $p = 0.34$). In a test condition, the test tap was triggered with minimal delay by the subject tapping

with their right index finger on a force sensor fixed above their left index finger. This situation simulates directly tapping onto one's own finger through a solid object. As in the control condition, subjects compared the perceived strengths of the test tap and a comparison tap that was unrelated to the tapping movement and applied to the left index finger a short interval later. In contrast to the control condition, perceptual equality was achieved when the comparison tap was substantially smaller than the test tap ($M = 71\%$ of test tap, $SE = 5\%$) and significantly smaller than in the control condition ($F_{1,11} = 13.7$; $p = 0.004$), implying substantial attenuation of the test tap. These results are consistent with the finding of Chapters 3 and 4 that a self-generated force is perceived as considerably weaker than an externally-generated force of the same magnitude.

In addition to the trials that simulated a self-generated tap with no delay, the test condition included trials in which the time interval between the subject's active tap on the force sensor and the test tap delivered to the subject's passive finger was varied parametrically. The relative amplitude of the comparison tap to test tap for perceptual equality for each time interval is shown as the filled circles in Figure 5-2 A. The amount of attenuation decreased with increasing temporal asynchrony, regardless of whether the test tap came before or after the active tap. When the test tap occurred 300 ms after the active tap, the maximum delay tested, the response was not significantly different from the baseline (dotted line Figure 5-2 A) set by the control condition ($F_{1,11} = 1.3$; $p = 0.27$). When the test tap occurred in the range 200-400 ms before the active tap, a significant difference from baseline was still observed ($F_{1,11} = 5.8$; $p = 0.034$) but the level of attenuation was substantially reduced compared to the zero-delay trials ($F_{1,11} = 13.4$; $p = 0.004$).

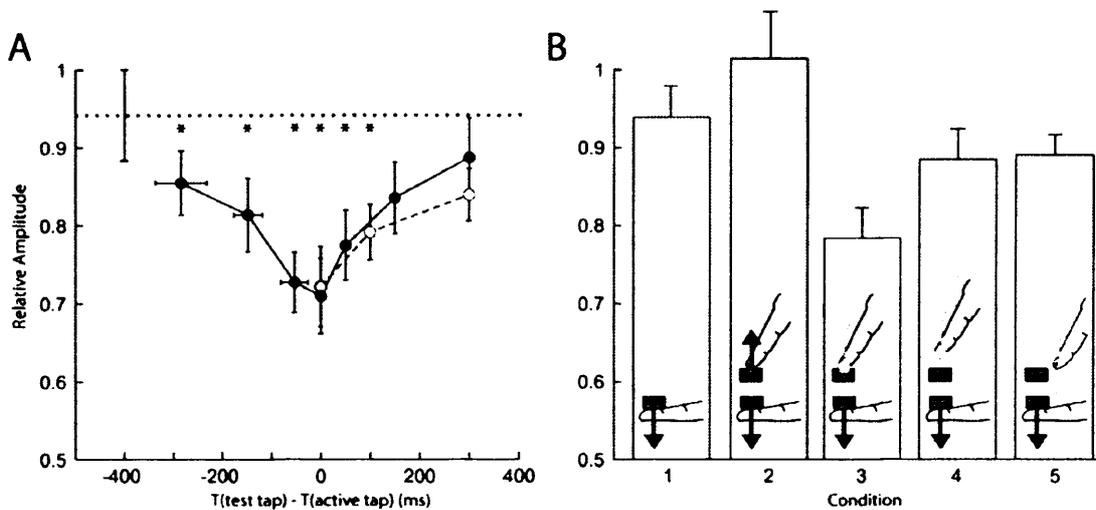


Figure 5-2 Mapping the time-course of tactile sensory attenuation. (A) Relative amplitude of the comparison tap to the test tap at the point of perceptual equality, as a function of asynchrony between test tap and active tap. Filled circles show mean relative amplitude for group A, empty circles for group B. Dotted line shows mean relative amplitude for group A in the no-movement condition. Vertical error bars represent ± 1 S.E. In the case of negative asynchronies, the position on the abscissa represents the mean asynchrony over all trials within the corresponding timing bin (see Methods), and horizontal error bars represent ± 1 S.D. Asterisks indicate asynchronies at which the relative amplitude was significantly different ($p < 0.05$) from that observed in the no-movement condition of group A. (B) Mean relative amplitude as a function of experimental condition for subjects in group C. Error bars represent ± 1 S.E. Insets illustrate the position of the right finger at the time at which the test tap is triggered. Grey lines illustrate the movement path of the right fingertip with circles indicating the movement endpoint. Arrows represent force pulses delivered by the torque motors.

It is possible that the greatest attenuation occurred with zero delay because this was the mean temporal asynchrony experienced during the experiment. Similarly, the width of the attenuation window we have observed might result from the specific range of asynchronies experienced during the experiment. To test these possibilities, a second group of subjects participated in a modified version of the experiment

consisting only of trials in which the test tap followed the active tap, either with no delay or with delays of 100 or 300 ms. Results from this group (empty circles in Figure 5-2 A) did not differ significantly from those in the first group ($F_{1,20} < 0.58$; $p > 0.45$) and the greatest attenuation was again seen when there was no delay, despite the change in the mean delay from 0 ms to 133 ms and the change in the range of asynchronies from 600 ms to 300 ms. We can therefore conclude that the window of attenuation is independent of the delays experienced and is maximal at the time at which the active hand contacts the surface above the passive hand.

Movement-related sensory attenuation (Angel and Malenka, 1982) has been extensively documented by Chapman and colleagues (Chapman et al., 1987). For example, the threshold for detection of an electrical stimulus is raised in a moving finger compared to the finger at rest. However, little change in detection threshold is seen in the finger contralateral to the movement (Williams et al., 1998). To confirm that the attenuation observed in the current study did not result from the movement alone, or simply from the synchronous tactile inputs received in the two fingers, a third group of subjects was tested. For these subjects the test tap was either triggered by contact with the force sensor as before, or by similar movements of the right finger that stopped just above or passed in front of the force sensor. Significant attenuation was observed only when the movement resulted in contact (comparison to no-movement condition: $F_{1,7} = 6.8$; $p = 0.035$; Figure 5-2 B). In addition, no significant attenuation was seen when synchronous taps were experienced by both fingers in the absence of movement. These results suggest that the attenuation seen when one finger strikes another is the result of a predictive mechanism, rather than being related to either movement or synchronous sensory inputs alone.

5.4 Discussion

Consistent with the findings of previous chapters, we have demonstrated substantial attenuation in the perceived intensity of a self-generated tap made by one finger on a finger of the other hand. Subjects used their right index finger to tap a force sensor mounted above their left index finger. When a motor generated a tap on the left finger synchronous with the right tap, simulating contact between the fingers, the sensation of force in the left finger was attenuated compared to the same tap experienced during rest. By delaying or advancing the left tap relative to the active right tap, we have mapped out the time-course of this tactile attenuation and found a roughly symmetrical and relatively broad period of attenuation centred on the precise time at which the action would normally cause a tactile sensation.

No attenuation was seen for taps on the left finger triggered by movements of the right finger that stopped above or passed wide of the sensor, nor when synchronous taps were experienced by both fingers in the absence of movement. These results suggest that sensory attenuation does not result from either movement or sensation in the active effector alone but rather is linked to the predicted time of the contact event arising as a consequence of the action.

Our results are consistent with a previous study (Blakemore et al., 1999a) which found that an artificially introduced delay of 300 ms was sufficient to abolish the attenuation of a self-generated tickle and that smaller delays produced a partial reduction in attenuation. However, in this previous study, the delay was introduced

between a continuous movement of the active hand and an identical movement of the stimulus on the passive hand. Thus, even when a delay was present, there was a strong relationship between the activity of the active hand and the simultaneous sensation in the passive hand, which would tend to obscure the actual time-course of attenuation. In contrast, in the current study, when a time delay was introduced there was little or no overlap between the force-generating activity in the active hand and the sensation in the passive hand.

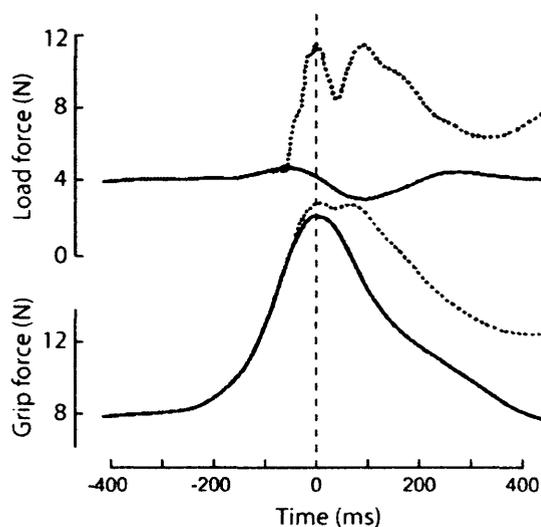


Figure 5-3 Anticipatory modulation of grip force when dropping a ball into a grasped cup. Average load force (top) and grip force (bottom) on trials when the ball lands in the cup (dotted line) or is prevented from doing so (solid line). Abscissa shows time relative to the first peak in the mean load force due to impact (dashed line). Subsequent load force peaks reflect ball rebounds and dynamics of the hand and arm. (Adapted from Johansson and Westling, 1988).

There are interesting parallels between the results of the current study and the findings of a grip force study which also investigated force pulses (Johansson and Westling, 1988). In this previous study, subjects dropped a ball from one hand into a cup supported in a precision grip by the other hand. The initial impact of the ball in the cup generated a brief force pulse similar to the taps used as test stimuli in the current study (dotted line, Figure 5-3 top). To prevent the cup from slipping out of their grasp as a result of the impact, subjects increased their grip force around the time of contact.

Occasionally, the experimenter prevented the dropped ball from hitting the cup, revealing a purely anticipatory component of the grip force modulation. The time-course of this grip force increase (solid line, Figure 5-3 bottom) bears a number of similarities to the time-course of attenuation seen in the current study: it has a similar temporal width, is roughly symmetrical, and is centred on the expected time of the initial force peak. These similarities support the hypothesis that tactile attenuation, like grip force modulation, depends on a prediction of the consequences of action generated by an internal model. In both cases the time profile is considerably broader than the actual duration of the force pulse. This could reflect inaccuracy or uncertainty of the internal model in predicting the time of the contact event, or a 'safety margin' built into the attenuation and grip force systems to allow for the possibility of a prediction error.

One of the key features of an internal model is the ability to adapt to account for changes in the body or environment. As discussed in Chapter 1, the motor system has to be able to account for delays in transmission of sensory inputs and motor outputs, and it has been proposed that this involves an adaptive predictive mechanism (Kalman and Bucy, 1961; Miall et al., 1993). Consistent with this, a number of studies suggest that the motor system is able to compensate for additional delays in sensory feedback. Foulkes and Miall (2000) introduced 200 or 300 ms delays to visual feedback while subjects used a joystick to track an unpredictably moving target. The delay initially caused a substantial decrement in performance, but tracking errors decreased with practice under the delayed feedback. Similar results have been obtained in primates for an ocular pursuit task with delayed visual feedback (Deno et al., 1989).

Witney et al. (1999) simulated a virtual object held between the hands to investigate adaptation of anticipatory grip force. Subjects were trained to apply force pulses with their left hand while gripping the object with the right hand. When a 250 ms delay was introduced between the force pulse and the transmission of force to the right hand, the normal anticipatory peak in right hand grip force became inappropriate, as it was tuned to the time of the left hand force pulse. Over the course of 250 trials, the normal grip force peak decayed and a second peak developed, tuned to the new expected time of the force pulse on the right hand.

If, as proposed, tactile attenuation results from a predictive mechanism, these studies suggest that it may also adapt to temporal delays. No evidence for adaptation was observed in the current study, even though one group of subjects (B) on average experienced a delay of 133 ms in force transmission between the hands. However, the magnitude of the time delay varied from trial to trial, with no delay on many trials, so it is perhaps not surprising that adaptation was not observed in this case. A proper test of the hypothesis might involve mapping the time window of attenuation both before and after a long period of training with a fixed time delay.

CHAPTER 6: ATTENUATION OF SELF-GENERATED TACTILE SENSATION IS PREDICTIVE NOT POSTDICTIVE

6.1 Introduction

In the preceding chapters it has been demonstrated that self-generated constant forces (Chapters 3 & 4) and force pulses (Chapter 5) are perceived as weaker than the same stimuli externally imposed. As discussed in the introduction to this thesis, this kind of sensory filtering has generally been thought to result from a predictive mechanism. According to this hypothesis, when a motor command is generated, an efference copy of the command is used to predict the sensory consequence of the action (Sperry, 1950; von Holst and Mittelstaedt, 1950; von Holst, 1954). A component of this predictable input is removed from the incoming sensory signals, thereby increasing the relative salience of sensations with an external cause. In such a mechanism the sensory signal is altered online and the original sensory input is no longer available for further processing.

While the results of previous psychophysical studies, including those described in the preceding chapters of this thesis, are consistent with a predictive mechanism, they are equally consistent with a reconstructive or postdictive mechanism. A postdictive mechanism is one in which the percept of a sensory event is constructed from sensory

information received around the time of the event (Dennett and Kinsbourne, 1992; Eagleman and Sejnowski, 2000; Rao et al., 2001). In this mechanism the original sensory input is available for a period after the event and its processing can depend substantially on other events that occur in close temporal proximity. The “cutaneous rabbit” illusion (Geldard and Sherrick, 1972) provides an example of postdiction in the tactile modality. A rapid series of taps applied to the hand are reported to “hop” up the arm if immediately followed by one or more taps near the elbow, but remain localized at the hand if no subsequent taps are delivered. Thus, the processing of the initial taps depends on the subsequent taps.

If a postdictive mechanism is responsible for tactile sensory attenuation, a given sensation will be identified as either self- or externally-generated on the basis of all the sensory events that occurred at around the same time. For example, a tap on a passive finger may be more likely to be judged to be self-generated, and therefore attenuated, if the active or tapping finger receives tactile feedback at the same time. In this study we distinguish between predictive and postdictive hypotheses by constructing a stimulus that a postdictive mechanism will identify as externally generated but that is nonetheless predictable on the basis of the motor command, and hence will be attenuated by a predictive mechanism.

6.2 Methods

After providing written informed consent, 20 right-handed subjects aged 18-40 participated in the experiment, 10 in group A (4 male, 6 female) and 10 in group B (9

male, 1 female). A local ethics committee approved the experimental protocols. The experimental design and apparatus was similar to that in the previous chapter. Each subject rested his or her left index finger in a moulded support beneath a force sensor (Nano-17 6-axis F/T sensor, ATI Inc.) mounted on a lever that was attached to a torque motor (Maxon Motors UK, Model RE35; geared in ratio 1:4.8). Their right index finger was held above the left finger in a support that constrained it to a single flexion-extension movement, and the angle of flexion was recorded by a rotary encoder (Incremental Encoders Direct Ltd, Model SA40). At an auditory go-signal subjects tapped with their right index finger (active finger) on a force sensor fixed above, but not in contact with, their left index finger (passive finger). Two taps (test tap followed by comparison tap) were delivered to the left index finger by the torque motor separated by an interval of 700-1200 ms. Subjects indicated which of the two taps on the left index finger they perceived as harder by pressing one of two response buttons. Both taps had a fixed duration of 80 ms. The peak force amplitude of the comparison tap was varied across trials according to a maximum-likelihood procedure (see below) so as to find the amplitude at which it was perceived as identical to the test tap (which had a fixed amplitude of 2.7 N).

Each subject completed fifty sets each of six trials. For Group A, the majority of trials (four trials in each set of six) were Contact trials (Figure 6-1 top). On these trials, the test tap on the left finger was triggered by the subject's active tap on the top force sensor with almost zero delay (CPU processing time and the dynamics of the torque motor inevitably introduced a small delay of approximately 11 ms); thus for the subject the situation closely mimicked tapping directly on the left index finger with the right. Subjects had been trained (during an earlier practice session) to produce a

tap with an amplitude between 1.75 N and 3.5 N; during the experimental session, trials in which the amplitude of the subject's active tap fell outside of this range were rejected.

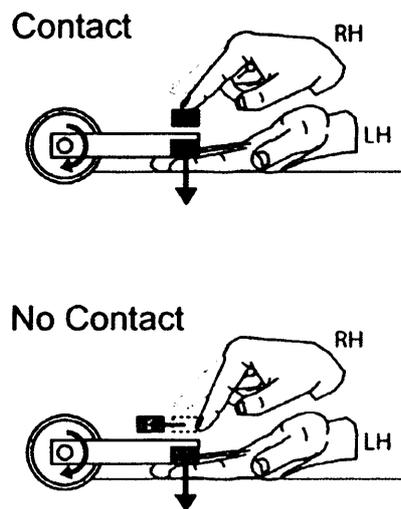


Figure 6-1 Schematic of the apparatus and task. On Contact trials (top), in response to an auditory go signal, subjects produced a brief force pulse with their right index finger on a force sensor fixed above their left index finger. A similar force pulse was delivered to the left index finger by a torque motor. On No-Contact trials (bottom) the force sensor was moved at the start of the trial so that subjects made a tapping movement with their right index finger but did not make contact.

On Delay trials (one trial in each set), the test tap was delayed by 500 ms relative to the active tap. On No-Contact trials (one trial in each set), the top force sensor was moved, without the subject's knowledge (both force sensors were always hidden from view), prior to the go signal. This meant that when the go signal was given, the subject made a tapping movement but did not make contact with the top force sensor (Figure 6-1 bottom). On these trials the test tap was triggered when the right index finger passed through the flexion angle at which contact would have been made with the top force sensor. Group B underwent an identical protocol to group A, except that no contact was made with the force sensor on any trial: thus the majority (five trials in each set) were No-Contact trials, as described above, and on Delay trials (one trial in each set) the test tap was triggered in the same way as in the No-Contact trials, but with a 500 ms delay. Subjects in this group were trained (in an earlier practice session) to make movements with similar amplitude and velocity to the movements

made in No-Contact trials by subjects in group A. For this reason, trials with movement amplitude outside the range $45-70^\circ$ or peak downward velocity outside the range $550-1000^\circ\text{s}^{-1}$ were rejected. The motor output a subject had to generate to successfully complete a trial was therefore very similar in groups A and B. In both groups the order of trials within each set was pseudorandomized.

At the end of each trial, the comparison tap amplitude and the subject's response on that trial were pooled with the data from all previous trials under the same condition. The data from each condition were fitted with a logistic function according to a maximum-likelihood procedure and the response threshold (the 50% point on the fitted psychometric curve) was calculated to estimate the comparison tap amplitude that would make the test and comparison taps perceptually equal. For the first ten trials in each condition, a force amplitude was chosen from a uniform random distribution in the range 0.5 N to 5.5 N and this amplitude was used for the comparison tap on the next trial in the same condition. For subsequent trials, the comparison tap amplitude was chosen from a narrower range defined by the 1% and 99% points on the fitted psychometric curve. This procedure focuses sampling in the region of the current estimate of the response threshold, without overly restricting the range of amplitudes tested (the average final sampling range was 3.3 N). In subsequent analysis, the response threshold was calculated over all responses for each subject and trial condition. Within-subject and between-subject comparisons between trial conditions were made using repeated-measures analysis of variance.

6.3 Results

Subjects in one group (A) were required to judge which of two taps delivered sequentially to their left index finger was harder. The first tap (test tap) was of fixed magnitude (2.7 N) whereas the size of the second tap (comparison tap) was varied from trial to trial. A maximum-likelihood procedure was used to determine the perceived magnitude of the test tap: that is, the ratio of the comparison tap to the test tap at which the two taps were perceived as equal (see Methods). On Contact trials, which made up the majority of trials, the test tap was triggered with minimal delay by the subject tapping with their right index finger on a force sensor fixed above their left index finger (Figure 6-1 top). This situation simulates directly tapping onto one's own finger through a solid object. In the previous chapter we showed that sensation of the test tap is substantially attenuated in this condition. Delay trials were identical except that the test tap was delayed by 500 ms relative to the subject's tap on the force sensor. In the previous chapter we showed that attenuation in the passive finger is closely synchronised with the contact time of the active finger and that attenuation was not observed when the test tap is delayed by 300 ms. The Delay trials therefore provided a baseline measure without attenuation of subjects' performance on the comparison task, taking into account any small response bias or 'time error' (Hellström, 1985) that might influence the comparison. As expected, the perceived magnitude of the test tap on Contact trials (M 0.71 SE 0.08; Figure 6-2) was significantly reduced compared to the baseline set by the Delay trials (M 0.95 SE 0.04; $F_{1,9} = 6.4$; $p = 0.032$).

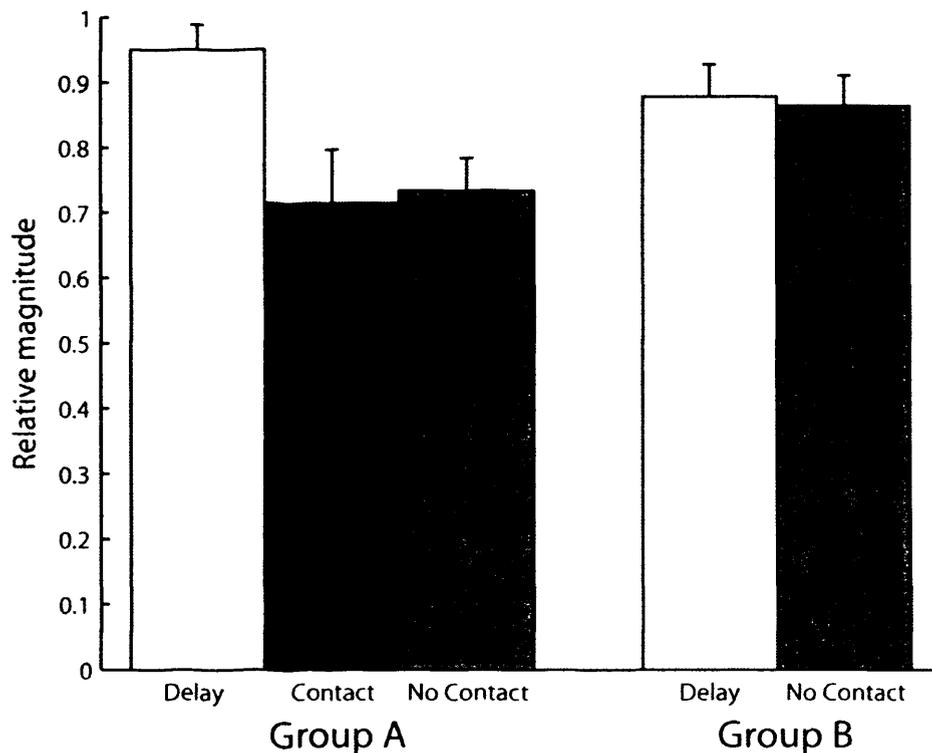


Figure 6-2 Mean relative magnitude of the comparison tap to the test tap at the point of perceptual equality as a function of trial type and subject group. Error bars represent ± 1 S.E.

On infrequent No-Contact trials, unknown to the subject, the force sensor was moved at the start of the trial, so that at the go signal the subject made a tapping movement, but made no contact (Figure 6-1 bottom). On these trials the test tap was triggered when the subject's finger passed through the position at which contact would have been made with the force sensor had it not been moved. The perceived magnitude of the test tap on these trials was substantially reduced (M 0.73 SE 0.05; Figure 6-2) compared to Delay trials ($F_{1,9} = 15.5$; $p = 0.0034$), and did not differ significantly from that seen in Contact trials ($F_{1,9} = 0.11$; $p = 0.75$). This is consistent with the action of a predictive attenuation mechanism: as the test tap in these trials occurred at the same time as it would have in a Contact trial, a predictive mechanism would correctly predict the tap and attenuate it. In contrast, if attenuation were the result of a

postdictive mechanism that integrates sensory input from around the time of the tap, then on these trials the test tap would not be recognised as self-generated (as no contact occurred) and attenuation would not be observed. We can therefore conclude that a postdictive mechanism is not responsible for tactile sensory attenuation.

This interpretation depends on the assumption that the sensation of contact in the active finger is necessary for attenuation in the passive finger. It may be that the attenuation mechanism comes to associate the occurrence of the test tap with a particular movement or location of the active finger. To test this possibility, a second group of subjects (B) participated in an experiment that was similar, but in which the active finger never made contact with the force-sensor. The test tap was triggered as the finger passed through the position at which contact would have been made in the first experiment either immediately (No-Contact trials, the majority of the trials), or after a 500 ms delay (Delay trials). In contrast to the first group, the perceived magnitude of the test tap did not differ significantly between these two types of trial ($F_{1,9} = 1.1$; $p = 0.31$; Figure 6-2). A significant group-condition interaction ($F_{1,18} = 12.7$; $p = 0.0022$) confirmed the difference between the two groups. We can conclude that a consistent relationship between motor activity in one finger and sensation in another finger is not sufficient to induce attenuation.

An examination of individual subject data shows that the responses of the majority of subjects were in accordance with the group mean results described above. Of the ten subjects in group A, seven showed a reduction of at least 10% in perceived magnitude on Contact trials compared to Delay trials. Of these subjects who showed clear attenuation, all but one also showed a reduction of at least 10% on No-Contact trials.

In contrast, in group B the difference in perceived magnitude between No-Contact and Delay trials was less than 10% in every subject.

6.4 Discussion

We have found strong evidence to suggest that attenuation of self-generated tactile sensation results from a predictive mechanism. When one finger made a tapping movement above a finger of the other hand, sensation in the passive finger was attenuated only when contact was expected between the fingers. The level of attenuation observed when contact was expected was the same whether or not the contact actually occurred. These results are inconsistent with a postdictive mechanism, which would have access to the actual sensory feedback in determining the level of attenuation. Our results are instead consistent with the action of a predictive mechanism: an online process that predicts self-generated sensory events on the basis of planned motor activity and attenuates the incoming sensory stream so as to reduce the sensory salience of those events.

The absence of attenuation in subjects in group B, who experienced taps in the passive finger but never experienced a contact event in the active finger, is an important result for several reasons. Firstly, it serves as a control for effects of divided attention. Subjects in group A had to attend to two different tasks at the same time: generating a tap with the active finger and judging a sensation in the passive finger. This division of attention may be less pronounced in Delay trials, where the two tasks are separated by 500 ms, than in Contact and No-Contact trials, where the two tasks

are simultaneous. This difference in attentional demand could conceivably be responsible for the difference in magnitude judgement between these trial types. However, group B was essentially identical to group A with respect to attention: subjects had to generate tapping movements with amplitudes and velocities matched to those made by subjects in group A, and the judgement task in the passive finger was identical in both groups. If divided attention were responsible for the differences in magnitude judgement between trials with and without a delay in group A, the same differences would be seen between No-Contact and Delay trials in group B. As no such differences are observed we can conclude that the reduction in perceived magnitude seen in group A is due to a specific attenuation mechanism and not the attentional demands of the task.

Secondly, group B serves to rule out a postdictive mechanism based only on motion cues. In group A, attenuation is observed in the passive finger even when the active tap fails to make contact. While this result is precisely what is expected from a predictive mechanism, it is also consistent with a postdictive mechanism that relies only on motion cues and ignores tactile cues. Such a hypothetical mechanism would attenuate the sensation of the tap in the passive finger simply due to its temporal and spatial proximity to the movement of the active finger. However, such a mechanism would also produce attenuation in the No-Contact trials in group B, and this is not observed. We can conclude that postdictive processes do not play a significant role in the attenuation of self-generated tactile sensation.

The attenuation that we have observed in this and the previous chapter is distinct from the increase in detection threshold to cutaneous stimuli observed in a moving effector

(Angel and Malenka, 1982) in that it is present in a passive digit and is synchronised to the expected time of self-contact. Moreover, a movement-related increase in detection threshold is also seen in advance of a passive movement that occurs at an unpredictable time (Williams and Chapman, 2002), suggesting it involves a postdictive or masking mechanism rather than the kind of predictive mechanism demonstrated in this study.

CHAPTER 7: REPRESENTATION OF CAUSE AND EFFECT IN PREDICTIVE MOTOR LEARNING

7.1 Introduction

The study described in the previous chapter has shown that the tactile attenuation observed when one hand makes contact with the other is the result of a predictive mechanism. Such a mechanism maps the planned motor activity of the active hand into a prediction of the force that will be felt in the passive hand. As discussed in the introduction, this kind of prediction may also underlie coordination between different parts of the body, such as the anticipatory adjustment of grip force during object manipulation. Grip force modulation is one of many anticipatory mechanisms involved in maintaining stability of posture during motor activity. Another example is the unloading task: when one hand lifts a weight from the palm of the other hand, muscle activity in the load bearing arm is decreased in parallel with the lift in order to minimise the change in posture (see Massion, 1992 for review). This anticipatory adjustment is thought to depend on a prediction of the change in load force based on efference copy, as it does not occur unless the lift is self-generated (Diedrichsen et al., 2003).

Anticipatory responses in the unloading task are absent or inaccurate in young children (Schmitz et al., 1999, 2002) as are anticipatory grip force adjustments during object manipulation (Forssberg et al., 1991; Forssberg et al., 1992). This suggests that the prediction required for these tasks is not innate, but rather acquired by experience during early life. Over shorter timescales, grip force responses have also been shown to adapt to account for temporal delays between the force applied by one hand and the force experienced in the other (Witney et al., 1999) and to changes in the relative direction of the forces (Witney and Wolpert, 2003). This implies that the underlying mechanism can adapt to novel contexts in order to continue generating accurate predictions. In this study we investigate the acquisition of prediction when subjects experience an entirely novel relationship between the movement of one hand and the force experienced on the other.

Within a single limb, adaptation to novel relationships between movement and force has been extensively investigated by Shadmehr and colleagues. In these studies (described in detail in Chapter 1), a ‘force field’ is applied to a subject’s hand during target-directed movements, with the force applied at any given moment determined by the velocity of the hand. On first exposure, these novel forces cause large deviations from the intended movement, but these movement errors decrease with practice. If the force field is then unexpectedly removed, deviations of the hand path are observed in the opposite direction to the earlier errors (‘after-effects’). This implies that the subject’s motor control system generates a prediction of the expected forces during a movement and produces opposing forces to compensate.

Adaptation to such a force field is not purely local to the positions in which it has been experienced. When subjects subsequently make movements in a new workspace which requires a change in the posture of the arm, after-effects are again observed, implying that the motor system generalises the adaptation beyond the trained workspace. An analysis of these after-effects can reveal the forces the motor system expects to encounter in the new workspace, and hence the way in which the predictive mechanism represents the force field. Shadmehr and Mussa-Ivaldi (1994) considered two alternative coordinate systems in which the force field could be represented: 'extrinsic,' related to the dynamics of the external environment, and 'intrinsic,' related to the internal dynamics of the body. In an extrinsic representation, the force field is modelled as a transformation from the endpoint velocity of the hand to the force applied at the hand. When movements are made in a new workspace, such a model will predict identical forces on the hand as for the same movement in the trained workspace. Alternatively, in an intrinsic representation, the force field is modelled as a transformation from the angular velocities of the joints of the arm to the torques experienced at those joints. For identical movements of the hand in external space, this model will predict different forces on the hand for different arm configurations.

When Shadmehr and Mussa-Ivaldi examined generalisation of after-effects to a new workspace, they observed substantial differences from the after-effects seen in the trained workspace. When a force field was then applied in the new workspace, subjects performed better if the force field was an intrinsic transformation of the one on which they had trained than if it was identical in extrinsic coordinates. The authors concluded that the motor system had represented the force field in an intrinsic coordinate system.

In this study, we extend the force field learning paradigm to examine the acquisition of predictive coordination between the arms. Forces are generated on the left hand determined by the velocity of the right hand. Based on examples such as the unloading task, we predict that the motor system should adapt to the novel context, maintaining stability of the left arm by predicting and actively opposing the forces applied to the left hand. Following adaptation, we test generalisation to new configurations of the left and right arms to reveal in which coordinate frames the transformation from velocity to force is represented. In Shadmehr and Mussa-Ivaldi's study, changing the arm configuration altered the joint coordinates of both the arm movement that determined the force and the force itself. In the current study we are able to examine the representation of the movement independently of the representation of the force.

To establish the coordinate system in which the movement is represented, we assess the direction of forces generated by the subject's left hand during movements under a new joint configuration of the right arm. If the movement is represented in an intrinsic coordinate frame, movements of the right hand that are identical in Cartesian space will predict different left hand forces under different right arm configurations. Changing the right arm configuration will therefore change the direction of the opposing force generated by the subject to counter the expected force. If the representation of the movement is extrinsic, changing the right arm configuration will have no effect.

Similarly, to establish the coordinate system in which the force on the left hand is represented, we assess the direction of the opposing force generated by the subject

under a new configuration of the left arm. If the force is represented in intrinsic coordinates, changing the left arm configuration will, for a given right hand movement, change the direction of the opposing force; if the representation of the force is extrinsic, the opposing force will not change.

7.2 Methods

After providing written informed consent, 6 right-handed subjects (4 male, 2 female, age 23-32) participated in the experiment. The experimental protocol was approved by a local ethics committee. While seated, subjects grasped with each hand the handle of a vBOT force-generating robotic manipulandum which could be moved with minimal inertia in the horizontal plane (Figure 7-1 A; see Chapter 2 for full details). The subjects' arms were supported in the horizontal plane by slings. The positions and velocities of the hands were calculated online at 1000 Hz. The positions of the hands were displayed as spheres (white; 0.8 cm radius) in the plane of the arm via a reflected rear-projection system; subjects could not see their hand or arm.

7.2.1 Procedure

The experiment consisted of a series of trials in which the subject made out-and-back movements with the right hand to visually-displayed targets, while attempting to keep the left hand still. To begin each trial subjects positioned their left and right hands in home positions displayed as blue cubes (1.6 cm side). A target sphere (magenta; 0.8 cm radius) was then presented at a distance of 10 cm from the right hand home position. Subjects were instructed to move their right hand out to the target and back

to the starting position in a single quick continuous motion. The right manipulandum was passive throughout the experiment and generated minimal resistance to the movement. An auditory signal was given 500 ms after the hand left the home position and subjects were told to time each movement so that they arrived back at the home position coincident with this signal. Subjects were instructed to keep their left hand as still as possible throughout each trial.

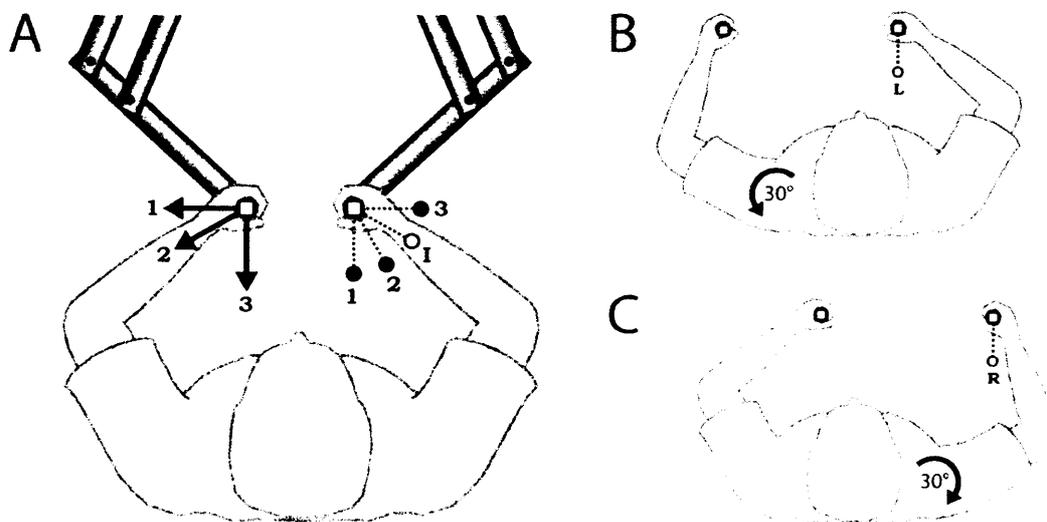


Figure 7-1 Apparatus and task. (A) Posture during the training session. Each trial began with the hands positioned in home positions (white squares) 43 cm in front and 8 cm to either side of the subject's midline. Subjects made an out-and-back movement of their right hand to one of three target locations (1-3, solid circles). Forces were applied to the left hand determined by the motion of the right hand. Arrows illustrate the direction of force generated during a straight-line outward movement to each target. On 'intermediate target' trials, subjects made right hand movements to a fourth target location (I, empty circle). (B) Posture and target location (L, empty circle) on 'left arm rotation' trials. (C) Posture and target location (R, empty circle) on 'right arm rotation' trials.

Subjects completed three consecutive experimental sessions. During the initial familiarisation session (135 trials) subjects practised making right hand movements to

all targets and in all limb configurations they would experience during the experiment (Figure 7-1 A, B & C; see below for details). No forces were applied to the left hand during the familiarisation session, with the exception of occasional ‘catch’ trials, described in detail below, in which the left manipulandum was locked in place to measure any forces generated by the subject.

The familiarisation session was followed by a training session (360 trials) in which subjects were exposed to a novel force field generated by the manipulandum held in the left hand. Subjects made movements to three training targets situated at angles of 180°, 150° and 90° (targets 1, 2 and 3 respectively) from the home position (where 0° is the forward direction parallel to the subject’s mid-sagittal plane; Figure 7-1 A, filled circles). In analogy to studies of unimanual motor learning (e.g. Brashers-Krug et al., 1996), the force applied to the left hand was proportional to the instantaneous velocity of the right hand and directed 90° clockwise to the velocity vector. Specifically, the force was given by,

$$\begin{bmatrix} F_{x_L} \\ F_{y_L} \end{bmatrix} = k \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix} \begin{bmatrix} \dot{x}_R \\ \dot{y}_R \end{bmatrix}$$

where F_{x_L} and F_{y_L} are Cartesian components of the force applied to the left hand (respectively perpendicular and parallel to the subject’s midline), \dot{x}_R and \dot{y}_R are Cartesian components of the velocity of the right hand, and k is 18 Ns/m. The direction of the force on the left hand resulting from an outward movement to each target is illustrated by the arrows in Figure 7-1 A; the force during the return part of the movement is in the opposite direction.

Subjects completed 60 sets of 6 trials: within each set each target was presented twice in a pseudorandom order. Five trials of each set were ‘field’ trials in which the force field was applied to the left hand. The remaining trial was a ‘catch’ trial, in which the manipulandum was locked in position at the start of the trial so that any forces generated by the subject’s left hand could be recorded. To achieve this, the left manipulandum simulated a stiff spring (20 N/cm spring constant) centred on the position of the handle at target onset. The high stiffness of this virtual spring meant that forces generated by the subject’s left hand on the handle were opposed by approximately equal and opposite forces from the manipulandum, resulting in very little movement. Visual feedback of the left hand position was withheld on catch trials.

In order to encourage subjects to maintain control over left hand posture, on field trials a circle (red; initial radius 10 cm) was presented centred on the left home position. Subjects were told to try to keep their left hand within the circle at all times; if the left hand moved outside of the circle during a trial the display flashed red to signal an error. The radius of the circle was adjusted on each trial to match the mean of the peak left hand displacement on all previous field trials.

The training session was followed by a ‘generalisation’ session (225 trials). Two in every set of three trials was a field trial to one of the three training targets. The remaining trial was a catch trial in which forces generated by the subject’s left hand were measured. The catch trials in the generalisation session were of three types (25 trials of each in a pseudorandomized order). On ‘intermediate target’ trials subjects made a right hand movement to a target at 120° from the home position, intermediate

between training targets 2 and 3 (Figure 7-1 A, empty circle). On ‘left rotation’ trials, subjects began the trial by moving their left hand into a new home position. This position was calculated for each subject based on the position of the shoulder and lengths of the upper and lower arm to produce a 30° rotation about the shoulder, with no elbow rotation (Figure 7-1 B). The trial then proceeded as normal with a right hand movement to a target at 180° (the same location as training target 1). On ‘right rotation’ trials, subjects began the trial by moving their right hand to a new home position, again calculated to produce a 30° rotation about the shoulder. A right hand movement was then made to a target at 180° relative to this new home position (Figure 7-1 C).

7.2.2 Analysis

All force, position, and velocity data from each trial were temporally aligned with the start of the right hand movement, defined as the first time the velocity of the right hand towards the target exceeded 2.0 cm/s. To enable comparison between different target directions, force and velocity data were further separated into components parallel and perpendicular to the direction of the target from the right home position. Average time profiles were obtained by calculating mean forces and velocities for each time point across trials.

The direction and magnitude of forces generated by the subject on catch trials were assessed by calculating the left hand force vector at the time of peak right hand velocity towards the target. As the left hand moved very little against the virtual spring (maximum deviation 0.7 cm across all trials and subjects) the system could be considered to be in equilibrium and the force generated by the subject estimated by

rotating the manipulandum force vector through 180°. For each subject, the mean force vector was calculated for each of the three training targets (averaged across catch trials in the second half of the training session) and for each of the three catch trial conditions in the generalisation session. Differences in direction and magnitude between these mean force vectors were assessed using paired-sample t-tests.

7.3 Results

7.3.1 Adaptation over the training session

Subjects made out-and-back movements to targets with their right hand while attempting to keep their left hand still. Right hand movements were predominantly accurate in magnitude, with a peak displacement towards the target of 10.7 cm (1.0 cm s.d. across all subjects and trials), and in direction, with a peak displacement perpendicular to the target direction of 0.9 cm (0.4 cm s.d). Mean movement duration was 678 ms (131 ms s.d.).

The robotic manipulandum applied forces to the subject's left hand proportional to the velocity of the right hand and directed at 90° to the direction of motion. Initially these novel forces caused substantial deviations of the left hand during the right hand movement: the peak displacement of the left hand from the home position on the first movement in the force field was 7.4 ± 1.1 cm (mean \pm s.e. across subjects). However, these deviations reduced substantially in magnitude over the early part of the training session (Figure 7-2 A) falling to an average of 2.0 ± 0.3 cm over the second half of the session. This performance improvement can also be seen in Figure 7-2 B, which shows the velocity of the left hand at the time of peak right hand velocity towards the

target: the time at which the first peak occurs in the force on the left hand. This velocity measure also fell over the course of the session from 26.7 ± 4.2 cm/s on first exposure, to 9.4 ± 1.6 cm/s over the second half of the session, implying that subjects learned to minimise the acceleration caused by the forces on their left arm.

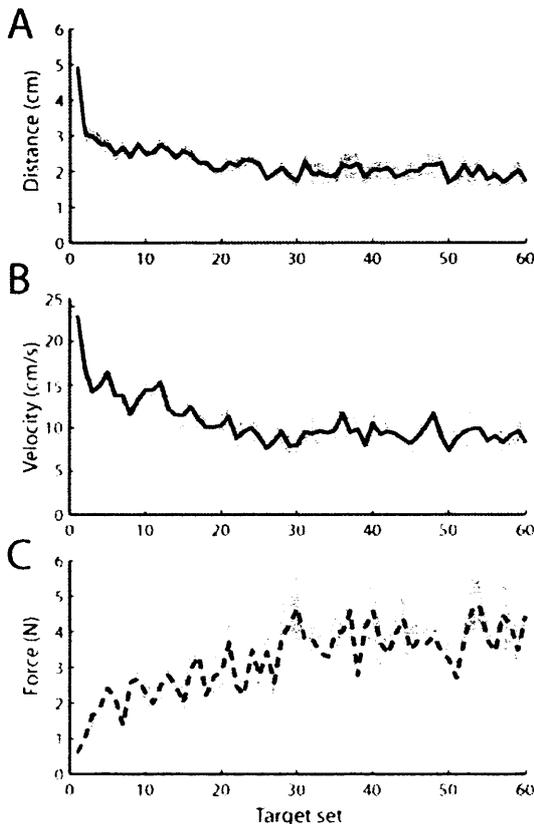


Figure 7-2 Adaptation over the training session. (A) Peak distance of left hand from home position. Mean across each set of six trials, grey area indicates ± 1 SE across subjects. (B) Magnitude of left hand velocity at peak right hand velocity towards target. Mean across each set of six trials, grey area indicates ± 1 SE. (C) Mean magnitude of force generated by left hand on catch trials at peak right hand velocity towards target. Grey area indicates ± 1 SE.

This improvement in stability of the left hand over the training session could result from an adaptation process in which subjects learned to anticipate the force from the manipulandum and generate an opposing force at the left hand to counter it. Alternatively, the improvement could be due to a non-specific co-contraction strategy in which subjects increased the stiffness of the muscles of their left arm to minimise the movement caused by the imposed force. On occasional 'catch' trials, the handle of the left manipulandum was unexpectedly locked in place and forces generated by the

subject's left hand recorded. Prior to the training session only very small forces were recorded on these trials (0.34 ± 0.05 N at peak velocity to target). Over the early part of the training session the forces generated by all subjects on catch trials rapidly increased (Figure 7-2 C), reaching an asymptote at an average of 3.8 ± 0.4 N over the latter half of the session. This suggests that subjects learned to maintain the posture of the left hand by generating opposing forces to counter the expected force from the manipulandum.

7.3.2 Timing and direction of forces

The average time course of forces applied to the left hand by the manipulandum during field trials is shown by the dotted lines in Figure 7-3 A. Movement of the right hand resulted in forces on the left hand perpendicular to the direction of movement and proportional to velocity. Therefore on each trial large forces were generated on the left hand in the direction perpendicular to the target direction (top), and very little force was generated parallel to the direction of the target (bottom). The magnitude of force reflects the velocity profile of the right hand, with an initial peak of 8.9 ± 0.6 N during the outward movement (labelled a), falling to zero as the right hand reaches the target, followed during the return movement by a second force peak (b; 8.8 ± 0.3 N) in the opposite direction to the first.

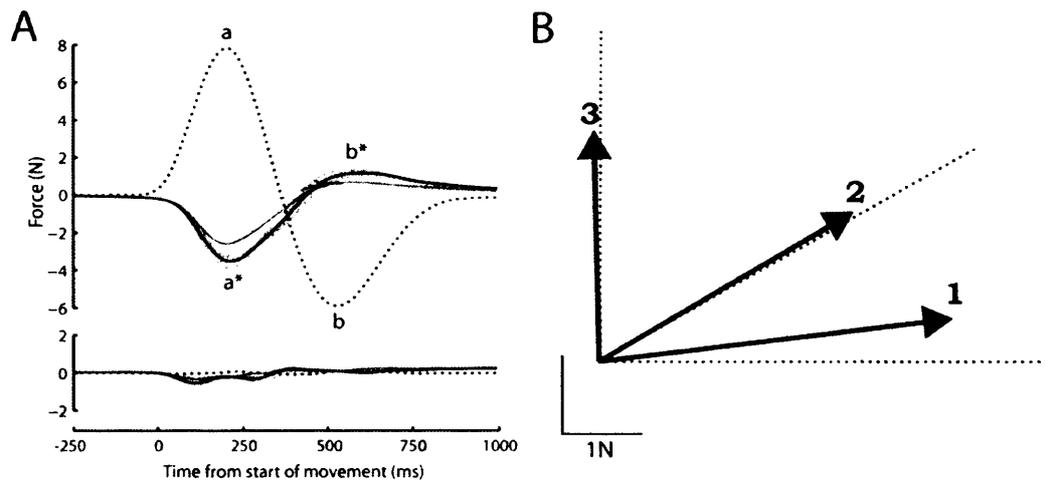


Figure 7-3 Time course and direction of left hand forces during the training session. (A) Mean left hand force perpendicular (top) and parallel (bottom) to the right hand target direction, as a function of time from right hand movement onset. Dotted line shows mean force applied by the manipulandum on field trials. Solid lines show mean forces generated by subjects on the first catch trial (light grey), and averages across catch trials 1-10 (mid-grey), 11-30 (dark grey), and 31-60 (black, grey area represents ± 1 SE across subjects). (B) Arrows indicate mean force vectors generated by subjects on catch trials 31-60 for each training target, with 95% confidence ellipses (grey). Dotted lines indicate direction of mean force vector generated by the manipulandum on field trials for each target.

The black line in Figure 7-3 A shows the average time course of opposing forces generated by subjects on catch trials during the latter half of the training session (i.e. once the initial phase of rapid adaptation was complete). In the perpendicular direction (top), subjects produced opposing forces timed to counter the expected force from the manipulandum. An initial force peak (a^*) was produced on average 231 ms after the start of the right hand movement (77 ms s.d. across all subjects and trials). This closely matched the time of peak velocity to the target, at 248 ms (63 ms, s.d.), when the first maximum in the force from the manipulandum would be expected. Although appropriately timed to counter the expected external force, the magnitude of this peak force (4.0 ± 0.4 N) represents only 46% of the expected force, suggesting

that adaptation to the force field remained incomplete. The return movement of the right hand to the home position generated a second peak in the expected force at 549 ms (98 ms, s.d.) which was again matched by a peak in the opposing force generated by the subject, also at 549 ms (282 ms, s.d.; b*). This second force peak was much more variable in timing than the first, and weaker (2.1 ± 0.3 N, 23% of expected force). This may be because by this stage of the movement sensory feedback from the hand and arm had indicated that the force field was absent.

Very little of the subject-generated force recorded on catch trials was directed parallel to the target direction (Figure 7-3 A bottom), suggesting that the direction as well as the timing of the force was well matched to oppose the expected force from the manipulandum. Solid arrows in Figure 7-3 B indicate, for each target, the mean opposing force vector at peak right hand velocity, i.e. at the time the first peak in force from the manipulandum would be expected. The direction of the opposing force differed significantly between targets ($F_{1,5} > 42.5$, $p < 0.002$), and for each target did not differ significantly from a 180° rotation of the average force applied by the manipulandum on field trials to the same target (dotted lines; $F_{1,5} < 3.5$, $p > 0.12$). This implies that subjects adjusted the direction of the opposing force for each target so as to counter the expected external force.

7.3.3 Generalisation of learning to new targets and postures

Following the training session, subjects completed a further session in which we tested the generalisation of adaptation to targets and arm postures different from those on which they had been trained. On 'intermediate-target' trials subjects made right-hand movements to a target situated at an angle intermediate between training targets

2 and 3. Opposing forces generated by the subject's left hand were measured by locking the left manipulandum in place, as in the catch trials in the training session. Although subjects never experienced the force field during movements to this target, after training they nonetheless generated substantial forces with the left hand. The mean opposing force on these trials ($2.9 \text{ N} \pm 0.2 \text{ N}$) did not differ significantly in magnitude from the mean opposing force for adjacent targets in the latter half of the training session ($3.3 \text{ N} \pm 0.4 \text{ N}$; $F_{1,5} = 3.5$, $p = 0.12$). Had the force field been active on these trials, right hand movements towards the target (at 120°) would have resulted in forces on the left hand at an angle of 210° , requiring a 30° force from the subject to counter it. The actual direction of the mean opposing force vector on these trials ($35^\circ \pm 4^\circ$ at peak right hand velocity; Figure 7-4 A, empty arrow) was not significantly different from this predicted direction (dashed line; $F_{1,5} = 1.9$, $p = 0.22$), and differed significantly from the direction of forces generated on training targets 2 and 3 ($F_{1,5} > 47.4$, $p < 0.001$). This suggests that adaptation to the force field was not merely local to the training target movements, but that subjects had instead learned a mapping between right hand movement and left hand force which could generalise to new movement directions.

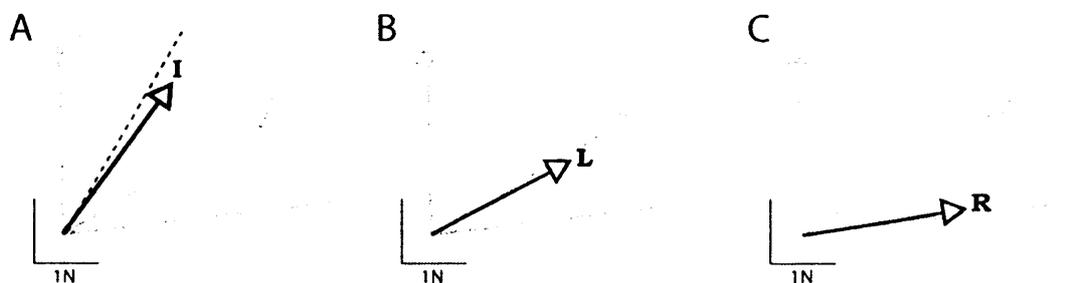


Figure 7-4 Generalisation of learning. Mean force vectors (empty arrows) generated by subjects on generalisation trials, with 95% confidence ellipses. Training target forces are re-plotted for comparison (solid arrows). (A) Intermediate target trials. Dashed line indicates 30° . (B) Left arm rotation trials. (C) Right arm rotation trials.

On 'left arm rotation' catch trials, subjects moved their left hand to a new position corresponding to a 30° rotation at the shoulder (Figure 7-1 B) prior to making a right hand movement to target 1. Again, despite having never experienced the force field in this posture, subjects generated substantial opposing forces with the left hand (2.4 ± 0.6 N), although the magnitude was significantly reduced compared to movements to the same target during the training session (4.5 ± 0.5 N; $F_{1,5} = 53.2$, $p < 0.001$). The direction of force we expect subjects to generate on these trials depends on the way in which the motor system represents the structure of the force field. If the force applied to the left hand is represented in an extrinsic coordinate frame, then subjects should generate an opposing force in the same Cartesian direction as on movements to the same target in the training session. However, if subjects represent the force in an intrinsic reference frame related to the muscles and joints of the arm, for instance as joint torques, then the opposing force should remain constant relative to the joints, and hence be rotated 30° clockwise. The mean opposing force direction on these trials ($59^\circ \pm 7^\circ$; Figure 7-4 B, empty arrow) differed significantly from the opposing force to the same target in the training session ($83^\circ \pm 3^\circ$; $F_{1,5} = 12.0$, $p = 0.018$), and did not differ from a 30° clockwise rotation of that force ($F_{1,5} = 1.0$, $p = 0.37$). This implies that the force on the left hand is represented in intrinsic coordinates.

On 'right arm rotation' catch trials, subjects moved their right hand to a new position corresponding to a 30° rotation at the shoulder (Figure 7-1 C) prior to making a right hand movement to a target at 180°. As with the 'left arm rotation' trials, opposing forces generated by the left hand were substantial (2.5 ± 0.5 N), but less than those produced during the training session. Again, the force we expect subjects to generate on these trials depends on the way in which the motor system represents the force

field. The required movement of the right hand on these trials was identical in Cartesian coordinates to a movement to target 1 in the training session. However, because of the shoulder rotation, the movement required the same changes to the joint angles of the arm as a movement to target 2 in the training session. Therefore, if the right arm movement is represented in extrinsic space, subjects should produce the same opposing force as for training target 1, and if the movement is represented in intrinsic space the opposing force should be the same as for training target 2. The mean opposing force direction on these trials ($81^\circ \pm 2^\circ$; Figure 7-4 C, empty arrow) differed significantly from that generated on movements to target 2 in the training session ($59^\circ \pm 2^\circ$; $F_{1,5} = 170$, $p < 0.001$), and did not differ from the force generated on movements to training target 1 ($F_{1,5} = 0.6$, $p = 0.46$). This result implies that the movement of the right hand is represented in extrinsic coordinates.

7.4 Discussion

Previous studies of motor learning have examined adaptation to novel forces applied to a moving hand. If the applied forces are determined by some parameter of the state of the hand, such as its velocity, then the motor system is able to minimise the disturbance to the hand trajectory by producing opposing forces to counter the external force. On short timescales, this kind of adaptation may allow the motor system to maintain desired movement trajectories in novel contexts, such as when holding a new object in the hand. Over longer time periods, it may allow the motor system to compensate for developmental changes in the length of limb segments and the size and strength of muscles.

Moving a limb or limb segment generates a perturbation that can have effects throughout the body, due to interaction forces arising from the torques at the joints (Gahery and Massion, 1981; Massion, 1992). When manipulating an object between the hands, activity of one hand will often result in a force on the other. In both cases, the motor system must actively generate opposing forces to maintain postural stability. In this study we have investigated adaptation to a novel relationship between movement of the right hand and force on the left. As with unimanual learning, the novel forces initially produced large deviations of hand position, but these errors decreased during an initial period of rapid adaptation, as subjects learned to produce appropriate forces to oppose the external perturbation and maintain the stability of the left hand. However, at the end of the initial learning phase these opposing forces had not reached sufficient magnitude to fully counter the external force and the stability of the hand had not returned to pre-exposure levels. This finding is qualitatively similar to the results of unimanual studies, in which movements in the force field are generally found not to return fully to the pre-exposure trajectory.

In unimanual learning, adaptation to a force field generalises to new movements on which forces have not previously been experienced. For example, subjects trained to make reaching movements in a velocity-dependent force field subsequently show transfer of learning to circular movements in the same workspace (Conditt et al., 1997), and to reaching movements of different velocities and amplitudes (Goodbody and Wolpert, 1998). If subjects adapt to a force field for one direction of reaching movement, generalisation is observed on movements to neighbouring directions, decaying with angular distance from the trained direction (Gandolfo et al., 1996). These results imply that adaptation does not simply consist of learning a stereotyped

pattern of muscle activations for each target, but rather involves the development of a more general representation of the force field. Similar generalisation to neighbouring directions is observed for adaptation to novel inertial loads (Sainburg et al., 1999). In the current study, learning was also found to generalise to a new movement direction in which the force field had not been experienced. This suggests that the motor system had developed a model of the force field that could be used to predict the expected force on the left hand based on the parameters of the planned right hand movement.

Shadmehr and Mussa-Ivaldi (1994) showed that unimanual force field learning generalises to new joint configurations of the arm. Based on the pattern of generalisation to the new arm configuration, they concluded that the force field was represented by the motor system in an intrinsic reference frame, related to the velocities and torques at the joints. In the current study, we also observed generalisation of learning to new joint configurations of both the left and right arms. However, an analysis of the forces generated by subjects in these new arm postures revealed a dissociation in representation between the movement of the right hand and the force on the left.

When the left arm was rotated about the shoulder prior to a right hand movement, the direction of the opposing forces generated by the subject remained constant relative to the joints of the arm. This implies that the motor system generates a prediction of the expected consequences of the movement in intrinsic coordinates, for instance as expected joint torques. This was the case despite the fact that the force field generated by the manipulandum was translation invariant in Cartesian coordinates, and is consistent with the results for unimanual learning. In contrast, when the right arm was

rotated at the shoulder prior to movement, the direction of the opposing force generated by the subject was the same as on unrotated movements to the same location in Cartesian coordinates. This was the case even though the movements involved substantially different joint velocities, and implies that the motor system generates a prediction of the expected force based on a representation of the movement in an extrinsic coordinate frame.

Generalisation in extrinsic coordinates has previously been observed in visuomotor learning. In studies of visuomotor learning, the normal relationship between the actual position of the hand and its visual location is altered, for instance by prism glasses (Helmholtz, 1867; Welch, 1985), by a novel mapping between hand position and a screen cursor (Cunningham, 1989), or in virtual reality (Ghahramani et al., 1996). As with force field learning, the visual perturbation initially causes movement errors which decay with practice, and after-effects are observed if the perturbation is subsequently removed. Visuomotor learning has been shown to generalise to neighbouring hand positions (Ghahramani et al., 1996), and joint configurations (Baraduc and Wolpert, 2002), implying that the motor system develops a model of the transformation, as with novel dynamics. Krakauer et al. (2000) trained subjects to make reaching movements to a single target under a 60° rotation of visual feedback, and then tested generalisation of learning to the same target in a new arm configuration. Subjects produced movements in the same direction across arm configurations, even though this involved producing substantially different joint rotations and muscle activations. This result implies that the motor system represented the visuomotor perturbation in an extrinsic coordinate system.

In combination with the findings of Krakauer et al., the results of the current study could be taken to imply a dissociation in representation between kinematic and dynamic planning, with trajectories represented by the motor system in extrinsic coordinates and forces represented in intrinsic coordinates. If this is the case, it should also be reflected in the generalisation of unimanual force field learning. While the pattern of generalisation observed by Shadmehr and Mussa-Ivaldi appears to be consistent with an intrinsic representation both of movement and force, their study did not explicitly test the possibility of an extrinsic representation of movement combined with an intrinsic representation of force, and further investigation will be required to rule this out. Alternatively, the findings of the current study may relate specifically to learning of novel interactions between parts of the body, which could involve a mechanism partially or wholly independent of that involved in compensating for novel dynamics within a limb.

CHAPTER 8: EVIDENCE FOR SENSORY PREDICTION DEFICITS IN SCHIZOPHRENIA

8.1 Introduction

Predictive mechanisms may play a range of key roles in human sensory and motor systems (Wolpert and Flanagan, 2001; Davidson and Wolpert, 2005). The previous chapter investigated the role of prediction in maintaining control of posture. Earlier chapters have demonstrated predictive filtering in the tactile sensory system: a process in which the sensory consequences of action are anticipated and used to attenuate the sensory input. A further role of predictive mechanisms may be to identify movements as either self- or externally-generated. If the predicted sensory input associated with a movement matches the actual sensory input, the movement is labelled as one's own. However, if the predicted and actual sensory inputs are discordant, as when one's arm is passively moved by someone else, the movement is labelled as externally-generated.

If the mechanism that predicts the sensory consequences of action were dysfunctional and produced inaccurate predictions, this could cause the misattribution of self-generated actions as externally-generated (Frith, 1992; Frith et al., 2000). Many patients with schizophrenia demonstrate just such a deficit, in which self-generated

actions are experienced as being under outside control or self-generated speech is misperceived as an auditory hallucination (Schneider, 1959).

Both psychophysical and neuroimaging studies support the view that self-monitoring is dysfunctional in schizophrenia. As discussed in Chapter 1, tactile stimulation is generally perceived as less ticklish when it is self-generated (Claxton, 1975), but this is not the case for patients who suffer from auditory hallucinations or delusions of control (Blakemore et al., 2000), suggesting a failure to distinguish between self- and externally-generated sensations. A similar failure may underlie hallucinations: an fMRI study has shown that both Broca's area and primary auditory cortex are activated during auditory hallucinations (Dierks et al., 1999). Broca's area is associated with speech production, but inner speech does not activate primary auditory cortex in healthy subjects (McGuire et al., 1996). The imaging results therefore support the view that auditory hallucinations in schizophrenia result from a dysfunction in the processing of self-generated speech. Such a dysfunction is also suggested by an EEG study in which evoked response potentials (ERPs) to speech sounds were measured (Ford et al., 2001). Healthy subjects showed a reduction in the N1 component of the ERP when the speech was self-generated, but patients with schizophrenia did not.

In this chapter, we directly test the hypothesis that patients with schizophrenia are defective in predicting the sensory consequences of their actions. In Chapter 3 it was shown that while healthy subjects are accurate at reproducing a target force when using a joystick, they significantly overestimate the force required when it is directly self-generated. This occurs because self-generated forces are perceived as weaker

than externally-generated forces of the same magnitude. The results of Chapter 6 support the theory that this tactile attenuation results from a predictive mechanism, in which the sensory consequences of movement are anticipated and partially removed from the sensory input. Our hypothesis was that patients with a diagnosis of schizophrenia would be more accurate in reproducing an external force compared to healthy controls. This increased accuracy would reflect the failure of the normal sensory attenuation mechanism due to a dysfunctional sensory predictive process. In contrast, reproducing the force indirectly via the joystick does not engage predictive mechanisms (Blakemore et al., 1998b) and so we anticipated that both patients and controls should be accurate at this task.

8.2 Methods

Forty subjects, 20 patients and 20 healthy volunteers, participated after providing informed consent. The patients all had a diagnosis of schizophrenia according to DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). The experimental protocols were approved by a local ethics board. The experimental apparatus was identical to that used in the second experiment in Chapter 3. Each subject rested his or her left index finger in a moulded support beneath the lever of a torque motor. On each trial the torque motor generated a target force between 0.5 and 2.75 N for 3 seconds (80 trials in a pseudo-randomized order). Subjects were then required to reproduce the force they had just experienced, either by pressing directly with the index finger of their right hand or indirectly by using a joystick that controlled the torque motor. Each subject participated in both conditions

in a counterbalanced order. The applied forces were measured using a force sensor mounted in the lever of the torque motor.

8.3 Results

The 20 patients and 20 healthy control subjects were well matched for age (patients $M = 36.4$, $SD = 13.4$; control $M = 35.9$, $SD = 14.0$), gender (12 male, 8 female in each group), handedness (all right-handed) and premorbid IQ (National Adult Reading Test (Nelson, 1991); patients $M = 110$, $SD = 8$; control $M = 114$, $SD = 6$). All except one of the patients were treated with antipsychotic medication but the patients were nonetheless moderately symptomatic with a mean score of 36 ($SD = 11$) on the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). Most patients had prominent positive symptoms: 16 subjects scoring 4 or more points on BPRS items related to suspiciousness or hallucinatory behaviour. On initial analysis of data, two participants (one patient and one healthy subject) were found to have produced matching forces that did not significantly correlate with the corresponding target forces in either task ($r^2 < 0.04$; $p > 0.10$). We concluded that they had not properly understood the instructions and removed their data from further analysis.

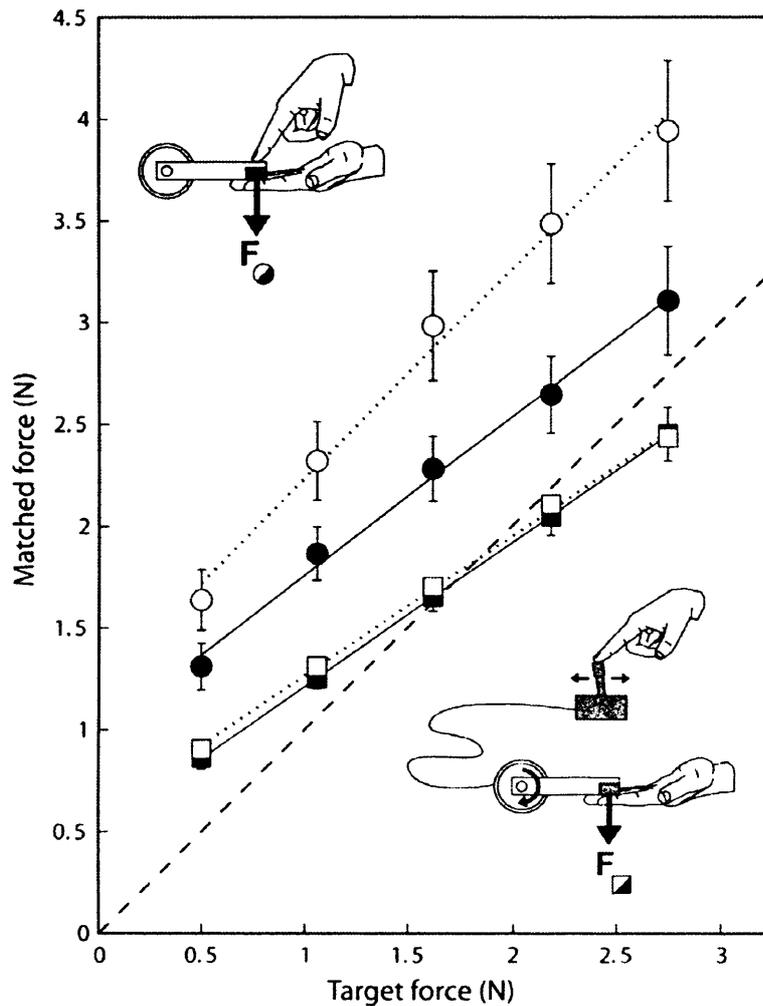


Figure 8-1 Matching force generated using the right index finger (circles) and joystick (squares) as a function of the externally-generated target force, for patients (filled shapes) and healthy volunteers (empty shapes). Error bars indicate ± 1 SE across participants. Dashed line represents perfect performance.

As in the previous studies in this thesis, participants consistently applied a greater force when using their right index finger to match the externally applied target force. This results from an attenuation of the self-generated sensation that causes subjects to underestimate how much force they are applying. To quantify this attenuation in the patient and control groups, we calculated the percentage of the matching force by which the matching force exceeded the target force. The patients were more accurate at the task showing 27.5% attenuation (Figure 8-1, solid circles) compared to 43.5%

in the control group (empty circles). When subjects matched the target force using the joystick, both patients and healthy volunteers reproduced the original force much more accurately (squares). A repeated measures two-way ANOVA (patients vs. control group and direct vs. joystick) of the mean matching force normalised by the mean target force showed a significant interaction ($F_{1,36} = 4.88$; $p = 0.034$). This interaction arose because the patients displayed significantly less attenuation in the direct force-generation task ($F_{1,36} = 4.71$; $p = 0.037$) but no significant difference from the healthy controls in the joystick task ($F_{1,36} = 0.16$; $p = 0.69$).

8.4 Discussion

The results of this study show that self-generated forces were attenuated less in the patient group than controls, suggesting a dysfunction in the patients' ability to predict the sensory consequences of their actions. Schizophrenia is characterised by a broad range of cognitive and behavioural abnormalities which can lead to non-specific performance deficits in many different tasks. In the current study, however, the patient group actually performed better on the experimental task than healthy controls, in that they were more accurate in reproducing the target forces presented to them. The present study therefore provides strong evidence for a dysfunctional predictive mechanism in schizophrenia.

Although most of the patients were treated with antipsychotic medication, the absence of any difference between patients and healthy volunteers in the joystick matching task suggests that there is no systematic effect of medication upon motor

performance. The similarity in performance of patients and controls in the motor aspects of the experiment is typical of the common observation that schizophrenia does not involve major abnormalities in motor performance. Given the range of proposed roles for predictive mechanisms in motor control, this suggests that the deficit in schizophrenia must be more specific than a general breakdown of prediction. Within the internal model framework, the forward dynamic model is responsible for predicting changes to the state of the body and the environment on the basis of planned motor commands. This prediction is used for anticipatory motor control: for instance to generate appropriate grip forces (Johansson and Cole, 1992; Flanagan and Wing, 1997) and to maintain posture (see Chapter 7). The forward sensory model uses this predicted change to the state to generate a prediction of the sensory consequences of the action. It is this sensory prediction that is implicated in both sensory attenuation and identification of self-action, and so the current results suggest that schizophrenia may be associated with a specific deficit in this mechanism.

CHAPTER 9: EFFERENT COPY SIGNALS USED IN TACTILE SENSORY ATTENUATION ARISE UPSTREAM OF PRIMARY MOTOR CORTEX

9.1 Introduction

In previous chapters, we have found evidence for a predictive mechanism underlying tactile sensory attenuation. Such a mechanism generates a prediction of the expected sensory consequences of one's actions based on an efference copy of the motor command (Sperry, 1950; von Holst and Mittelstaedt, 1950) and a forward internal model of the environment (Wolpert et al., 1995; Miall and Wolpert, 1996). The incoming sensory stream is attenuated on the basis of this prediction, reducing the perceived intensity of self-generated sensations. This prediction may also be used to decide whether an action is self- or externally-generated, by comparing the predicted and actual sensory input. The aim of this study is to investigate the stage of neural processing at which the efference copy of the motor command is generated. We assess tactile attenuation before and after administration of a novel rTMS protocol, theta-burst stimulation (TBS), over primary motor cortex (MI).

TBS has recently been shown to produce long lasting effects on the excitability of motor cortex (Huang et al., 2005), observed as changes to the amplitude of motor evoked potentials (MEPs) elicited by single pulses of TMS. Two protocols of TBS are

used in this study: continuous TBS stimulation (cTBS) has been shown to decrease MEP amplitudes for up to 40 minutes following stimulation, whereas intermittent stimulation (iTBS) induces a long lasting increase in MEP amplitudes (see Chapter 2 for more details).

If efference copy signals arise upstream of MI, then an increase or decrease in the excitability of MI will produce a mismatch between the efference copy and the actual motor command sent to the muscles. This will create a discrepancy between the predicted sensory input, based on efference copy, and the actual sensory input related to the motor activity (Figure 9-1 A illustrates the effects of cTBS under this model). This kind of discrepancy is usually found when a body part is moved passively by an external force, so the action may be misinterpreted as having an externally-generated component. The normal attenuation of self-generated sensations is therefore likely to be reduced in this situation. In contrast, if the efference copy signal is a copy of the motor output generated by MI, then changes to the excitability of MI should affect the efference copy and the actual motor command equally, and no discrepancy will result (Figure 9-1 B). We would therefore not expect to see any affect on sensory attenuation.

In this study, tactile attenuation is assessed using the force-matching task (first described in Chapter 3) prior to and following TBS over left MI. Attenuation is assessed when the right index finger applies a force to the left index finger, as in previous chapters, and also with the hands reversed. If efference copy signals arise upstream of MI, a mismatch should be generated between efference copy and motor

commands sent to the contralateral side of the body. An effect on tactile attenuation should therefore be seen only for sensations produced by activity of the right hand.

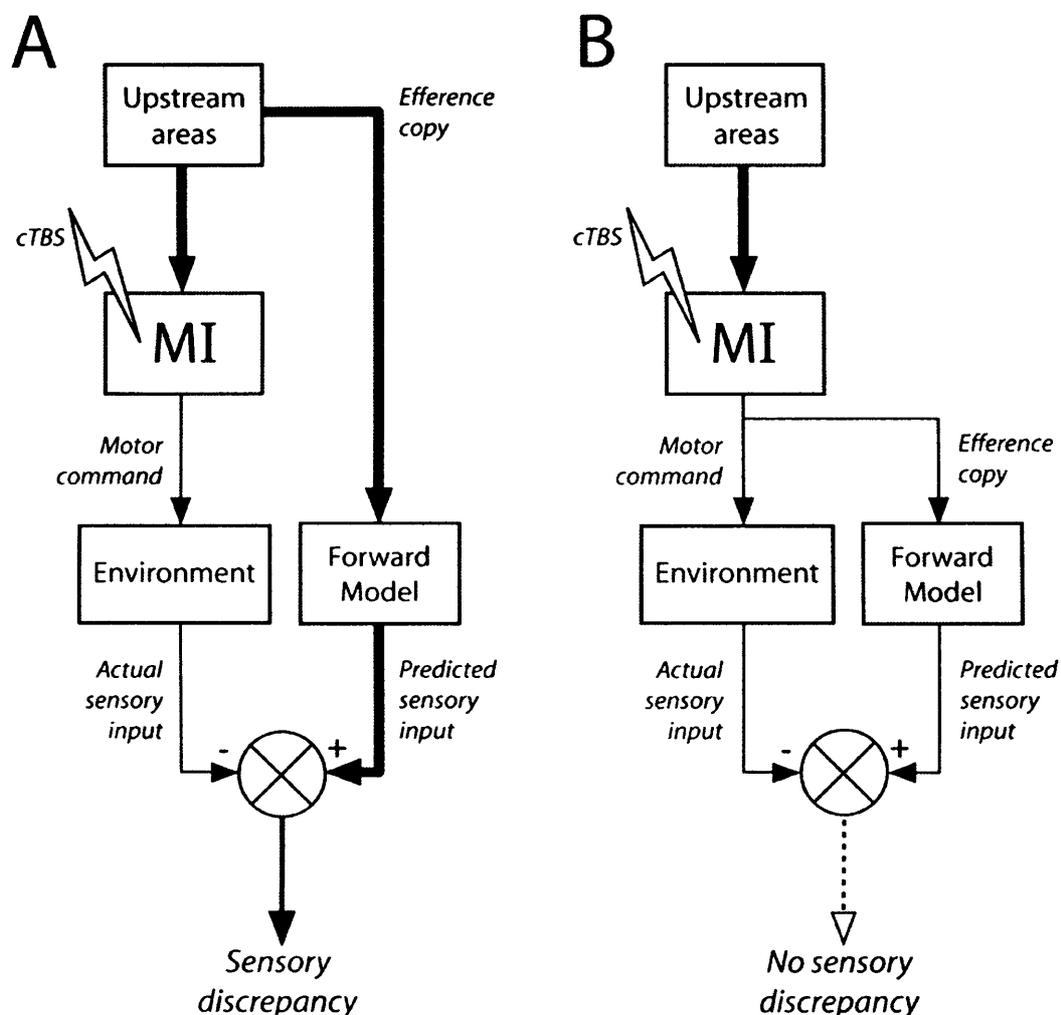


Figure 9-1 Two alternative models of the effect of cTBS on sensory prediction. (A) A decrease in excitability of MI induced by cTBS results in a weakening of the motor command signal. If efference copy is generated in motor planning areas upstream of MI, this will result in a discrepancy between predicted and actual sensory inputs, which may reduce the certainty with which an action can be identified as self-generated. (B) If efference copy is generated in or downstream of MI, both the efference copy and the motor command will be weakened by cTBS, and there will be no sensory discrepancy.

9.2 Methods

Sixteen healthy right-handed subjects (9 male, 7 female; age 20–31) participated in the experiments. They were naive to the specific purpose of the experiment. All participants gave informed consent. The study was conducted in accordance with the Declaration of Helsinki and the methodology was approved by the local ethics committee.

9.2.1 Experimental procedure

The force-matching task was similar to that described in previous chapters, but whereas previously the right hand has always been used to generate the force, in this study the matching task was also performed with the hands reversed. Subjects rested either their left or right index finger in a moulded support. A force sensor (Nano-17 6-axis F/T sensor, ATI Inc.) rested on the tip of the finger at the end of a lever attached to a torque motor (Maxon Motors UK, Model RE35; geared in ratio 1:4.8). To start each trial the torque motor applied one of five constant target forces in the range 1 to 3 N to the tip of the subject's index finger for 3 s. Following an auditory go-signal, subjects were then required to reproduce the force they had just experienced by pressing with their opposite index finger on the resting finger through the force sensor. After 3 s an auditory stop-signal indicated the end of the trial.

Prior to stimulation, subjects completed two blocks of 20 trials in a pseudorandom order: one block in which the left finger applied forces to the right and one block in which the right finger applied forces to the left. Subjects then received either a 20 second train of continuous TBS (8 subjects) or a 190 second train of intermittent TBS

(8 subjects) over the left primary motor cortex. After TBS, subjects sat with their hands completely relaxed for 10 min. Subjects then completed two further blocks of 20 trials in the same order as before. Each block took 7.5 min to complete.

The matching force level generated by the subject was calculated for each trial by taking the mean force recorded by the force sensor between 2000 and 2500 ms after the go-signal. As in previous chapters, the attenuation on each trial was then calculated as the percentage of the matching force level by which it exceeded the target force level. This reflects the percentage of the matching force that is not perceived. This measure was averaged across trials to give the mean attenuation for each subject and condition.

To investigate the effects of continuous and intermittent TBS on attenuation two separate 2 x 2 repeated-measures ANOVAs were performed (pre- vs. post-TBS; left vs. right finger active). Within-subject post-hoc comparisons were made using paired t-tests.

9.2.2 TBS procedure

Prior to TBS stimulation, Focal Transcranial Magnetic Stimulation (TMS) with a figure-of-eight coil (Magstim Comp., Dyfed, UK; 7 cm diameter coils) was used to find the optimal focus for the stimulation. Magnetic evoked potentials were elicited in the first dorsal interosseous muscle of the relaxed right hand. The coil was kept tangential to the head. The orientation was approximately perpendicular to the central sulcus of the left cortex (45 degrees from the anterior-posterior axis) with the handle pointing posteriorly. The magnetic evoked potentials were recorded with surface

electrodes. First, the optimal spot on the skull was determined as the cortical site where muscle responses could be evoked with the lowest stimulator output intensity. This position was marked with ink to allow an exact re-positioning of the coil throughout the experiment. After the optimal focus was found, subjects were asked to produce a tonic pinch grip between the index finger and thumb. The active motor threshold was defined as the stimulator intensity that evoked 5 muscle responses out of 10 consecutive single TMS stimulations.

Cortex stimulation was carried out using the recently developed theta-burst stimulation protocol in which trains of TMS are delivered in bursts of 3 pulses at 50 Hz (Huang and Rothwell, 2004). The bursts were either delivered continuously at a rate of 5 Hz (200 ms gap between each burst) at 80% active motor threshold over a 20 s period (continuous TBS; cTBS) or in a 2 s train repeated every 10 s for a total of 190 s (intermittent TBS; iTBS). These stimulation protocols are known to either depress (cTBS) or increase (iTBS) motor cortex excitability for up to 40 minutes as shown in a significant reduction or enhancement of MEP amplitudes (Huang et al., 2005). This change in cortical excitability is maximal approximately 10 min after TBS, so subjects were made to rest for 10 min following the end of stimulation prior to starting the post-TBS experimental block.

9.3 Results

In the pre-TBS blocks, as in previous chapters, all participants consistently overestimated the force required to reproduce the target force (Figures 9-2 & 9-3).

Significant attenuation was observed pre-TBS in both groups whether the matching force was generated with the left or right finger (28% mean attenuation; $F_{1,7} > 28.4$, $p < 0.002$). There was no significant difference in attenuation in either group between generating the force with the left finger on the right or vice-versa ($F_{1,7} < 1.2$, $p > 0.31$).

In the group that received continuous TBS, a significant reduction in attenuation was observed post-stimulation when the matching force was generated with the finger contralateral to stimulation (pre-TBS attenuation: 30%, post-TBS: 18%; $F_{1,7} = 15.4$, $p = 0.0057$; Figure 9-2 A right). There was no significant effect of stimulation on attenuation when the ipsilateral finger generated the force (pre: 27%, post: 26%; $F_{1,7} = 0.15$, $p = 0.71$; Figure 9-2 A left), and the specificity of the effect to the contralateral side was confirmed by a significant interaction term ($F_{1,7} = 6.62$, $p = 0.037$).

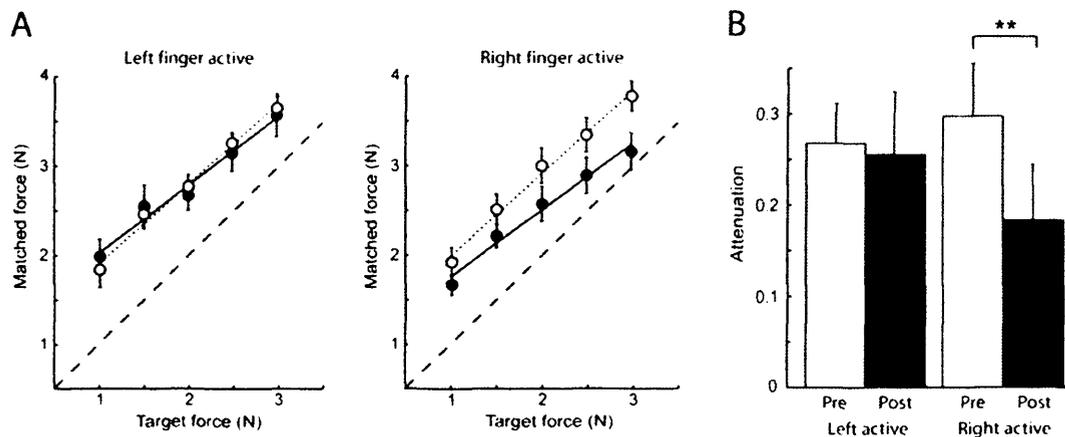


Figure 9-2 Effects of continuous TBS on attenuation. (A) Matching force generated with left or right index finger before (empty circles) and after (filled circles) cTBS over left MI, as a function of the externally-generated target force. Error bars indicate ± 1 SE across subjects. Dashed line represents perfect performance. (B) Mean level of attenuation pre- and post-cTBS with left or right hand active (** indicates $p < 0.01$).

No significant effects of intermittent TBS were found for either the left or right finger ($F_{1,7} < 0.54$, $p > 0.48$; Figure 9-3), and there was no significant interaction ($F_{1,7} = 0.03$, $p = 0.86$). Intermittent TBS, therefore, did not alter the amount of attenuation seen during the task regardless of which finger generated the matching force.

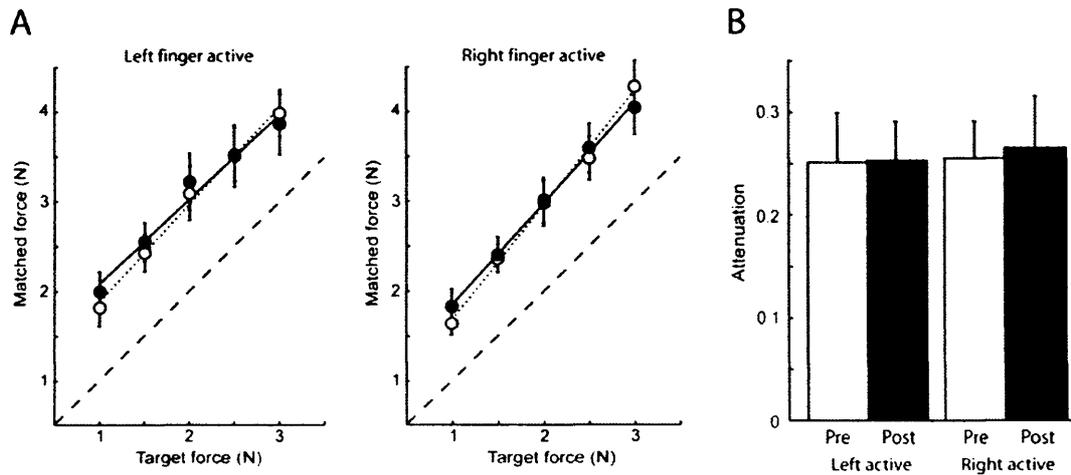


Figure 9-3 Effects of intermittent TBS on attenuation. (A) Matching force generated with left or right index finger before (empty circles) and after (filled circles) iTBS over left MI, as a function of the externally-generated target force. Error bars indicate ± 1 SE across subjects. Dashed line represents perfect performance. (B) Mean level of attenuation pre- and post-iTBS with left or right hand active.

9.4 Discussion

In this study we have shown that application of continuous theta-burst stimulation (cTBS) over the primary motor cortex reduces the attenuation of self-generated sensation. This was observed as an improved ability to reproduce an externally-applied force following cTBS. We controlled for non-specific effects of the stimulation by assessing attenuation both when the finger contralateral to the stimulation generated the force, and when it was the passive finger to which force was

applied. Only in the former condition is a motor command generated by the affected hemisphere. Therefore, the situation in which the finger ipsilateral to the stimulation site generates the matching force serves as a control condition and our experiment does not require sham or control-site TMS. The fact that improvement in the task was only observed when the contralateral finger generated the force excludes the possibility that attenuation occurred because of impaired sensory processing due to current spread to primary sensory areas. Moreover, the results can not be interpreted as a diffuse ‘motor impairment’ or weakness resulting from the stimulation, as subjects post-TBS were still able to generate forces as high as 3 N to match the largest target forces and yet showed reduced attenuation at all levels of the target force.

Although intermittent TBS has been shown to facilitate MI, we did not see any change in attenuation in this condition. However, whereas the effects of cTBS have been shown to be robust across subjects and long lasting, the effects of iTBS show greater variability across subjects and often only last a short time after stimulation (Huang et al., 2005).

The reduced attenuation observed in the cTBS group suggests that efference copy signals arise upstream of MI, and that the change in the excitability of MI produces a mismatch between the actual motor command output and the efference copy. This mismatch reduces the confidence with which the sensation of force in the passive finger can be attributed to self-action, and so the level of attenuation is reduced. A similar reduction in attenuation was seen in Chapter 4, when a spatial separation between active and passive fingers made the context less consistent with self-generation. This interpretation is also consistent with the results of the previous

chapter, in which patients with schizophrenia were found to have a significantly lower level of attenuation than age-matched healthy control subjects. In these patients, the discrepancy between predicted and actual sensory input may arise from a dysfunction in the predictive system.

In Chapter 4, changing the gain between the force generated by the active finger and the force transmitted to the passive finger was found to have no effect on attenuation. Changing the gain will initially create a discrepancy between the actual sensory input and the sensory input predicted on the basis of efference copy, as in the current study. However, unlike the effects of cTBS, the discrepancy is confined to the sensory input from the passive finger: the active finger generates the intended force and receives the expected sensory input. This kind of discrepancy may simply indicate that the force is being applied through an object with unexpected properties. The current context estimate can then be updated so that the predicted sensory input matches the actual sensory input, and the normal level of attenuation is maintained. In contrast, if cTBS reduces the output force without affecting efference copy, it will result in a sensory discrepancy in both active and passive fingers. This cannot be accounted for by the properties of the object between the fingers, and may instead reduce the confidence with which the sensations are attributed to self-action.

The conclusion that efference copy signals do not arise in primary motor cortex is consistent with a previous study in which muscle twitches were elicited by TMS over MI (Chronicle and Glover, 2003). Ticklish sensations produced by the TMS-induced movements were found to be just as intense as when the same stimuli were generated by the experimenter. The fact that this self-generated tickle did not undergo normal

predictive attenuation (Weiskrantz et al., 1971; Claxton, 1975) suggests that TMS of MI generates a motor output but not an efference copy.

Our results are also consistent with a study which investigated sensory suppression of muscle twitches induced by TMS in the right index finger (Haggard and Whitford, 2004). The perceived intensity of the muscle twitches was reduced during active movement of the finger, in agreement with the widespread finding of sensory gating in a moving body part (Angel and Malenka, 1982; Chapman et al., 1987). However, a TMS pulse delivered to the supplementary motor area (SMA) 10 ms prior to the stimulus pulse was found to reduce the sensory gating caused by the movement. The authors suggested that this reduction in sensory suppression reflects a disruption of an efference copy signal generated in SMA. This hypothesis is consistent with the current finding that the efference copy signal involved in predictive attenuation is generated upstream of MI. However, as discussed in Chapter 1, the role of efference copy in movement-related gating is currently unclear, as similar suppression is also seen during passive movements (Milne et al., 1988; Williams and Chapman, 2002).

Although TBS was carefully focused on the hand area of MI we cannot entirely exclude the possibility that the observed results are due to ‘remote effects’ of the stimulation. Recent studies show that rTMS over MI can activate a large cortical network including basal ganglia, premotor and cerebellar regions (Bestmann et al., 2004). These remote effects could conceivably cause a weakening of predictive mechanisms, for example by disrupting activity in the cerebellum, which has been implicated in the generation of sensory predictions (see Chapter 10).

In summary we show an improvement in the perception of self-generated tactile stimuli following continuous theta-burst stimulation of primary motor cortex. This effect was only observed when the stimulus was generated with the finger contralateral to the stimulated motor cortex and only when an inhibitory TBS protocol was used. We propose that TBS over MI interferes with the mechanism of sensory attenuation by disrupting motor output without altering efference copy, which we therefore conclude arises upstream of MI.

CHAPTER 10: DISCUSSION

10.1 Summary of Experimental Results

The previous chapters have described a series of psychophysical and behavioural studies investigating the perception of self-generated touch. The results demonstrate that self-generated tactile sensations are attenuated by a predictive mechanism. The attenuation is temporally tuned to the expected time of contact and modulated by the certainty with which a sensation can be attributed to self-action. The underlying mechanism may predict the sensory consequences of action based on an internal model of the environment and an efference copy of the motor command. We have found evidence to suggest that this efference copy arises upstream of primary motor cortex. Patients with schizophrenia were found to show less attenuation than healthy controls, consistent with an underlying deficit in sensory prediction.

Chapter 3 showed that when subjects were instructed to reproduce an external force felt on their finger by pressing with a finger of the other hand, they consistently overestimated the force required. However, subjects were accurate at the task when they reproduced the force indirectly via a joystick. These results imply that constant forces are perceived as weaker when they are self-generated. We showed that this attenuation of self-generated sensation could produce rapid escalation of force between subjects, potentially related to the escalation of real-world physical conflicts.

Chapter 4 extended the force-matching paradigm to investigate some of the factors that influence attenuation. In this study subjects reproduced target forces applied to their finger by pressing through a virtual object, simulated by two torque motors. As in the previous study, subjects overestimated the force required, implying attenuation of the self-generated sensation. When a lateral spatial separation was introduced between the fingers, the level of attenuation was reduced. This suggests that a spatial co-alignment between force production and sensation may be one of the factors by which sensations are identified as self-generated. In contrast, doubling or halving the force transmitted from the active finger to the passive finger had no effect on attenuation in the passive finger. This implies that an equal magnitude of force production and sensation is not an important factor in identifying self-generated sensations.

Chapter 5 investigated the time course of tactile attenuation. The perception of force was assessed when subjects tapped with one finger on another through a virtual object. By introducing varying time intervals between the action and the resulting sensation, we revealed a roughly symmetrical and relatively broad period of attenuation centred on the precise time at which the action would normally result in a sensation. Movement of the active finger without contact was shown to be insufficient to produce attenuation, as was a sensation of contact without movement.

Chapter 6 tested the hypothesis that tactile attenuation results from a predictive mechanism, rather than a postdictive or masking mechanism. Attenuation of a self-generated tap was shown to occur at the time of an expected contact between two fingers even if the contact did not occur. Movement was again found to be insufficient

by itself to produce attenuation, even when the stimulus was consistently paired with a particular flexion angle of the active finger. These results are inconsistent with a postdictive mechanism, which would have access to the actual sensory feedback in judging whether or not a sensation was self-generated. These results instead suggest that tactile attenuation results from a predictive mechanism that attenuates self-generated sensations on the basis of an efference copy of the motor command.

Chapter 7 investigated how this prediction is acquired. Subjects were exposed to a novel relationship between the motion of the right hand and force applied to the left. With practice, subjects learned to stabilise the left hand by predicting and actively opposing the force. Once learned this prediction generalised to untrained movements and postures. The patterns of generalisation to new postures indicated that the motor system represented the force on the left hand in intrinsic joint-based coordinates, but represented the movement of the right hand in an extrinsic coordinate frame.

The study in Chapter 8 used the force-matching paradigm to investigate tactile attenuation in patients with schizophrenia. It has previously been proposed that schizophrenia involves a deficit in self-monitoring, and that this may be the cause of the auditory hallucinations and delusions of control commonly suffered by these patients. Consistent with this hypothesis, our study found that patients with schizophrenia show less attenuation of self-generated sensation than healthy controls. This suggests that the illness may be specifically characterised by a deficit in predicting the sensory consequences of action.

Chapter 9 investigated the neural basis of the efference copy signal implicated in predictive attenuation. A novel protocol of transcranial magnetic stimulation was used to modulate the excitability of primary motor cortex. If efference copy is generated in primary motor cortex, we hypothesised that TMS should affect efference copy and motor output equally, producing no effect on attenuation. Using the force-matching paradigm, we showed that attenuation was in fact reduced by a decrease in excitability of motor cortex contralateral to the active hand. This finding suggests that efference copy is generated upstream of primary motor cortex, and that TMS creates a mismatch between efference copy and motor output which reduces attenuation.

10.2 Meta-analysis of results from the force-matching task

Many of the studies in this thesis involved variations on the force-matching task first described in Chapter 3. In the majority of these studies at least one experimental condition was identical to the ‘direct resting’ condition in Experiment 2 of that chapter, in that the subject reproduced a range of target forces applied to his or her resting left index finger by pressing directly with the finger of the other hand. A total of 124 subjects, including participants in pilot experiments and healthy controls in patient studies, completed a block of 40 or more trials of this basic force-matching task, differing only in the range of target forces tested. This presents the opportunity to conduct a meta-analysis with enhanced statistical power to investigate performance on this task in greater detail.

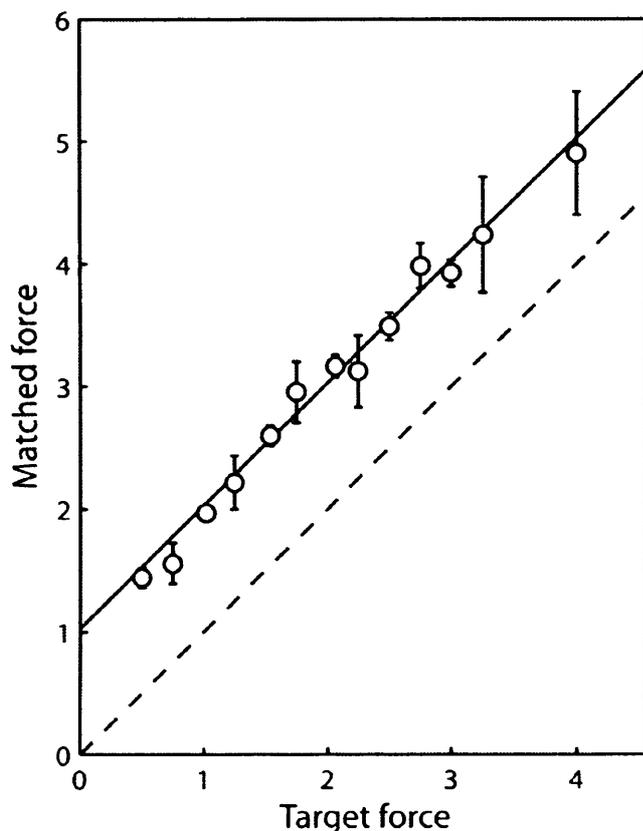


Figure 10-1 Mean performance of 124 subjects on the force-matching task described in Chapter 3. Subject-generated matching force as a function of externally-generated target force (mean \pm S.E. across subjects). Dashed line represents perfect performance. Solid line indicates the average line of best fit assuming a constant difference between matching and target force for each subject. Each subject was tested on between 5 and 10 target forces over the course of 40 to 80 trials. Task and analysis was otherwise identical to that described for Experiment 2, Chapter 3.

Figure 10-1 shows the average matching forces generated by all 124 subjects as a function of target force. As expected, subjects produced an exaggerated matching force at all levels of the target force tested, implying that the sensation of the self-generated matching force was attenuated so as to make it perceptually equal to the smaller target force. The results of the first force-matching study (Chapter 3) suggested that the difference between matching and target forces might involve a change in slope as well as offset. However, in this much larger data set (which includes the previous results) it appears that the amount by which the matched force exceeds the target force (the 'excess force') is approximately constant for all target forces. 47% of the total variance in the excess force can be accounted for by fitting each subject's data with a single offset parameter, representing a constant level of

excess force (the average fit is shown by the solid line in Figure 10-1). Adding a second slope parameter to the model, so the excess force can vary linearly with the target force, only accounted for an additional 8% of the variance. Although this parameter differed significantly from unity ($F_{1,123} = 5.0$, $p = 0.026$), it was very small, on average adding only 0.08 N to the matching force for every 1 N increase in the target force. Adding further polynomial terms accounted for <2% additional variance.

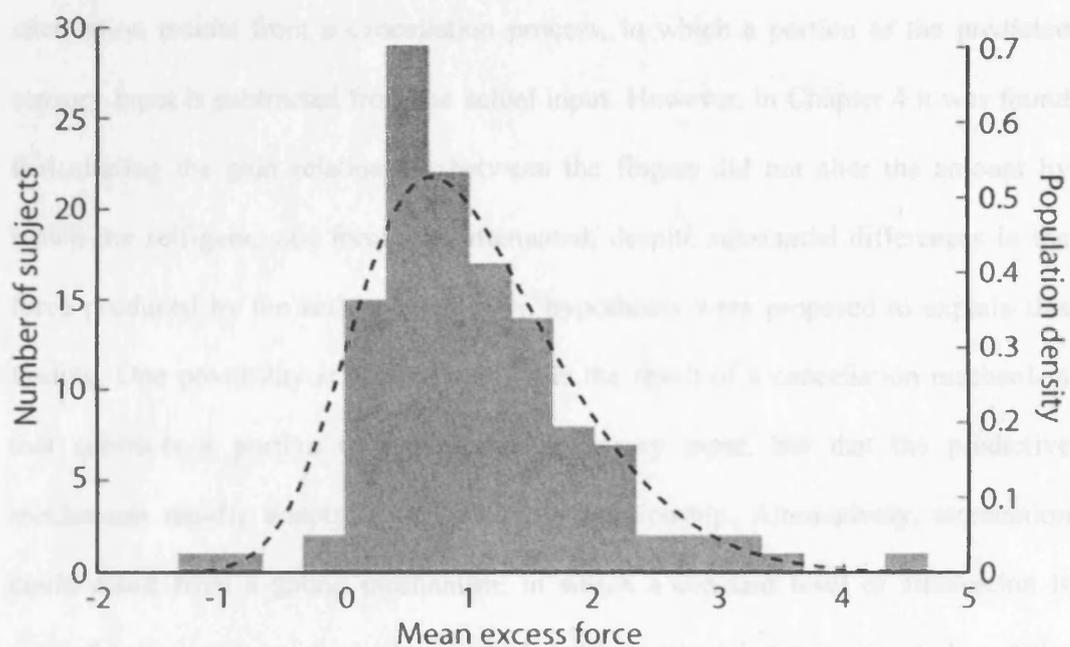


Figure 10-2 Histogram of the mean difference between matching and target forces across a sample of 124 subjects. Dotted line indicates the skew-normal distribution that best fits the data.

Figure 10-2 displays the variation in mean excess force across subjects. The data were well fit by a normal distribution (Kolmogorov-Smirnoff test, $p = 0.21$) with a positive skew (skewness = 1.0). The mean excess force was 1.03 N. Although a small number of subjects showed no or very weak attenuation (10% of sample produced mean excess force <0.2 N), there does not appear to be any substantial bimodality to the

distribution, and so the performance of these subjects is best explained by natural variation around the population mean. Only 4 subjects (3% of the sample) produced matching forces on average less than the target force.

In summary, the results of this meta-analysis suggest that the sensation of self-generated force is attenuated by a fixed amount, on average equivalent to a 1 N reduction in the perceived force. It has previously been proposed that sensory attenuation results from a cancellation process, in which a portion of the predicted sensory input is subtracted from the actual input. However, in Chapter 4 it was found that altering the gain relationship between the fingers did not alter the amount by which the self-generated force was attenuated, despite substantial differences in the force produced by the active finger. Two hypotheses were proposed to explain this finding. One possibility is that attenuation is the result of a cancellation mechanism that subtracts a portion of the predicted sensory input, but that the predictive mechanism rapidly adapts to the new gain relationship. Alternatively, attenuation could result from a gating mechanism, in which a constant level of attenuation is applied to any site on the body in which self-generated input is expected, and the predicted sensory input is used only to identify those sites. The results of this meta-analysis may at first appear to support the latter hypothesis, in that the attenuated portion of a self-generated force seems to remain constant while the overall force increases. However, there is no a priori reason to believe that a constant difference in force measured on a Newton scale corresponds to a constant subtraction in the perceived magnitude of the sensation. We therefore tested the perception of the constant forces used in the matching experiment in a group of 10 subjects using open magnitude scaling. Forces in the range 1 to 7 N were presented to subjects in the same

way as target forces in the force-matching task. Subjects were instructed to rate the intensity of each stimulus with a number. Each subject's responses were subsequently scaled to the range 0 to 1 so that means across subjects could be calculated. Results are shown in Figure 10-3.

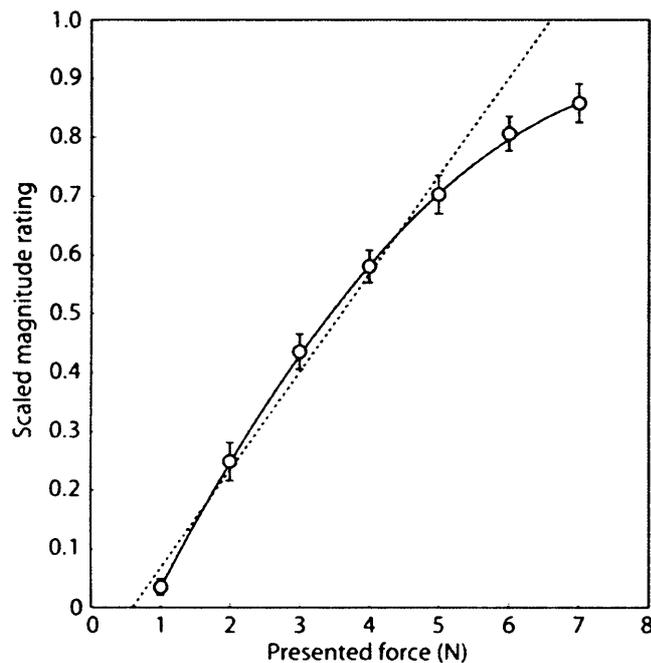


Figure 10-3 Perceived magnitude of constant forces applied to the fingertip. Mean \pm SE rating shown, with a second-order polynomial fit for all forces (solid line) and a line of best fit for forces in the range 1-5 N (dotted line).

Subjects' gave forces separated by 1 N significantly different intensity ratings throughout the tested range ($F_{1,9} > 9.2$, $p < 0.02$) implying that the 1 N attenuation observed on average in the matching task is large enough to produce perceptible differences in the intensity of self- and externally-generated forces. The magnitude rating was found to be approximately linearly related to the force in Newtons over the range 1 to 5 N (dotted line in Figure 10-3), although the rated intensity began to saturate at higher force levels and a significantly better fit was achieved overall by a second-order polynomial ($F_{1,9} = 61.9$, $p < 0.001$; solid line).

As the magnitude rating is roughly linearly related to force over the range tested in the force-matching task, we can conclude that the constant excess force observed in that task results from an approximately constant subtraction in the perceived intensity of the self-generated force. However, we still cannot conclude that the level of attenuation is independent of the magnitude of the predicted sensory input. To explain why, it will help to consider how a fixed attenuation might be implemented at a neuronal level. The underlying attenuation mechanism must apply some form of operation to the neural code representing the sensory input. For example, the sensory input could be represented in neuronal firing as a rate code, with the spike rate proportional to the magnitude of force in Newtons. There is evidence from primate studies that for small forces on the fingertip (<0.25 N) the primary sensory afferents do encode the force in this way (Goodwin et al., 1995), although this may not hold true for larger forces or at later stages of sensory processing. Attenuation could then be achieved by inhibition of the neurons carrying sensory information from areas predicted to be sites of self-contact. However, a mathematically simple operation such as subtraction is unlikely to result from an equally simple neuronal operation, such as a fixed inhibitory pre-synaptic potential. Indeed, in order to implement a constant subtraction at the neuronal level, the level of inhibition may have to be set by a network that includes the magnitude of the sensory input itself as a determining factor. In this framework, the crucial question becomes whether the factor that determines the level of inhibition is the magnitude of the actual sensory input, or the magnitude of the predicted sensory input. This question could potentially be answered using psychophysical methods if one created a discrepancy between the actual and expected magnitude of a brief self-generated force, such as a tap. If the perceived intensity of a tap of fixed magnitude varied with the expected magnitude, this would

imply a cancellation mechanism, whereas if the perceived force was independent of the expected magnitude, this would imply a gating mechanism. This remains a potential area for future research.

The distinction between gating and cancellation mechanisms is an important one. The principle role proposed for tactile attenuation is to increase the salience and detectability of externally-generated stimuli. A sensory cancellation mechanism is ideal for this role: by subtracting a portion of any self-generated component from the sensory input, any externally-generated component is enhanced by comparison. In contrast, a gating mechanism attenuates self- and externally-generated components equally, with no effect on the relative salience of the two. By attenuating the sense of touch in parts of the body which expect self-input, a gating mechanism may enhance the relative salience of external stimuli elsewhere on the body. However, unlike a cancellation mechanism, sensory gating cannot assist in detecting external tactile stimuli against a background of self-generated sensation. An example of a situation in which this is relevant is reading Braille, in which unpredictable tactile stimuli (the Braille dots) must be detected against a self-generated background stimulation caused by pressing one's finger to the paper and moving it across the page.

Studies which have examined performance on this kind of task have generally found no difference in detection between active touch, in which the subject moves his or her finger across the surface, and passive touch, in which the finger remains still and the surface is moved (see Chapman, 1994 for a review). A cancellation mechanism would be expected to assist in the active task by attenuating the self-generated component of the tactile input. The absence of any advantage of active over passive touch could

therefore be taken as evidence against the cancellation hypothesis. However, detection of tactile stimuli is known to be reduced in a moving body part even when the movement is not expected to result in tactile sensation (Angel and Malenka, 1982; Chapman et al., 1987; Williams et al., 1998; Williams and Chapman, 2002). This movement-related gating may hide any detection advantage in active touch resulting from a cancellation mechanism. The effects of predictive attenuation could potentially be disentangled from the effects of movement-related gating by examining discrimination in a passive finger when the surface is moved over the finger either by the experimenter or by the subject's other hand. A cancellation mechanism should produce a detection advantage in the case of self-generated movement, whereas a gating mechanism would not.

10.3 Neural mechanisms of sensory gating and cancellation

10.3.1 Movement-related sensory gating

As discussed above and in detail in Chapter 1, detection thresholds to cutaneous stimuli are increased in a moving body part. This is an example of a gating rather than a cancellation mechanism, in that the stimuli are attenuated despite being externally-generated and unpredictable. A possible neurophysiological mechanism for this phenomenon has recently been demonstrated in primates. Seki et al. (2003) stimulated primary tactile afferents in the superficial radial nerve while a monkey performed an active wrist movement. They obtained single-unit recordings from spinal interneurons that received direct synaptic connections from the stimulated afferents. The activity generated in these first-order interneurons by stimulation of the primary afferent was found to be reduced during active movement of the wrist. This is unlikely to reflect

inhibition of the interneurons themselves, as overall activity increased during movement. Instead, the most likely mechanism is presynaptic inhibition of the primary afferents, in which GABAergic synapse activity depolarises the afferent fibres, reducing the amount of transmitter released in response to an action potential (Eccles et al., 1961; Miller, 1998).

The reduction in the response of the interneurons to stimulation preceded the onset of EMG activity, implying that the presynaptic inhibition results from central commands in descending pathways rather than from peripheral feedback from the movement. This result is consistent with studies of sensory perception in humans, which have demonstrated an increase in detection thresholds prior to EMG onset (Williams and Chapman, 2002). As well as transmitting sensory signals in ascending pathways to sensory cortex, first-order interneurons also contribute to spinal circuitry that generates movement. Electrical microstimulation at the recording sites produced strong inhibition of EMG activity related to the wrist movement, suggesting that the interneurons are part of a reflex loop that acts to reduce muscle activity in response to tactile input. By reducing the activity of first-order interneurons, presynaptic inhibition may help overcome this reflex during a planned movement. This raises the interesting possibility that the gating of sensory perception during movement is simply a by-product of this process, and may have no adaptive value in itself.

Inhibition of sensory signals at the level of the spinal cord is also consistent with evidence obtained from electroencephalography (EEG). Electrical or tactile cutaneous stimuli result in changes in neuronal activity in somatosensory cortex that can be detected by surface electrodes. Early components of these somatosensory evoked

potentials (SEPs) are reduced in amplitude as a result of active movement of the stimulated body part (Rushton et al., 1981), and this reduction is again observed prior to the onset of EMG (Cohen and Starr, 1987; Shimazu et al., 1999). In monkeys, strong suppression of SEPs can be experimentally induced by microstimulation of sites in primary motor cortex that activate the appropriate muscle groups, even with stimulation intensities too weak to produce movement (Jiang et al., 1990). This clearly demonstrates the role of descending motor command signals in producing sensory gating.

For active movement, the results from single-unit recording, EEG, and sensory threshold studies all appear to be in agreement. However, data from passive movement conditions are considerably harder to synthesise. Seki et al. found no evidence of presynaptic inhibition during passive wrist movements, yet suppression of SEPs is observed during passive movement (Chapman et al., 1988). SEPs are suppressed only after the onset of passive movement, and yet an increase in detection thresholds is observed prior to movement onset and with a time-course very similar to that for active movement (Williams and Chapman, 2002). It seems likely from this data that movement-related sensory gating cannot be explained by one mechanism alone, but that there may instead be a number of different stages of sensory transmission and processing at which suppression can occur.

10.3.2 Sensory cancellation mechanisms

Whereas presynaptic inhibition inevitably suppresses self- and externally-generated sensory input equally, single-unit recording has also revealed mechanisms that selectively remove only the self-generated component of the input. The clearest

evidence for such a cancellation mechanism is found in the electrosensory system of the electric fish (Bell, 2001).

Electric fish possess both electroreceptors for sensing current and electric organs driven by motor commands for discharging current. To prevent the discharge of a fish's own electric organs interfering with its ability to sense its surroundings, the self-generated component is removed from the output of electrosensory cells by an adaptive predictive mechanism. Bell (1981; 1982; 1986) blocked the electric organs of mormyrid fish with curare, and then delivered an artificial electrical stimulus every time the fish generated a discharge motor command. At first, the artificial stimuli produced substantial activation in neurons receiving electrosensory input (Figure 10-4 centre), but these responses were greatly attenuated after a few minutes of consistent pairing of the stimulus with the motor command. When the artificial stimuli were subsequently stopped, a negative image of the expected activation was observed in response to each motor command (Figure 10-4 bottom). This is a clear example of predictive cancellation as proposed by Sperry and von Holst: a cancellation signal is generated based on an efference copy of the motor command, and subtracted from the activity of sensory neurons, removing the predictable component of the sensory input.

In Chapter 6 of this thesis we demonstrated that tactile sensation is attenuated at the predicted time of self-contact, even if the contact does not occur. This attenuation could result from a predictive cancellation mechanism very similar to the one observed in electric fish, although differing in that only part of the self-generated input is removed. In fish, the negative cancellation signal was found to be highly specific to the timing, location, polarity, and amplitude of the stimulus paired with the

motor command. This adaptability is consistent with the principle of a simple forward model, transforming planned motor output into predicted sensory input. The adaptability of this mechanism in electric fish may also be reflected in humans. Studies of anticipatory postural control, such as the one described in Chapter 7, have demonstrated that the predictive signal used by the human motor system can adapt to changes in the timing and direction of forces resulting from self-action (Witney et al., 1999; Witney and Wolpert, 2003). It remains to be seen whether this adaptability is also demonstrated by the mechanism responsible for attenuating self-generated sensation in humans.

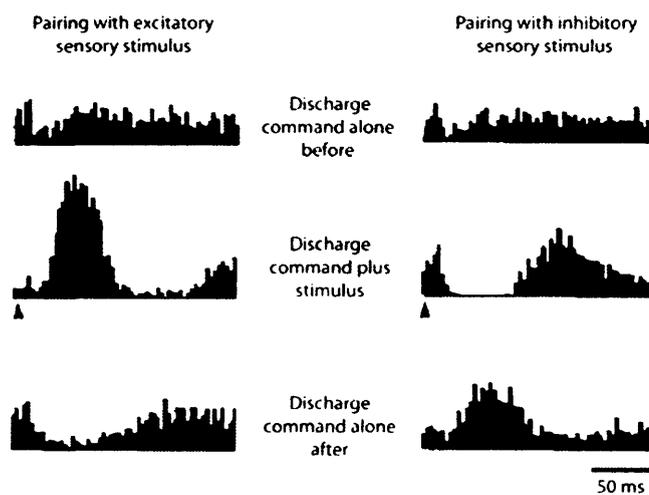


Figure 10-4 Negative images of predicted sensory responses in mormyrid fish. Histograms show responses to an electric discharge command of cells in the electrosensory lobe. Responses shown before (top), during (centre), and after (bottom) pairing for 5 mins with a 1 ms excitatory (left) or inhibitory (right) stimulus. (Adapted from Bell, 1986.)

In addition to cancellation based on efference copy, electric fish also display cancellation of inputs that are predictable only on the basis of incoming sensory information such as proprioception. For example, Bastian (1995; 1999) paired an artificial electrical stimulus with a particular phase of a passive sinusoidal tail bend. Consistent pairing over several minutes again resulted in cancellation of the predictable input. In this respect it appears that electric fish and humans differ. In

Chapter 6, we showed that a consistent pairing of a tactile stimulus with a particular angle of active finger flexion was not sufficient to produce attenuation, despite the tactile input being predictable based both on proprioceptive feedback and on the motor command. It appears that in the human somatosensory system attenuation depends on the prediction of a specific event—contact—rather than affecting any arbitrarily predictable stimulus.

Another example of sensory cancellation is found in the primate vestibular system. As in electric fish, sensory filtering occurs not at the primary afferent stage (Cullen and Minor, 2002) but at the next stage of processing. A subclass of neurons within the vestibular nucleus receive input from the semicircular canals, and project to spinal motor neurons that innervate muscles in the neck. These ‘vestibular-only’ neurons mediate a reflex which generates compensatory muscle responses in response to head motion, stabilising the head in space. While beneficial at rest, this reflex would be inappropriate during active head movements, and these neurons receive a cancellation signal that attenuates responses to active movements (McCrea et al., 1999; Roy and Cullen, 2001). If an actively-generated head rotation is matched by an opposite passive rotation of the whole body, so that the predicted vestibular input does not arise, this cancellation signal is revealed as a negative image in the neuronal activation (Roy and Cullen, 2004).

Attenuation of the vestibular signal was not observed when the monkeys generated head rotations indirectly, by driving a turntable via a steering wheel (Roy and Cullen, 2001). This finding parallels our observation in Chapter 3 that forces generated via a joystick are not attenuated. Vestibular attenuation was also not seen when monkeys

attempted to make head movements when their heads were restrained (Roy and Cullen, 2004). This may reflect an updating of a predictive model to take into account the presence of the head restraint, and hence maintain accurate prediction. The presence of the restraint may be identified by a discrepancy between the predicted and actual neck proprioceptive input resulting from an attempted head movement. Similarly, in Chapter 9 we suggested that rTMS of MI reduced attenuation by creating a discrepancy between the predicted and actual somatosensory input resulting from an action.

10.3.3 Sensory attenuation and the cerebellum

Converging evidence from theoretical, neurophysiological, and functional imaging studies suggests a role for the cerebellum in predictive sensory attenuation. The primate ‘vestibular-only’ neurons described above are thought to receive projections from the nodulus-uvula region of the cerebellum (Xiong and Matsushita, 2000). This region receives input from areas involved in producing head and neck movements as well as proprioceptive input from the neck. This makes it a strong candidate site for integrating efference copy and proprioceptive input to generate the predictive cancellation signal. Similarly, in electric fish, the neurons identified as sites of attenuation are found in the electrosensory lobes, regions with a strong anatomical similarity to the cerebellum. These neurons also receive projections carrying both proprioceptive input and central input related to the motor command. Adaptation of the predictive cancellation signal has been shown to result from plasticity at these synapses (Bell et al., 1993).

In humans, the neural basis of tactile attenuation has been investigated using fMRI (Blakemore et al., 1998a, 1999b). In these studies a tactile stimulus was moved sinusoidally across the subject's left hand, either by the subject or by the experimenter. When the tactile stimulation was externally generated, significant activation was observed in contralateral primary and bilateral secondary somatosensory cortex. When the stimulation was self-generated, the activation in secondary somatosensory cortex was significantly reduced. A similar suppression of neural activity may underlie the attenuation in the perceived intensity of tactile stimuli investigated in this thesis.

These studies also support a role for the cerebellum in tactile attenuation. Activity in the right anterior cerebellar cortex was reduced when the stimulus was self- rather than externally-generated. This may reflect the generation of a predictive cancellation signal in cerebellar areas ipsilateral to the active hand. A significant correlation was found between activation in the cerebellum and the somatosensory cortex, but only in the self-generated condition. This is again consistent with modulation of the input to sensory areas by a signal originating in the cerebellum.

No significant differences in activation were found in primary somatosensory cortex (SI) between self- and externally-generated stimulation. This could be taken to suggest that attenuation in humans occurs only at later stages in sensory processing. However, there was a significant correlation between activity in contralateral SI and cerebellum in the self-generated condition, so we cannot rule out the possibility that attenuation is taking place in SI or even earlier.

The involvement of cerebellar areas in sensory attenuation is consistent with proposals that the cerebellum is a component of the forward model system that predicts the consequences of planned actions (Ito, 1970; Miall et al., 1993; Wolpert and Kawato, 1998). In support of this view, patients with degenerative cerebellar lesions fail to correctly modulate grip force when lifting objects, suggesting a deficit in predicting the changes to the load force that will result from the movement (Muller and Dichgans, 1994a). These patients are also less efficient than healthy controls at adapting their grip force over successive trials to match an object's weight, suggesting a failure to update the forward model to account for the current context (Muller and Dichgans, 1994b). Patients with cerebellar damage also show deficits in coordinated arm movements, and an unusual reliance on visual feedback, that are consistent with a failure in the predictive representation of limb position (Haggard et al., 1994; Haggard et al., 1995).

The physiological structure of the cerebellum makes it a strong candidate for learning and maintaining internal models. Purkinje cells, the only output neurons from the cerebellar cortex, receive synaptic inputs from parallel fibres and climbing fibres. Parallel fibres originate in granule cells which transmit input from association areas of the cerebral cortex. Parallel fibres may make as many as 200,000 synapses on a single Purkinje cell (Ito, 1984), and it has been proposed that the complex transformation from parallel fibre input to Purkinje cell output may implement an internal model. If the parallel fibre input signals desired movement goals, the parallel fibre-Purkinje cell synapses could implement an inverse model, with the Purkinje cell output signalling the error in the current motor output (Kawato, 1999). Alternatively, if the parallel fibre input carries an efference copy of the motor command, the Purkinje cell output

may signal predicted sensory feedback, implementing a forward model (Miall et al., 1993). The cerebellar architecture appears to be highly modular (Oscarsson, 1979; Bower and Woolston, 1983), so it is possible that the cerebellum implements many forward and inverse models simultaneously (Wolpert et al., 1998). This is consistent with the MOSAIC model discussed in Chapter 1, in which multiple forward and inverse models work in pairs to represent different sensorimotor contexts (Wolpert and Kawato, 1998; Haruno et al., 2001).

A key feature of internal models is their adaptability, and this is paralleled by a remarkable level of synaptic plasticity in the cerebellar cortex (Ito, 1984). In addition to parallel fibre inputs, Purkinje cells receive input from climbing fibres originating in the inferior olive. The climbing fibre input appears to modulate the efficacy of the parallel fibre-Purkinje cell synapses via long-term depression (Marr, 1969; Albus, 1971; Fujita, 1982; Ito, 2001). Electrophysiological studies in primates have observed increased climbing fibre activity during initial movements under a novel load or changed visual feedback (Gilbert and Thach, 1977; Ojakangas and Ebner, 1992). These and other studies (e.g. Gellman et al., 1985; Andersson and Armstrong, 1987) suggest that climbing fibre inputs signal discrepancies between expected and actual sensory input. Climbing fibre input may therefore act as a training signal which, via plasticity of the parallel fibre-Purkinje cell synapses, adapts the internal model to minimise errors in prediction.

Several imaging studies support cerebellar involvement in acquiring new internal models. Imamizu et al. (2000) conducted an fMRI study in which subjects learned to control a screen cursor using a computer mouse under a novel rotated relationship

between hand and cursor position. This kind of motor learning is believed to involve the acquisition of a new internal model in a similar way to the learning of novel dynamics discussed in Chapters 1 and 7. Initially, activation was observed in large regions of the cerebellum. This activation was proportional to the movement error and decayed as learning progressed. Once learning was complete activation remained only in a small region of the cerebellum near the posterior superior fissure. The authors interpreted these results within the MOSAIC framework: they suggested that the initial widespread activation reflects the activity of multiple internal models as they compete to minimise the error signal, whereas the subsequent localised activation is generated by the one or several successful internal models that have become specialised to represent the hand-cursor transformation.

In a subsequent study in which subjects learned to switch between two different hand-cursor transformations, cerebellar activation became localised in different areas under the two different transformations (Imamizu et al., 2003). This may reflect the acquisition of distinct internal models implemented in spatially segregated regions of the cerebellum's modular architecture.

10.4 Other mechanisms of prediction within the CNS

This thesis has primarily focused on mechanisms that predict the outcome of planned actions based on an efference copy signal. However, it is often valuable to be able to predict upcoming events that one is not oneself involved in producing, and the CNS has a number of mechanisms in place to achieve this.

One instance where accurate prediction should be possible without efference copy is in predicting how the environment will evolve under the influence of natural laws, such as gravity. As discussed in Chapter 5, Johansson & Westling (1988) observed that when subjects dropped a ball from one hand to the other they generated an anticipatory grip force increase to maintain posture at the expected time of contact. The timing of the grip force response remained accurate across different lengths of drop, suggesting that the CNS was at least approximately modelling the laws of gravity. In that instance, the start of the drop could be signalled to a forward model by an efference copy of the motor command to release the ball. However, the fact that we are able to catch an object thrown by someone else suggests that the movement of an object under gravity can be predicted based on sensory input alone.

In order to appropriately synchronize the movements involved in catching a ball, the CNS must be able to predict the time-to-contact of the approaching object based on visual input. However, this does not necessarily require an internal model of gravity: a first-order approximation of the time-to-contact can be obtained based only on the size of the object's retinal image. The ratio of the current retinal size to its rate of change provides a simple and neurologically plausible way of estimating the time-to-contact that it has been suggested may be sufficiently accurate for many situations (Lee et al., 1983; Savelsbergh et al., 1992). However, a mechanism that also took into account the object's acceleration would be able to time a catch more precisely.

This issue was recently addressed in a study in which subjects on a space shuttle mission caught a ball in 0 g (McIntyre et al., 2001). Under these conditions subjects mistimed their catching movements, with errors that increased with decreasing ball

velocity. This finding is inconsistent with a first-order estimate of time-to-contact, and instead suggests that the prediction involves a model of the acceleration due to Earth's gravity which becomes inappropriate under 0 g. Over the course of the 17-day spaceflight the amplitude of the erroneous movement decayed and a more accurately timed movement began to develop. This may be preliminary evidence for an adaptation of the internal model to account for the absence of gravity: similar changes are seen in grip force responses when a constant delay is introduced in the timing of a load force (Witney et al., 1999). As yet it is unknown whether the prediction of object motion based on sensory input depends on the same underlying mechanism as the prediction based on efference copy. One approach to this question might be to look for attenuation in the perception of force when an object is dropped onto a passive body part, and investigate differences between self-triggered and externally-triggered drops.

Outside of the motor system, prediction may play a substantial role in our perception of dynamic events in the external world. One of the clearest examples of this is the phenomenon of representational momentum, first documented by Freyd and Finke (1984). In their original paradigm subjects viewed a rotating rectangle and then, after a brief retention interval, made a judgement about its final orientation. Subjects' responses suggested that they recalled the rectangle as having rotated slightly further than it actually had. This basic finding has subsequently been replicated for many different visual stimuli and varieties of motion, demonstrating a systematic tendency for observers to extrapolate dynamic events in memory beyond their actual ending point.

Subsequent investigations have shown that the error in the recalled endpoint increases with increasing retention interval (Freyd and Johnson, 1987) and depends on the velocity and acceleration of the moving stimulus (Finke et al., 1986). These findings suggest that the mental extrapolation of motion might result from an internalisation of the physical principle of momentum. According to this view, the error in the recalled endpoint reflects a tendency to assign the observed object a physical mass: the memory of the observed endpoint is biased by a prediction of the movement endpoint based on an internal model of physical laws. In support of this theory, the endpoint error has been shown to depend on the implied weight of the target (Hubbard, 1997) and the implied friction experienced by the target (Hubbard, 1995). However, subsequent research has shown a wider conceptual influence on representational momentum that does not fit so easily with the idea of an internal model. For instance, the error in recalled endpoint of a moving arrow depends on the direction in which the arrow is pointing (Freyd and Pantzer, 1995). Also, differences have been observed between the unconscious extrapolation of movement endpoints and the judgements made when subjects are explicitly asked to predict how the motion will continue (Cooper and Munger, 1993). This has led to a number of alternative explanations for representational momentum, including the suggestion that errors in localising endpoints for linear motion may be merely the result of eye movements following the disappearance of the target (Kerzel, 2000). It seems likely that representational momentum results from a combination of different mechanisms related to intrinsic properties of the visual system, predictive internalisation of physical laws, and more general expectations about object behaviour. It must be hoped that future research will disentangle these influences and reveal in more detail the role prediction plays in perception.

One area in which prediction undoubtedly plays a key role is associative learning. According to associative learning theory, an association is acquired when a particular sensory stimulus or behavioural activity is closely and regularly followed by a reinforcer: a reward or a punishment. Once formed, this association between the stimulus or action and the reinforcer can be used to guide future behaviour, by predicting which activities and situations will result in positive outcomes and which negative (Mackintosh, 1975; Dickinson, 1980). Associative learning represents a simple and widespread form of prediction, specifically tuned to events with motivational significance, and is observed in even the simplest nervous systems such as that of the sea slug (Kandel, 1976).

In the earliest formulations of associative learning, every pairing between the stimulus or action and the reinforcer was thought to increase the strength of the association. However, this simple learning rule is often insufficient to explain the conditions under which associations are formed. For instance, in a 'blocking' procedure (Kamin, 1969; Martin and Levey, 1991), a particular stimulus is consistently paired with a reinforcer until an association is established. A second stimulus is then presented along with the original stimulus, again repeatedly paired with the reinforcer. A simple contiguity-based learning rule suggests that an association will be formed between the second stimulus and the reinforcer, but this is not the case. Based on this finding, Kamin (1969) suggested that associations form only when a reinforcer is surprising or unpredicted. This hypothesis was formalised by Rescorla & Wagner (1972), who proposed a learning algorithm in which the increment in the associative strength is proportional to the error in the prediction of the reinforcer.

Electrophysiological and theoretical studies suggest a primary role for dopamine neurons in the neural implementation of associative learning. In primates, midbrain dopamine neurons show short latency responses to primary reward-related stimuli, for instance when food or liquid rewards are delivered. However, when a reward is reliably paired with a stimulus, responses to the primary reward decrease and dopamine neurons begin to respond to the reward-predicting stimulus instead (Ljungberg et al., 1992; Schultz et al., 1993; Mirenowicz and Schultz, 1996; Hollerman and Schultz, 1998). If a predicted reward does not occur then activity is depressed at the expected time of the reward, suggesting that dopamine neurons receive a predictive cancellation signal similar to the cancellation signals involved in sensory filtering. The result is that dopamine activity signals the prediction error, as required by neural network models of Rescorla and Wagner's associative learning algorithm (McLaren, 1989). Midbrain dopamine neurons have widespread and divergent projections which innervate a substantial proportion of neurons in the striatum and frontal cortex (Berger et al., 1988; Williams and Goldman-Rakic, 1993). By broadcasting a prediction error signal to large populations of neurons, dopamine neuron activity may act as a teaching signal, modulating the efficacy of concurrently active synapses to affect the generation of subsequent predictions or to alter future behaviour (Schultz, 1998).

In summary, prediction is a key mechanism involved in many aspects of brain function. Within the sensory system, the role of prediction is thought to extend from the filtering of incoming sensory input at the earliest stages of processing to high-level influences on representation and perception. In the planning of motor output, the

influence of prediction may extend from low-level preparation and coordination of muscle activity to the abstract guidance of behaviour in the pursuit of long-term goals.

10.5 Overall conclusions

This thesis has advanced our understanding of the role of prediction in human sensory and motor systems by investigating the perception of self-generated touch. Attenuation of self-generated tactile sensation has been shown to result from an internal prediction of the sensory consequences of planned actions, and key features of this predictive mechanism have been elucidated. A simple force-matching paradigm has been demonstrated as a powerful approach to the investigation of sensory prediction in healthy individuals and of deficits in prediction caused by disease.

REFERENCES

- Albus JS (1971) A theory of cerebellar functions. *Math Biosci* 10:25-61.
- Andersson G, Armstrong DM (1987) Complex spikes in Purkinje cells in the lateral vermis (b zone) of the cat cerebellum during locomotion. *J Physiol* 385:107-134.
- Angel RW, Malenka RC (1982) Velocity-dependent suppression of cutaneous sensitivity during movement. *Exp Neurol* 77:266-274.
- Baraduc P, Wolpert DM (2002) Adaptation to a visuomotor shift depends on the starting posture. *J Neurophysiol* 88:973-981.
- Bastian J (1995) Pyramidal-cell plasticity in weakly electric fish: a mechanism for attenuating responses to reafferent electrosensory inputs. *J Comp Physiol [A]* 176:63-73.
- Bastian J (1999) Plasticity of feedback inputs in the apteronotid electrosensory system. *J Exp Biol* 202:1327-1337.
- Bell CC (1981) An efference copy which is modified by reafferent input. *Science* 214:450-453.
- Bell CC (1982) Properties of a modifiable efference copy in an electric fish. *J Neurophysiol* 47:1043-1056.
- Bell CC (1986) Duration of plastic change in a modifiable efference copy. *Brain Res* 369:29-36.
- Bell CC (2001) Memory-based expectations in electrosensory systems. *Curr Opin Neurobiol* 11:481-487.

References

- Bell CC, Caputi A, Grant K, Serrier J (1993) Storage of a sensory pattern by anti-Hebbian synaptic plasticity in an electric fish. *Proc Natl Acad Sci U S A* 90:4650-4654.
- Berger B, Trottier S, Verney C, Gaspar P, Alvarez C (1988) Regional and laminar distribution of the dopamine and serotonin innervation in the macaque cerebral cortex: a radioautographic study. *J Comp Neurol* 273:99-119.
- Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2004) Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci* 19:1950-1962.
- Bick PA, Kinsbourne M (1987) Auditory hallucinations and subvocal speech in schizophrenic patients. *Am J Psychiatry* 144:222-225.
- Bizzi E, Accornero N, Chapple W, Hogan N (1984) Posture control and trajectory formation during arm movement. *J Neurosci* 4:2738-2744.
- Blakemore SJ, Wolpert DM, Frith CD (1998a) Central cancellation of self-produced tickle sensation. *Nat Neurosci* 1:635-640.
- Blakemore SJ, Goodbody SJ, Wolpert DM (1998b) Predicting the consequences of our own actions: the role of sensorimotor context estimation. *J Neurosci* 18:7511-7518.
- Blakemore SJ, Frith CD, Wolpert DM (1999a) Spatio-temporal prediction modulates the perception of self-produced stimuli. *J Cogn Neurosci* 11:551-559.
- Blakemore SJ, Wolpert DM, Frith CD (1999b) The cerebellum contributes to somatosensory cortical activity during self-produced tactile stimulation. *Neuroimage* 10:448-459.
- Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD (2000) The perception of self-produced sensory stimuli in patients with auditory hallucinations and

References

- passivity experiences: evidence for a breakdown in self-monitoring. *Psychol Med* 30:1131-1139.
- Bleuler E (1911) *Dementia Praecox, or the Group of Schizophrenias*. New York: International University.
- Bower JM, Woolston DC (1983) Congruence of spatial organization of tactile projections to granule cell and Purkinje cell layers of cerebellar hemispheres of the albino rat: vertical organization of cerebellar cortex. *J Neurophysiol* 49:745-766.
- Brashers-Krug T, Shadmehr R, Bizzi E (1996) Consolidation in human motor memory. *Nature* 382:252-255.
- Bridgeman B, Hendry D, Stark L (1975) Failure to detect displacement of the visual world during saccadic eye movements. *Vision Res* 15:719-722.
- Burdet E, Osu R, Franklin DW, Milner TE, Kawato M (2001) The central nervous system stabilizes unstable dynamics by learning optimal impedance. *Nature* 414:446-449.
- Capocchi G, Zampolini M, Larson J (1992) Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. *Brain Res* 591:332-336.
- Chapman CE (1994) Active versus passive touch: factors influencing the transmission of somatosensory signals to primary somatosensory cortex. *Can J Physiol Pharmacol* 72:558-570.
- Chapman CE, Jiang W, Lamarre Y (1988) Modulation of lemniscal input during conditioned arm movements in the monkey. *Exp Brain Res* 72:316-334.
- Chapman CE, Bushnell MC, Miron D, Duncan GH, Lund JP (1987) Sensory perception during movement in man. *Exp Brain Res* 68:516-524.

References

- Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 48:1398-1403.
- Chronicle EP, Glover J (2003) A ticklish question: does magnetic stimulation of the primary motor cortex give rise to an 'efference copy'? *Cortex* 39:105-110.
- Claxton G (1975) Why can't we tickle ourselves? *Percept Mot Skills* 41:335-338.
- Cohen LG, Starr A (1987) Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. *Brain* 110 (Pt 2):451-467.
- Conditt MA, Gandolfo F, Mussa-Ivaldi FA (1997) The motor system does not learn the dynamics of the arm by rote memorization of past experience. *J Neurophysiol* 78:554-560.
- Cooper LA, Munger MP (1993) Extrapolating and remembering positions along cognitive trajectories: Uses and limitations of analogies to physical motion. In: *Spatial representation* (Eilan N, Brewer W, McCarthy R, eds). London: Blackwell.
- Cullen KE, Minor LB (2002) Semicircular canal afferents similarly encode active and passive head-on-body rotations: implications for the role of vestibular efference. *J Neurosci* 22:RC226.
- Cunningham HA (1989) Aiming error under transformed spatial mappings suggests a structure for visual-motor maps. *J Exp Psychol Hum Percept Perform* 15:493-506.
- Daprati E, Franck N, Georgieff N, Proust J, Pacherie E, Dalery J, Jeannerod M (1997) Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. *Cognition* 65:71-86.

References

- Davidson PR, Wolpert DM (2005) Widespread access to predictive models in the motor system: a short review. *J Neural Eng* 2:S313-319.
- Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC, Thompson PD (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *J Physiol* 412:449-473.
- Decety J, Michel F (1989) Comparative analysis of actual and mental movement times in two graphic tasks. *Brain Cogn* 11:87-97.
- Delevoeye-Turrell Y, Giersch A, Danion JM (2003) Abnormal sequencing of motor actions in patients with schizophrenia: evidence from grip force adjustments during object manipulation. *Am J Psychiatry* 160:134-141.
- Dennett D, Kinsbourne M (1992) Time and the Observer. *Behav Brain Sci* 15:183-247.
- Deno DC, Keller EL, Crandall WF (1989) Dynamical neural network organization of the visual pursuit system. *IEEE Trans Biomed Eng* 36:85-92.
- Descartes R (1664) *Treatise of Man*. Amherst, NY: Prometheus Books.
- Dickinson A (1980) *Contemporary Animal Learning Theory*. Cambridge, UK: Cambridge Univ. Press.
- Diedrichsen J, Verstynen T, Hon A, Lehman SL, Ivry RB (2003) Anticipatory adjustments in the unloading task: is an efference copy necessary for learning? *Exp Brain Res* 148:272-276.
- Dierks T, Linden DE, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W (1999) Activation of Heschl's gyrus during auditory hallucinations. *Neuron* 22:615-621.

References

- Eagleman DM, Sejnowski TJ (2000) Motion integration and postdiction in visual awareness. *Science* 287:2036-2038.
- Eccles JC, Eccles RM, Magni F (1961) Central inhibitory action attributable to presynaptic depolarization produced by muscle afferent volleys. *J Physiol (Paris)* 159:147-166.
- Faraday M (1831) Effects on the production of electricity from magnetism. In: *Michael Faraday* (Williams LP, ed), p 531. New York: Basic Books.
- Feinberg I (1978) Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophr Bull* 4:636-640.
- Feldman AG (1966) On the functional tuning of the nervous system in movement control or preservation of stationary pose. II. Adjustable parameters in muscles. *Biophysics* 11:498-508.
- Finke RA, Freyd JJ, Shyi GC (1986) Implied velocity and acceleration induce transformations of visual memory. *J Exp Psychol Gen* 115:175-188.
- Flanagan JR, Wing AM (1993) Modulation of grip force with load force during point-to-point arm movements. *Exp Brain Res* 95:131-143.
- Flanagan JR, Wing AM (1995) The stability of precision grip forces during cyclic arm movements with a hand-held load. *Exp Brain Res* 105:455-464.
- Flanagan JR, Wing AM (1997) The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J Neurosci* 17:1519-1528.
- Flanagan JR, Vetter P, Johansson RS, Wolpert DM (2003) Prediction precedes control in motor learning. *Curr Biol* 13:146-150.
- Flash T (1987) The control of hand equilibrium trajectories in multi-joint arm movements. *Biol Cybern* 57:257-274.

References

- Flash T, Gurevich I (1997) Models of motor adaptation and impedance control in human arm movements. In: *Self-organization, Computational Maps, and Motor Control* (P. M, V. S, eds), p 423–481. Amsterdam: Elsevier Science.
- Ford JM, Mathalon DH, Heinks T, Kalba S, Faustman WO, Roth WT (2001) Neurophysiological evidence of corollary discharge dysfunction in schizophrenia. *Am J Psychiatry* 158:2069-2071.
- Forsberg H, Eliasson AC, Kinoshita H, Johansson RS, Westling G (1991) Development of human precision grip. I: Basic coordination of force. *Exp Brain Res* 85:451-457.
- Forsberg H, Kinoshita H, Eliasson AC, Johansson RS, Westling G, Gordon AM (1992) Development of human precision grip. II. Anticipatory control of isometric forces targeted for object's weight. *Exp Brain Res* 90:393-398.
- Foulkes AJ, Miall RC (2000) Adaptation to visual feedback delays in a human manual tracking task. *Exp Brain Res* 131:101-110.
- Freyd JJ, Finke RA (1984) Representational momentum. *J Exp Psychol Learn Mem Cogn* 10:126-132.
- Freyd JJ, Johnson JQ (1987) Probing the time course of representational momentum. *J Exp Psychol Learn Mem Cogn* 13:259-268.
- Freyd JJ, Pantzer TM (1995) Static patterns moving in the mind. In: *The Creative Cognition Approach* (Smith SM, Ward TB, Finke RA, eds). Cambridge, MA: MIT Press.
- Frith CD (1987) The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychol Med* 17:631-648.

References

- Frith CD (1992) *The Cognitive Neuropsychology of Schizophrenia*. UK: Lawrence Erlbaum Associates.
- Frith CD, Blakemore S, Wolpert DM (2000) Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. *Brain Res Brain Res Rev* 31:357-363.
- Fujita M (1982) Adaptive filter model of the cerebellum. *Biol Cybern* 45:195-206.
- Gahery Y, Massion J (1981) Co-ordination between posture and movement. *Trends Neurosci* 4:199-202.
- Gandolfo F, Mussa-Ivaldi F, Bizzi E (1996) Motor learning by field approximation. *Proc Natl Acad Sci Usa* 93:3843-3846.
- Geldard FA, Sherrick CE (1972) The cutaneous "rabbit": a perceptual illusion. *Science* 178:178-179.
- Gellman R, Gibson AR, Houk JC (1985) Inferior olivary neurons in the awake cat: detection of contact and passive body displacement. *J Neurophysiol* 54:40-60.
- Ghahramani Z, Wolpert DM, Jordan MI (1996) Generalization to local remappings of the visuomotor coordinate transformation. *J Neurosci* 16:7085-7096.
- Gibson JJ (1962) Observations on active touch. *Psychol Rev* 69:477-491.
- Gilbert PF, Thach WT (1977) Purkinje cell activity during motor learning. *Brain Res* 128:309-328.
- Gomi H, Kawato (1996) Equilibrium-point control hypothesis examined by measured arm stiffness during multijoint movement. *Science* 272:117-120.
- Goodbody SJ, Wolpert DM (1998) Temporal and amplitude generalization in motor learning. *J Neurophysiol* 79:1825-1838.

References

- Goodwin AW, Browning AS, Wheat HE (1995) Representation of curved surfaces in responses of mechanoreceptive afferent fibers innervating the monkey's fingerpad. *J Neurosci* 15:798-810.
- Goodwin GC, Sin KS (1984) *Adaptive Filtering Prediction and Control*. Englewood Cliffs, New Jersey: Prentice-Hall.
- Gordon AM, Westling G, Cole KJ, Johansson RS (1993) Memory representations underlying motor commands used during manipulation of common and novel objects. *J Neurophysiol* 69:1789-1796.
- Gould LN (1949) Auditory hallucinations and subvocal speech. *Journal of Nervous and Mental Disease* 109:418-427.
- Green P, Preston M (1981) Reinforcement of vocal correlates of auditory hallucinations by auditory feedback: a case study. *Br J Psychiatry* 139:204-208.
- Grusser OJ, Krizic A, Weiss LR (1987) Afterimage movement during saccades in the dark. *Vision Res* 27:215-226.
- Haggard P, Whitford B (2004) Supplementary motor area provides an efferent signal for sensory suppression. *Brain Res Cogn Brain Res* 19:52-58.
- Haggard P, Jenner J, Wing A (1994) Coordination of aimed movements in a case of unilateral cerebellar damage. *Neuropsychologia* 32:827-846.
- Haggard P, Clark S, Kalogeras J (2002) Voluntary action and conscious awareness. *Nat Neurosci* 5:382-385.
- Haggard P, Miall RC, Wade D, Fowler S, Richardson A, Anslow P, Stein J (1995) Damage to cerebellocortical pathways after closed head injury: a behavioural and magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* 58:433-438.

References

- Hall C, Buckolz E, Fishburne GJ (1992) Imagery and the acquisition of motor skills. *Can J Sport Sci* 17:19-27.
- Haruno M, Wolpert DM, Kawato M (2001) Mosaic model for sensorimotor learning and control. *Neural Comput* 13:2201-2220.
- Hellström A (1985) The time-order error and its relatives: Mirrors of cognitive processes in comparing. *Psychological Bulletin* 97:35-61.
- Helmholtz H (1867) *Handbuch der Physiologischen Optik*. Leipzig: Voss.
- Heusler P, Cebulla B, Boehmer G, Dinse HR (2000) A repetitive intracortical microstimulation pattern induces long-lasting synaptic depression in brain slices of the rat primary somatosensory cortex. *Exp Brain Res* 135:300-310.
- Hodgson AJ, Hogan N (2000) A model-independent definition of attractor behavior applicable to interactive tasks. *IEEE Trans Syst Man Cybern* 30:105-118.
- Hogan N (1984) An organizing principle for a class of voluntary movements. *J Neurosci* 4:2745-2754.
- Hollerman JR, Schultz W (1998) Dopamine neurons report an error in the temporal prediction of reward during learning. *Nat Neurosci* 1:304-309.
- Huang YZ, Rothwell JC (2004) The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. *Clin Neurophysiol* 115:1069-1075.
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. *Neuron* 45:201-206.
- Hubbard TL (1995) Cognitive representation of motion: evidence for friction and gravity analogues. *J Exp Psychol Learn Mem Cogn* 21:241-254.

References

- Hubbard TL (1997) Target size and displacement along the axis of implied gravitational attraction: Effects of implied weight and evidence of representational gravity. *J Exp Psychol Learn Mem Cogn* 23:1484-1493.
- Imamizu H, Kuroda T, Miyauchi S, Yoshioka T, Kawato M (2003) Modular organization of internal models of tools in the human cerebellum. *Proc Natl Acad Sci U S A* 100:5461-5466.
- Imamizu H, Miyauchi S, Tamada T, Sasaki Y, Takino R, Putz B, Yoshioka T, Kawato M (2000) Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature* 403:192-195.
- Ito M (1970) Neurophysiological aspects of the cerebellar motor control system. *Int J Neurol* 7:162-176.
- Ito M (1984) *The Cerebellum and Neural Control*. New York: Raven Press.
- Ito M (2001) Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol Rev* 81:1143-1195.
- Jiang W, Chapman CE, Lamarre Y (1990) Modulation of somatosensory evoked responses in the primary somatosensory cortex produced by intracortical microstimulation of the motor cortex in the monkey. *Exp Brain Res* 80:333-344.
- Johansson RS, Westling G (1984) Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res* 56:550-564.
- Johansson RS, Westling G (1988) Programmed and triggered actions to rapid load changes during precision grip. *Exp Brain Res* 71:72-86.
- Johansson RS, Cole KJ (1992) Sensory-motor coordination during grasping and manipulative actions. *Curr Opin Neurobiol* 2:815-823.

References

- Johansson RS, Hager C, Riso R (1992a) Somatosensory control of precision grip during unpredictable pulling loads. II. Changes in load force rate. *Exp Brain Res* 89:192-203.
- Johansson RS, Riso R, Hager C, Backstrom L (1992b) Somatosensory control of precision grip during unpredictable pulling loads. I. Changes in load force amplitude. *Exp Brain Res* 89:181-191.
- Johnstone EC, Crow TJ, Johnson AL, MacMillan JF (1986) The Northwick Park Study of first episodes of schizophrenia. I. Presentation of the illness and problems relating to admission. *Br J Psychiatry* 148:115-120.
- Jordan MI (1995) Computational motor control. In: *The cognitive neurosciences* (Gazzaniga MS, ed), pp 597-609. Cambridge, MA: MIT Press.
- Jordan MI, Rumelhart DE (1992) Forward models: supervised learning with a distal teacher. *Cognitive Science* 16:307-354.
- Kalman RE, Bucy RS (1961) New results in linear filtering and prediction. *Journal of Basic Engineering* 83:95-108.
- Kamin LJ (1969) Selective association and conditioning. In: *Fundamental Issues in Instrumental Learning* (Mackintosh NJ, Honig WK, eds). Halifax, Canada: Dalhousie Univ. Press.
- Kandel ER (1976) *Cellular Basis of Behavior*. San Francisco: Freeman Publications.
- Kawato M (1999) Internal models for motor control and trajectory planning. *Curr Opin Neurobiol* 9:718-727.
- Kawato M, Furukawa K, Suzuki R (1987) A hierarchical neural-network model for control and learning of voluntary movement. *Biol Cybern* 57:169-185.
- Kerzel D (2000) Eye movements and visible persistence explain the mislocalization of the final position of a moving target. *Vision Res* 40:3703-3715.

References

- Kornmuller AE (1930) Eine experimentelle Anesthesie der aussen Augenmuskeln am Menschen und ihre Auswirkungen. *Journal fur Psychologie und Neurologie* 41.
- Krakauer JW, Pine ZM, Ghilardi MF, Ghez C (2000) Learning of visuomotor transformations for vectorial planning of reaching trajectories. *J Neurosci* 20:8916-8924.
- Kuo AD (1995) An optimal control model for analyzing human postural balance. *IEEE Trans Biomed Eng* 42:87-101.
- Lackner J, Dizio P (1994) Rapid adaptation to Coriolis force perturbations of arm trajectory. *J Neurophysiol* 72:299-313.
- Lackner JR, DiZio P (1998) Adaptation in a rotating artificial gravity environment. *Brain Res Brain Res Rev* 28:194-202.
- Laskin SE, Spencer WA (1979) Cutaneous masking. I. Psychophysical observations on interactions of multipoint stimuli in man. *J Neurophysiol* 42:1048-1060.
- Lee DN, Young DS, Reddish PE, Lough S, Clayton TM (1983) Visual timing in hitting an accelerating ball. *Q J Exp Psychol A* 35:333-346.
- Liddle PF (1987) The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *Br J Psychiatry* 151:145-151.
- Ljungberg T, Apicella P, Schultz W (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol* 67:145-163.
- Mach E (1885) *Analysis of Sensations*.
- Mack A, Bachant J (1969) Perceived movement of the afterimage during eye movements. *Perception and Psychophysics* 6:379-384.
- Mackintosh NJ (1975) A theory of attention: variations in the associability of stimulus with reinforcement. *Psychol Rev* 82:276-298.

References

- Marg E, Rudiak D (1994) Phosphenes induced by magnetic stimulation over the occipital brain: description and probable site of stimulation. *Optom Vis Sci* 71:301-311.
- Marr D (1969) A theory of cerebellar cortex. *J Physiol* 202:437-470.
- Martin I, Levey AB (1991) Blocking observed in human eyelid conditioning. *Q J Exp Psychol B* 43:233-256.
- Massion J (1992) Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol* 38:35-56.
- Martin L, Picoult E, Stevens JK, Edwards MW, Jr., Young D, MacArthur R (1982) Oculoparalytic illusion: visual-field dependent spatial mislocalizations by humans partially paralyzed with curare. *Science* 216:198-201.
- McCrea RA, Gdowski GT, Boyle R, Belton T (1999) Firing behavior of vestibular neurons during active and passive head movements: vestibulo-spinal and other non-eye-movement related neurons. *J Neurophysiol* 82:416-428.
- McGuire PK, Silbersweig DA, Murray RM, David AS, Frackowiak RS, Frith CD (1996) Functional anatomy of inner speech and auditory verbal imagery. *Psychol Med* 26:29-38.
- McIntyre J, Zago M, Berthoz A, Lacquaniti F (2001) Does the brain model Newton's laws? *Nat Neurosci* 4:693-694.
- McLaren I (1989) The computational unit as an assembly of neurones: an implementation of an error correcting learning algorithm. In: *The Computing Neuron* (Durbin R, Miall C, Mitchison G, eds). Amsterdam: Addison-Wesley.
- Merfeld DM, Zupan L, Peterka RJ (1999) Humans use internal models to estimate gravity and linear acceleration. *Nature* 398:615-618.

References

- Miall RC, Wolpert DM (1996) Forward models for physiological motor control. *Neural Networks* 9:1265-1279.
- Miall RC, Weir DJ, Wolpert DM, Stein JF (1993) Is the Cerebellum a Smith Predictor? *J Mot Behav* 25:203-216.
- Miller RJ (1998) Presynaptic receptors. *Annu Rev Pharmacol Toxicol* 38:201-227.
- Milne RJ, Aniss AM, Kay NE, Gandevia SC (1988) Reduction in perceived intensity of cutaneous stimuli during movement: a quantitative study. *Exp Brain Res* 70:569-576.
- Milner TE, Cloutier C (1993) Compensation for mechanically unstable loading in voluntary wrist movement. *Exp Brain Res* 94:522-532.
- Mirenowicz J, Schultz W (1996) Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. *Nature* 379:449-451.
- Mountcastle VB, LaMotte RH, Carli G (1972) Detection thresholds for stimuli in humans and monkeys: comparison with threshold events in mechanoreceptive afferent nerve fibers innervating the monkey hand. *J Neurophysiol* 35:122-136.
- Muller F, Dichgans J (1994a) Impairments of precision grip in two patients with acute unilateral cerebellar lesions: a simple parametric test for clinical use. *Neuropsychologia* 32:265-269.
- Muller F, Dichgans J (1994b) Dyscoordination of pinch and lift forces during grasp in patients with cerebellar lesions. *Exp Brain Res* 101:485-492.
- Nelson H (1991) National Adult Reading Test. Windsor, Berks: NFER-Nelson.
- Ojakangas CL, Ebner TJ (1992) Purkinje cell complex and simple spike changes during a voluntary arm movement learning task in the monkey. *J Neurophysiol* 68:2222-2236.

References

- Oscarsson O (1979) Functional units of the cerebellum-sagittal zones and microzones. *Trends Neurosci* 2:143-145.
- Overall J, Gorham D (1962) The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799-812.
- Pascual-Leone A, Bartres-Faz D, Keenan JP (1999) Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of 'virtual lesions'. *Philos Trans R Soc Lond B Biol Sci* 354:1229-1238.
- Pascual-Leone A, Walsh V, Rothwell J (2000) Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol* 10:232-237.
- Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M (1995) Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol* 74:1037-1045.
- Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD (1998) Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 15:333-343.
- Pelz JB, Hayhoe MM (1995) The role of exocentric reference frames in the perception of visual direction. *Vision Res* 35:2267-2275.
- Rao RP, Eagleman DM, Sejnowski TJ (2001) Optimal smoothing in visual motion perception. *Neural Comput* 13:1243-1253.
- Rescorla RA, Wagner AR (1972) A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: *Classical Conditioning II: Current Research and Theory* (Black AH, Prokasy WF, eds). New York: Appleton Century Crofts.

References

- Romo R, Merchant H, Zainos A, Hernandez A (1996) Categorization of somaesthetic stimuli: sensorimotor performance and neuronal activity in primary somatic sensory cortex of awake monkeys. *Neuroreport* 7:1273-1279.
- Rothwell JC, Thompson PD, Day BL, Boyd S, Marsden CD (1991) Stimulation of the human motor cortex through the scalp. *Exp Physiol* 76:159-200.
- Roy JE, Cullen KE (2001) Selective processing of vestibular reafference during self-generated head motion. *J Neurosci* 21:2131-2142.
- Roy JE, Cullen KE (2004) Dissociating self-generated from passively applied head motion: neural mechanisms in the vestibular nuclei. *J Neurosci* 24:2102-2111.
- Rumelhart DE, Hinton GE, Williams RJ (1986) Learning representations by back-propagating errors. *Nature* 323:533-536.
- Rushton DN, Rothwell JC, Craggs MD (1981) Gating of somatosensory evoked potentials during different kinds of movement in man. *Brain* 104:465-491.
- Sainburg RL, Ghez C, Kalakanis D (1999) Intersegmental dynamics are controlled by sequential anticipatory, error correction, and postural mechanisms. *J Neurophysiol* 81:1045-1056.
- Savelsbergh GJ, Whiting HT, Burden AM, Bartlett RM (1992) The role of predictive visual temporal information in the coordination of muscle activity in catching. *Exp Brain Res* 89:223-228.
- Scheerer E (1973) Integration, interruption and processing rate in visual backward masking. I. Review. *Psychol Forsch* 36:71-93.
- Schmitz C, Martin N, Assaiante C (1999) Development of anticipatory postural adjustments in a bimanual load-lifting task in children. *Exp Brain Res* 126:200-204.

References

- Schmitz C, Martin N, Assaiante C (2002) Building anticipatory postural adjustment during childhood: a kinematic and electromyographic analysis of unloading in children from 4 to 8 years of age. *Exp Brain Res* 142:354-364.
- Schneider K (1959) *Clinical Psychopathology*. New York: Grune and Stratton.
- Schultz W (1998) Predictive reward signal of dopamine neurons. *J Neurophysiol* 80:1-27.
- Schultz W, Apicella P, Ljungberg T (1993) Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J Neurosci* 13:900-913.
- Seki K, Perlmutter SI, Fetz EE (2003) Sensory input to primate spinal cord is presynaptically inhibited during voluntary movement. *Nat Neurosci* 6:1309-1316.
- Shadmehr R, Mussa-Ivaldi F (1994) Adaptive representation of dynamics during learning of a motor task. *J Neurosci* 14:3208-3224.
- Shimazu H, Kaji R, Murase N, Kohara N, Ikeda A, Shibasaki H, Kimura J, Rothwell JC (1999) Pre-movement gating of short-latency somatosensory evoked potentials. *Neuroreport* 10:2457-2460.
- Sirigu A, Duhamel JR, Cohen L, Pillon B, Dubois B, Agid Y (1996) The mental representation of hand movements after parietal cortex damage. *Science* 273:1564-1568.
- Spencer TJ, Shuntich R (1970) Evidence for an interruption theory of backward masking. *J Exp Psychol* 85:198-203.
- Sperry RW (1950) Neural basis of the spontaneous optokinetic response produced by visual inversion. *J Comp Physiol Psychol* 32:482-489.

References

- Stevens JK, Emerson RC, Gerstein GL, Kallos T, Neufeld GR, Nichols CW, Rosenquist AC (1976) Paralysis of the awake human: visual perceptions. *Vision Res* 16:93-98.
- Thoroughman KA, Shadmehr R (1999) Electromyographic correlates of learning an internal model of reaching movements. *J Neurosci* 19:8573-8588.
- Tsakiris M, Haggard P (2003) Awareness of somatic events associated with a voluntary action. *Exp Brain Res* 149:439-446.
- Vallbo AB, Johansson RS (1978) The tactile sensory innervation of the glabrous skin of the human hand. In: *Active Touch* (Gordon G, ed), pp 29-54. New York: Pergamon.
- van Beers RJ, Sittig AC, Gon JJ (1999) Integration of proprioceptive and visual position-information: An experimentally supported model. *J Neurophysiol* 81:1355-1364.
- Vogt S (1995) On relations between perceiving, imagining and performing in the learning of cyclical movement sequences. *Br J Psychol* 86 (Pt 2):191-216.
- von Holst E (1954) Relations between the central nervous system and the peripheral organs. *Brit J Anim Behav* 2:89-94.
- von Holst E, Mittelstaedt H (1950) Das Reafferenzprinzip. *Naturwissenschaft* 37:464-476.
- Wada Y, Kawato M (1993) A neural network model for arm trajectory formation using forward and inverse dynamics models. *Neural Networks* 6:919-932.
- Weiskrantz L, Elliott J, Darlington C (1971) Preliminary observations on tickling oneself. *Nature* 230:598.

References

- Welch R (1985) Adaptation of space perception. In: Handbook of Perception and Human Performance (Boff K, Kaufmann L, Thomas J, eds). New York: Wiley.
- Williams SM, Goldman-Rakic PS (1993) Characterization of the dopaminergic innervation of the primate frontal cortex using a dopamine-specific antibody. *Cereb Cortex* 3:199-222.
- Williams SR, Chapman CE (2002) Time course and magnitude of movement-related gating of tactile detection in humans. III. Effect of motor tasks. *J Neurophysiol* 88:1968-1979.
- Williams SR, Shenasa J, Chapman CE (1998) Time course and magnitude of movement-related gating of tactile detection in humans. I. Importance of stimulus location. *J Neurophysiol* 79:947-963.
- Witney AG, Wolpert DM (2003) Spatial representation of predictive motor learning. *J Neurophysiol* 89:1837-1843.
- Witney AG, Goodbody SJ, Wolpert DM (1999) Predictive motor learning of temporal delays. *J Neurophysiol* 82:2039-2048.
- Wolpert DM, Kawato M (1998) Multiple paired forward and inverse models for motor control. *Neural Networks* 11:1317-1329.
- Wolpert DM, Flanagan JR (2001) Motor prediction. *Curr Biol* 11:R729-732.
- Wolpert DM, Ghahramani Z, Jordan MI (1995) An internal model for sensorimotor integration. *Science* 269:1880-1882.
- Wolpert DM, Miall RC, Kawato M (1998) Internal models in the cerebellum. *Trends Cogn Sci* 2:338-347.

References

- Xiong G, Matsushita M (2000) Connections of Purkinje cell axons of lobule X with vestibulospinal neurons projecting to the cervical cord in the rat. *Exp Brain Res* 131:491-499.
- Yue G, Cole KJ (1992) Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J Neurophysiol* 67:1114-1123.