NEURAL MECHANISMS OF INCORPORATING KNOWLEDGE OF PRIOR MOVEMENT EXPERIENCE INTO FEEDFORWARD MOTOR COMMANDS

by

Tommy H.B. Ng
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APPROVAL

Name: Tommy Ng
Degree: M.Sc. Kinesiology
Title of Thesis: Neural mechanisms of incorporating knowledge of prior movement experience into feedforward motor commands

Examining Committee:
Chair: Dr. S. Robinovitch
Chair, Graduate Program Committee
Associate Professor, School of Kinesiology, SFU

Dr. T.E. Milner
Senior Supervisor
Professor, School of Kinesiology, SFU

Dr. M.F. Beg
Supervisor
Assistant Professor, School of Engineering Science, SFU

Dr. M. Liotti
External Examiner
Associate Professor, Department of Psychology, SFU

Date Defended/Approved: 07 January 2008
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ABSTRACT

The central nervous system (CNS) predicts the amount of force needed so that the hands can grasp and hold objects securely. How does the CNS compute the dynamics and produce the appropriate forces required to perform tasks like holding a cup or a needle? It has been proposed that the CNS combines *a priori* information about the properties of a movement with sensory information from the peripheral sensory receptors, to obtain optimal force estimation. We propose a novel task that requires the subjects to experience the magnitude of a first torque pulse and subsequently estimate and compensate a second torque pulse that is equal in magnitude. By varying the magnitude of the torque pulses according to a normal probability distribution with a large standard deviation, we investigate the neural mechanisms of how the CNS combines prior knowledge of movement experience with sensory feedback, to produce accurate feedforward motor commands.

**Keywords:** motor learning; prior knowledge; probability; sensory information
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DEDICATION

I would like to thank God for His providence,

my wife and my son for their love,

and my family for their support and encouragement.
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LITERATURE REVIEW

Introduction

Our daily activities for basic survival are inundated with the interaction of our limbs and the physical environment. As a toddler learns to walk; a child learns to write; a teenager learns to drive; a neurologically lesioned patient learns to adapt, they go through a gradual transition of unrefined movements to a set of motor skills. Throughout the entire life span, it is remarkable to see how humans are able to continually interact with new physical entities, learn new skills, and adapt to new surroundings, such that our quality of life improves. As we learn, we usually start off not being good at the task, but through practice, we gradually become proficient at performing it. To achieve this, the central nervous system (CNS) needs to learn a set of motor commands such that muscle activations can be coordinated appropriately to yield the desired movement. Apart from learning, the CNS also needs to continually update and modify its array of motor commands in order to accommodate the variability inherent in the physical environment.

To effectively investigate the mechanisms underlying learning and adaptation, it is imperative to ensure that all subjects have no a priori experience
in performing a task. To do this, novel mechanical environments generated by a robot or virtual displacements/distortions created by a prism provide possible solutions. Haptic interfaces have been widely used to investigate the processes involved in motor learning and adaptation (Bock 1990; Lackner and DiZio 1994; Shadmehr and Mussa-Ivaldi 1994; Shadmehr and Brashers-Krug 1997). In these studies, the subjects performed point-to-point movements within a given time, while interacting with a robotic manipulandum. While in some experiments predictable force fields were used (Shadmehr and Mussa-Ivaldi 1994; Lackner and DiZio 1994), others were carried out in unpredictable environments (Takahashi et al. 2001; Scheidt et al. 2001; Franklin et al. 2003; Osu et al. 2003). After practicing the task without any perturbing force (null field environment), the subjects generally learned the coupled dynamics of the robotic structure and the arm to produce movements that were close to 'straight-line'. The learned straight-line trajectory was used as a reference to quantify movement errors in the presence of perturbing force fields. Subsequently, to investigate the adaptability of the CNS, perturbing force fields were introduced which caused the arm to deviate from the learned trajectory. Over a series of movements in the presence of the external perturbation, the subjects adapted to the new environment and almost completely recovered the original performance in the null field environment. When the force fields were unexpectedly removed (catch-trial), the trajectory deviated in the opposite direction, relative to the initial perturbed trajectories. These deviations in the opposite direction, termed 'aftereffects,' provided evidence that the CNS did not simply stiffen the joints through co-
contraction of antagonist muscles to adapt, but developed an internal model that was appropriate for counteracting the perturbing force fields (Thoroughman and Shadmehr 2000). An internal model is defined as a representation of the transformation from neural commands to the desired limb movement (Kawato 1999; Milner et al. 2005).

**Representations of the internal model by the CNS**

**Learning and adaptation in predictable environments**

To perform even a simple reaching movement, the CNS requires a controller that specifies a set of time-varying signals so that the internal model can generate motor commands to activate the appropriate muscles at the correct time to produce the desired movement. At the early stages of learning and adaptation, the internal model is inaccurate due to limited information available before the movement, causing a disparity between the internal model's approximation and the actual external environment. With practice in predictable force fields where perturbations are consistent from trial-to-trial, large movement errors would decrease exponentially and plateau to a baseline level. What changes does the internal model undergo such that the CNS is able to compute the inverse dynamics of the required task?
Although it is difficult to specify the parameters that have been modified within the internal model during learning and adaptation, it is possible to demonstrate the changes in the neural representation of the internal model through temporal shifts and rotations in spatial tuning of muscle electromyographic (EMG) functions (Thoroughman and Shadmehr 1999). In their experiment, the subjects made reaching movements in a velocity-dependent force field and attempted to correct the movement errors caused by the perturbations late in the trajectory. Perpendicular displacements measured at 250 ms after movement onset indicated significant deviations from the desired trajectory. The subjects responded 'online' by counteracting the perturbation in order to reach the target. The delayed error-feedback response corresponded with the peak of the agonist muscle activation late in the movement. By practicing in the force field, there was a gradual temporal shift in the peak of the EMG to very early in the movement, before proprioceptive or visual information was available. The temporal shift in the EMG indicated that the neural representation was modified from a feedback response to one that was feedforward and predictive in nature. Computational studies suggested that a copy of the error-feedback response could be sent to the brain to be used as a 'template' to train the internal model in a supervised learning paradigm (Kawato et al. 1987; Stroeve 1997). If so, the internal model that used feedback control to correct movement errors after their occurrence, could be trained and modified to code for feedforward motor commands to cancel out perturbing forces early in the movement.
To investigate other changes in the neural representation of the internal model during learning and adaptation, EMG generated 50 ms before to 100 ms after the initiation of the movement were used to construct muscle-tuning functions. EMG profiles during this period were likely to be influenced only by the feedforward component of the descending commands (Miall 1995; Kudo and Ohtsuki 1998). During learning and adaptation, changes in the neural representations of the internal model are represented by a spatial rotation of the muscle-tuning function’s resultant vector (preferred direction). During early force field training, the rotation of the muscle-tuning function’s preferred direction was marginal. However, late in force field training, the rotation was significant and the change in spatial orientation corresponded to the dynamics of the imposed perturbations.

Previous work using wrist movement (one degree of freedom - 1 d.o.f) showed that subjects reduced the level of co-contraction of the flexor and extensor muscles as they learned to move a novel load (Milner and Cloutier 1993). Thoroughman and Shadmehr (1999) and Franklin et al. (2003) reported that in 2 d.o.f. movements involving the shoulder and the elbow, there was also a rapid reduction in co-contraction as the subjects trained in the force field. These results suggested that the internal models which initially coded for high level of muscle co-contraction in order to stabilize the perturbing effect of the novel
dynamics subsequently reduced limb stiffness as the required dynamics of the task were learned.

Donchin et al. (2003) analyzed how errors in a specific trial affected subsequent movement as a function of its direction. When a subsequent movement was made in the same direction as the previous trial, kinematic errors yielded positive effect such that deviations from the desired trajectory were gradually reduced. However, when subsequent movements deviated progressively from the direction of the previous trial, the effect that the kinematic errors had on the internal model became less and less significant. For trajectories that differed by more than 90 degrees from the previous trial, there was a negative effect. This indicated that for trajectories that required arm configurations that differed significantly from those utilized in the preceding movement, performance would degrade accordingly due to modification of the prior internal model based on state-dependent information. This meant that for regions of the state-space that were not experienced during training, the joint torques necessary to move the arm along those trajectories would not have been learned. Thus, resulting in poorer performance as the limb movement deviated from the learned trajectory. These results suggested that the neural representation of the internal model appropriate for the dynamics of the imposed force field could be represented by a broadly tuned Gaussian-like basis functions relating force to direction of motion.
Milner and Hinder (2006) investigated what type of kinematic information the CNS utilizes to update its internal model during adaptation to a change in environmental dynamics. In their experiment, the subjects initially practiced in a null field condition, followed by training in a position-dependent force field environment of a fixed strength. Transition from the former to the latter condition yielded movement errors in the direction of the perturbation. These movement errors reduced rapidly after several trials in the force field reaching a plateau close to baseline level. Aftereffects showed that the CNS developed an internal model appropriate for counteracting the force field. Intermittently, two trials of the same force field but twice the strength were introduced in succession. By the second trial in the increased force field condition, the subjects had reduced movement errors considerably. When the second trial was replaced by an oppositely directed velocity-dependent force field, subsequent aftereffects showed that the subjects continued to apply forces in the direction that counteracted the position-dependent force field. Consequently, the movement assisted the perturbations in the velocity-dependent force field instead of counteracting it. This indicated that the CNS did not use the information about the direction of the force field to modify its feedforward commands, but the results were consistent with the use of information about the direction of the position error.
Learning and adaptation in unpredictable environments

Kinematic errors arise due to the discrepancies between the internal model's approximation and the actual dynamics of the external environment. Although studies have shown that kinematic information is used in adapting to changes in environmental dynamics, exactly how the CNS integrates sensory information in order to estimate end-point force remains unknown. Kording and Wolpert (2004) demonstrated that subjects combined a priori knowledge of the task dynamics and the reliability of sensory feedback in order to estimate compensatory movement accurately. In their experiment, the subjects made reaching movement in a virtual reality set-up that displaced the index finger laterally, relative to its true location. The magnitude of the displacement on each trial was drawn from a Gaussian distribution with fixed mean but varying standard deviation. The visual feedback provided midway through the movement allowed the subjects to evaluate how much the finger had been displaced. Subsequently, they adjusted their trajectory in order to reach the target. The visual feedback was manipulated such that the subjects received either clear or increasingly blurred vision of the lateral shift. After training on the task with lateral shift drawn from a particular Gaussian distribution, the displacement from the target in the absence of feedback was close to the mean of the distribution. Depending on the noise level of the visual feedback, the subjects compensated for the lateral shift by combining visual information and a priori knowledge of the distribution. When the visual feedback was provided clearly, the subjects depended primarily on the
information of the true index finger position to make compensatory movements towards the target. As the feedback became increasingly blurred, the subjects began to rely more on the \textit{a priori} knowledge of the finger displacement. When the feedback was completely obscured, the subjects compensated for the displacement of the finger by an amount approximately equal to the mean of the probability distribution from which the displacement was drawn. These results suggested that the CNS developed an optimal estimate by weighting the reliability of the visual feedback, using \textit{a priori} knowledge to estimate the compensatory movement when feedback became unavailable.

To demonstrate that Bayesian integration is not limited to the visual system, Kording et al. (2004) extended their earlier study to investigate how the brain integrated proprioceptive feedback and \textit{a priori} information of the task dynamics to estimate applied force. In their experiment, the subjects performed a guided movement during which their hand was perturbed by a force pulse whose amplitude was randomly drawn from a probability distribution. Later in the movement, they were required to counteract the same force pulse such that the cursor representing the hand position passed as close to the final target as possible. One group of subjects experienced a narrow distribution of force pulses over the first 2 days and a wide distribution on the 3\textsuperscript{rd} day, while another group had the protocol reversed. By plotting force estimation error ($\Delta F = F_{\text{true}} - F_{\text{estimated}}$) as a function of the presented force ($F_{\text{true}}$), the gradient of the function was compared for both groups. On the first day, there was no significant
difference in the gradient between the two groups, suggesting that the subjects made comparable misestimation of the presented force pulses. On the second day, the group that experienced the narrow distribution had a steeper gradient, suggesting that the subjects had learned the average force pulse of the probability distribution and relied on it to make estimations. The steeper gradient was a result of obvious estimation errors as the subjects attempted to compensate small and large force pulses with the average force pulse strength. Given that the force pulses varied over a larger range in the wide distribution, the subjects were not able to utilize the varying sensory feedback of the trials to learn the approximate mean force pulse of the distribution and appeared to rely more on information about the magnitude of the first pulse. On the third day, when distributions were exchanged between the groups, the subjects who trained with the narrow distribution could no longer depend on the *a priori* information of the task dynamics, but had to learn to depend on the sensory feedback from the first force pulse to make an optimal estimation. These results suggested that the CNS was able to integrate *a priori* information of the task dynamics and current sensory feedback to optimize performance in a way consistent with Bayesian integration. Other studies have examined how the CNS weights sensory inputs differently depending on the computations being performed, in order to minimize errors arising from noise and uncertainty in the sensory and motor systems. Sober and Sabes (2005) manipulated the modality and saliency of the feedback to examine if sensory integration was influenced by the cost of performing coordinate transformations on the sensory inputs. The subjects were required to
reach to either visual or proprioceptive targets located in different directions with their right index finger. The visual target consisted of a spot of light and the proprioceptive target was the sensed position of the subject's left index finger underneath the table. On all trials, the visual feedback of the right index finger appeared either as the true position, shifted leftward or rightward. Results showed that when the subjects reached to visual targets, the brain integrated the displaced visual inputs with the information arising from the position of the right index finger to plan the trajectory. Since the coordinate frame of the visual feedback was analogous to that of the target, it was suggested that the brain avoided transformation between coordinate frames by relying on the inaccurate visual signals, instead of the information provided by proprioception. This resulted in larger shift-induced movement errors, relative to those when subjects reached to proprioceptive targets. It was likely that the brain weighted the visual and proprioceptive feedback with a least coordinate transformation bias, and relied more on the information about the configuration of the joints of the right arm to plan the desired trajectory. In a follow-up experiment, the saliency of the visual feedback was manipulated by presenting the subjects with either the position of their right index fingertip or the whole arm. Results showed that when the feedback was constrained to only the fingertip, proprioception dominated the computation of the required motor commands. However, when the whole arm configuration could be perceived by the subjects, the two sensory modalities contributed nearly equally to the computation of the motor commands.
Scheidt et al. (2001) reported that as the subjects adapted to a viscous, perpendicular, force field environment whose gains were uncorrelated from trial to trial, they compensated for the approximate mean force field of the stochastic sequence and utilized only the memories of the most recent perturbations and performances to estimate the strength of the upcoming force field. Adaptation to a predictable force field yielded 'aftereffects' (limb movements that are symmetrically opposite to the initially perturbed trajectories) during the 'catch-trials' (Shadmehr and Mussa-Ivaldi 1994). However, during adaptation to an unpredictable force field there were no 'aftereffects' per se. Instead, the adaptation resulted in movements that were 'curved', where the direction and size of the curvature depended on the strength of the force field on a given trial (Scheidt et al. 2001). This meant that when the force field strengths were less than the estimated mean, hand-path deviations were consistently toward one side of the desired trajectory; and vice versa when the imposed force field strength was greater than the estimated mean. This strategy adopted by the CNS might not attenuate kinematic errors completely, but was able to minimize the errors to within a reasonable residual level. It was difficult to confirm that the CNS compensated for the mean and not the 'modal' force field of the distribution (force field with the highest frequency) because the mean and mode of a uni-modal Gaussian distribution were synonymous. To distinguish the two entities, a bi-modal distribution of differing means (6 Ns/m [175 trials], 25 Ns/m [225 trials]) was used to examine if the subjects adapted to the mean or the mode of the distribution. The results showed that the CNS did not compensate for the mode
of the force field distribution, even though the perturbations occurred more frequently near the range of 25 Ns/m. Instead, the CNS adapted to a perturbing field strength (11.33 Ns/m) that was most rarely experienced (zero crossing of the regression line that best fitted the data points of the two distinct distribution) in the task. This magnitude of the field strength (11.33 Ns/m) was not the exact mean force field of the distribution (15.5 Ns/m), but it was sufficient to show that the CNS adapted to the approximate mean (95% confidence interval of [8.61, 14.04]), and not the mode of the bi-modal distribution (Scheidt et al. (2001)).

Mathematically, the mean perturbation magnitude is defined as the sum of the individual magnitude divided by the number of perturbations. How does the brain carry out this computation? In the experiments aforementioned, the subjects could not have known the magnitude of all the perturbations and when the last trial would occur. Hence, it would not be possible for them to directly compute the mean field strength. In addition, to compute a 'running average' of all the trials they had experienced would place an exceptional computational demand on the CNS; requiring it to keep an update of the explicit memory of all previously encountered perturbations. Scheidt et al. (2001) proposed that the CNS relied on information of the most recent trials to estimate the next force. The authors used cross correlation analyses of the subjects' motor performance to show that there was significant correlation between 1) movement error and perturbation gain of the current and previous trial; 2) movement error of the current trial and error generated in the preceding trial; 3) peak hand force and
perturbation gain of the current and previous trial; and 4) movement error and peak hand force of the current and previous trial. These results coupled with the lack of correlations beyond two previous trials suggested that the CNS utilized only explicit memory representation from a limited number of previous trials to adjust the motor commands on subsequent trials. How could the mean of the force field distribution have been computed? One could only posit that the CNS compensated for the approximate mean of the distribution under these conditions: 1) the CNS averaged limited number of previous trials with magnitude that were close to the mean of the probability distribution and 2) the CNS averaged limited number of previous trials with magnitude that were both smaller and larger than the mean. Under these conditions, averages of the previous trials were likely to approximate the mean of the distribution. Additionally, given the boundary of the probability distribution, it was not possible for the force field magnitude to continuously deviate from the mean. For example, after a limited number of increasingly large force field, a perturbation smaller than the mean would 'reset' the average of the previous trials to approximate the mean of the distribution, and vice versa.
Control of Impedance

Components of impedance

Muscular impedance is defined as the resistive properties of muscles to external perturbations, and it is composed of passive and active elements. The passive component comprises of attached cross-bridges when the muscles are at rest and the structural makeup of the myofilaments. The active component comprises of resistance arising from muscle activations that generate force to bring about voluntary limb movements. The impedance of muscles is primarily observed in its resistance to displacement (stiffness) and velocity (damping); and to a lesser extent, the invariant property of inertia. Taken together, muscle stiffness and damping are referred to as viscoelastic impedance (Gasser and Hill 1924; Huxley and Simmons 1971). Factors that influence viscoelastic impedance are velocity, length, amplitude and, motor unit firing frequency, prior history of muscle activation (Kearney and Hunter 1990), and reflexive gains of sensory receptors (Rack 1981). Although the level of impedance changes during voluntary movement, co-contracting two or more antagonist muscles at a joint or limb, without altering joint torque or endpoint force, may also modulate it.
Impedance control strategy during learning and adaptation

During early stages of learning and adaptation in a stable dynamical environment, the brain responds to the novel dynamics by stiffening the limb through co-contraction of antagonist muscles in order to maintain stability and/or minimize movement errors (Milner and Cloutier 1993; Thoroughman and Shadmehr 1999; Franklin et al. 2003; Franklin and Milner 2003). With practice, the brain learns to generate feedforward motor commands to directly counteract perturbing forces from the environment, reducing the level of co-contraction as the internal model is developed.

Takahashi et al. (2001) investigated the control strategies that the CNS utilized to learn a reaching task in a randomly varying dynamical environment. In their experiment, the subjects made reaching movements in conditions interspersed with permutations of null field (no perturbation), mean field (constant force gain), and ‘noise’ field (inconsistent force gain). For subjects who learned first in a predictable dynamic environment (mean field) and then in a random environment (noise field), the aftereffect in the latter was smaller than that in the former. This diminished aftereffect did not imply that the subjects' performance was worse off in the noise field because there was no significant difference in performance as indexed by the movement errors, variance of error, and exponential time constants of the learning curves in both force field conditions.
within-subject repeated measure analysis of variance showed a steeper slope (mean squared error-force gain function) during initial exposure to the noise field, relative to later in the experimental session. Correspondingly, the movement errors were larger during early stages of movement, relative to later stages for the same range of force gain. These results suggested that the reduced noise field aftereffect was likely one of the strategies used by the CNS when the subjects learned in an unpredictable environment. In such circumstances, it was optimal for the CNS to increase limb impedance by co-contracting antagonist muscles so that movement errors could be minimized; and mean perturbation magnitude could be predicted.

**Neuroimaging**

Functional neuroimaging attempts to identify and localize region(s) of the brain that are associated with a given perceptual, motor, or cognitive function. Different techniques utilize different conceptual frameworks and theoretical principles to investigate the neural correlates of functional activity in the brain. For example, positron emission tomography (PET) relies on the injection of radioactive tracers to measure changes in the brain, including blood flow and/or glucose metabolism. This method has several disadvantages such as the detriments of the radioactive materials to the human body, the cost of generating radioactive isotopes, and the relatively slow speed at which the images are
acquired. Intracranial electrophysiological recordings are invasive because they involve the insertion of electrodes near neurons to localize activity. Although these methods enable the direct measurement of neuronal activity, they are not normally suitable for humans, but are restricted to animal studies and patients undergoing open brain procedures. In addition, it is not possible to record whole-brain activity. While electroencephalography (EEG) and magnetoencephalography (MEG) are not invasive, both require complex mathematical algorithms that are prone to error to identify the locations of the neural source that caused a given pattern of activity within the brain. Additionally, MEG requires stringent experimental procedures during data acquisition, in order to prevent movement artefacts. Although fMRI is also prone to movement artefacts, advances in the technique have facilitated high contrast-to-noise ratio data acquisition during whole-brain imaging with better temporal resolution than PET and better spatial resolution than any other whole-brain functional imaging technique (Ogawa et al. 1998).

**Components of an fMRI scanner**

The three main components of an fMRI machine are 1) static magnetic field, 2) radiofrequency coils, and 3) gradient coils. Strong static magnetic fields are required in fMRI scanners to align the protons (hydrogen within the water molecules) within the human body, so that mapping of tissue properties is
possible. In order to generate a large magnetic field, the wires of the solenoid (superconducting electromagnet) have to be cooled to a temperature near -261°C to reduce the resistance so that a strong and lasting electric current can flow to produce the desired field strength. Typically, field strength of 1 to 3 Tesla is used in experiments involving humans and up to 20 Tesla in animals. The quality of the functional images is not only affected by the strength of the magnetic field, but also its homogeneity. In order to achieve uniformity in the magnetic field space, a large cylindrical solenoid with high density of circularly compressed wires is positioned at the center of the scanner. While the strong static magnetic field causes the protons within the body to align to it, the static field itself does not produce any magnetic resonance (MR) signals. The purpose of a radiofrequency coil is to introduce a series of transient magnetic pulses (excitation pulse) to the aligned protons to perturb them from their state of equilibrium. When an excitation pulse is administered, the protons absorb electromagnetic energy from the pulse and begin to resonate at a particular frequency. When the pulse is turned off, the protons release the energy that was absorbed and return to its equilibrium state. The release of energy detected by the radiofrequency coil defines the raw MR signals. In an fMRI setting, the birdcage volume coil that is placed immediately around the head represents the radiofrequency coil. Hitherto, the static magnetic field and the radiofrequency coil provide the creation and detection of the MR signals, but these signals alone do not yield functional images of the brain. In this respect, a gradient coil is used to manipulate the spatial orientation of the MR signals so that different locations
within the brain space contribute uniquely to the measured signals over time. Subsequently, these acquired MR signals undergo Inverse Fourier Transformation (IFT) to produce 2-dimensional MR images. These images can then be mapped onto an individual's structural image to show regions of the brain that were activated during a specific functional task. In addition, by mapping the 2-dimensional MR images onto a reference brain, between-subjects comparison of the functional brain areas can be done (Figure 1).

**Figure 1:** Stages of 2-D magnetic resonance (MR) image formation. Solid boxes on the upper row represent the different stages of image formation and the dotted boxes on the lower row represent the processes involved in constructing 2-D MR images.

**Basic principles of MR signal generation**

In the absence of a strong magnetic field, the nuclear magnetic resonance (NMR) property of the hydrogen protons within the body causes them to spin about their own axis in a random fashion. However, when the body is positioned within the scanner bore, the protons not only spin with their axis of rotation tilted at an angle, but the axis of rotation itself gyrates about the longitudinal axis of the
external field. This gyroscopic motion of the proton is known as precession (Kandel et al. 2000). Within the magnetic field, the protons that are low in energy orientate their axis of spin along the direction of the external field, while the axis of spin of the high-energy protons is in the opposite direction. By emitting transient excitation pulses at the frequency of the spin precession (Larmor frequency), the protons transit from a low-energy state to a high-energy state by absorbing the electromagnetic energy. During this process, the net longitudinal magnetization of the proton spin is tipped into the transverse plane and the protons begin to precess in an inward spiral pattern. When the pulses are turned off, the excess protons spinning at the higher energy state return to the lower state, and in doing, release the excess electromagnetic energy to establish ‘energy-state’ equilibrium. The released energy detected by the radiofrequency coil constitutes the raw MR signals. The time constants that characterize the transition of energy states are 1) $T_1$, which describes the recovery of the longitudinal magnetization from the transverse plane, 2) $T_2$, which describes the decay of the MR signals in the transverse plane due to interaction between the protons (spin-spin interaction), and 3) $T_2'$, which describes the decay of the MR signals due to both the spin-spin interaction and the external magnetic field inhomogeneity experienced by the protons as they transit through the magnetic field space. While the functional images of the brain depend predominantly on time constant $T_2'$, the structural images depend on $T_1$. Typically, $T_2$ decay time is of the order of a few tens of milliseconds and $T_1$ recovery time is of the order of 1s. Therefore, after an excitation pulse, it is common for the recovery of the
longitudinal magnetization and the decay of the transverse magnetization to occur over a period of a few seconds and about 100 ms respectively.

**Parameters of pulse sequences and resolution control in fMRI**

After an excitation pulse, the change in the orientation of the net longitudinal magnetization of the proton spin to the transverse plane is termed flip angle. A 90-degree flip angle is commonly used to optimize the change in the direction of the net longitudinal magnetization so that the radiofrequency coils detect the largest measurable MR signals. Essentially, the greater the detected MR signals, the better the construction of the anatomical images of the brain.

Two parameters that determine the time at which the MR signals should be collected are repetition time (TR), which is the time interval between successive excitation pulse and echo time (TE), which is the time interval between excitation and data acquisition. TR and TE are components of a pulse sequence and the values that they take depend primarily on the type of images required. To generate images sensitive to $T_1$ contrast, the specified TR and TE values should facilitate maximal detection of MR signals arising from the recovery of the net longitudinal magnetization and minimal detection of MR signals from the decay of the proton precession, *vice versa* for images sensitive to $T_2$ contrast. For images sensitive to $T_2^*$ or blood-oxygen-level dependent
(BOLD) contrast, gradient-echo sequences are used (echo-planar imaging). This type of pulse sequence has TR and TE values similar to those used in $T_2$ contrast, with an addition of a magnetic field gradient to generate signal echo to eliminate field inhomogeneity effects (Huettel et al 2004). This procedure is important because as the proton precession decays, the net magnetization of the proton spin is concomitantly transiting from the transverse plane back to the longitudinal plane, and inhomogeneous static magnetic field would cause artefacts in the image formation.

The spatial resolution of a functional image is defined as the ability to distinguish changes in a brain mapping across different spatial locations and is determined by the dimensions of the voxels used in the image construction. Voxels are rectangular prisms and their dimensions are specified by three parameters: field of view (FOV), matrix size, and slice thickness. The FOV describes the extent of the imaging volume within a slice and is generally expressed in centimeters. The matrix size determines how many voxels are present in each dimension. Matrices used in functional imaging are generally powers of 2 (64, 128, and 256) to facilitate fast inverse Fourier transform for image construction. For example, if the FOV for a pulse sequence is 24 cm by 24 cm, and the matrix size is 64 by 64, the resulting within-slice (in-plane) voxel size is $3.75 \text{ mm} \times 3.75 \text{ mm}$ (FOV divided by matrix size). The third dimension (through-plane) of a voxel is defined by the slice thickness. The slice thickness may take the same value or larger than the in-plane voxel size, and in the former
case, the voxel is cubic and the spatial resolution is said to be isotropic. The
temporal resolution of a functional image is defined as the ability to distinguish
changes in the hemodynamic activity at a single location over time; and it is
dependent primarily on the TR used in the pulse sequence.

**Blood Oxygen Level Dependent (BOLD) fMRI**

FMRI constructs images of physiological activity that is correlated with
neuronal activity. The functional work of processing and signalling information
within the brain cells requires energy in the form of adenosine tri-phosphate
(ATP). In order to synthesize adenosine di-phosphate (ADP) and a free
phosphate to yield ATP, glucose and oxygen are required and are supplied to the
brain cells by the vascular system. Oxygen molecules pass through the
respiratory airways to the alveoli-capillary junction, diffuse across the membrane
and bind to the hemoglobin to be transported to the targeted brain cells. When
oxygen molecules bind to hemoglobin, the coupled structure (oxygenated
hemoglobin [Hb]) becomes diamagnetic, that is, having the property of weak
repulsion from magnetic fields. In contrast, deoxygenated hemoglobin (dHb) is
paramagnetic, that is, having the property of being attracted to magnetic fields,
albeit with concentration of magnetic flux lesser than ferromagnetic objects. At
the onset of functional processes within the brain cells, the small amount of
oxygen present at the targeted cells begins to be used up to support the neuronal
activity. This causes a net increase in dHb at the site of the neuronal activity, and since dHb is paramagnetic, it affects the relaxation time of the $T_2^*$ decay, subsequently having an effect of suppressing the MR signal intensity. After a short latency of about 1-2 s, the vascular system begins to increase blood flow to the targeted cells and nearby brain regions such that the supply of substrates and oxygen far exceeds the metabolic demands (Fox and Raichle 1986). The influx of the Hb to the targeted cells and nearby brain regions attenuates the paramagnetic effect of the dHb and facilitates the generation of the MR signals arising from the $T_2^*$ decay of the proton precession (Ogawa et al. 1990).

**Previous fMRI studies of somatosensory signal processing**

Results from previous psychophysical experiments had adequately shown that the CNS was able to learn and adapt even in stochastic and unpredictable mechanical environments (Scheidt et al. 2001; Kording et al. 2004). During learning, the brain integrated somatosensory signals arising from the interaction with the external environments, and utilized that information as *a priori* knowledge to compensate the mean perturbation of the stochastic sequence. During late phases of learning, the muscle activity clearly indicated that the CNS learned the dynamics of the external environments and employed a feedforward control rather than a universal co-contraction strategy, to counteract the perturbations. What areas of the brain are involved in the neural processes
subserving the CNS's ability to learn and adapt in a constantly changing environment? To this end, a number of functional imaging studies have been done to examine the neural correlates of somatosensory signal processing during motor task adaptation.

Using positron emission tomography (PET), Nezafat et al. (2001) examined how regional cerebral blood flow (rCBF) in the cerebellum changed during different phases of learning a novel motor task. In their experiment, the subjects made multi-directional reaching movements in both constant and randomly changing velocity-dependent force fields. By contrasting images of the cerebellum at different stages of adaptation in the constant field, patterns of rCBF in the cerebellar cortex and deep cerebellar nuclei (DCN) were found to be significantly anti-correlated. Early in the constant field, the rCBF in the ipsilateral cerebellar cortex was found to be higher, relative to later stages in the same field. Contrarily, the rCBF in the DCN was low early in the constant field and higher as adaptation occurred. The authors suggested that the sensory consequence (error signal) in the constant field was utilized by the CNS for comparison with the 'efferent copy' of the original motor plan. The error signals served as inputs for the updating of the existing motor plans, so that perturbations in the constant field could be directly counteracted. The error signals, assumed to be carried by the climbing fibers, increased the rCBF in the cerebellar cortex (Nezafat et al. 2001; Schweighofer et al. 1998; Kitazawa et al. 1998). With the reduction of movement errors during adaptation, there was a corresponding decrease in the
rCBF in the cerebellar cortex. Since the mossy fibers and climbing fibers synapse with the Purkinje cells in the cerebellar cortex (Jueptner and Weiller 1998; Kandel et al. 2000; Bosco and Poppele 1993; Grill et al. 1994), it was suggested that the increased rCBF in the cerebellar cortex early in the constant field led to an increase in the activity of the Purkinje cells (Nezafat et al. 2001). The axons of the Purkinje cells synapse with the cells in the DCN and inhibited the neuronal activity and output of the DCN (Kandel et al. 2000). As a result, there was low rCBF in the DCN early in the constant field (Nezafat et al. 2001). In the late stages of adaptation, the reduction of movement errors led to a decrease in the inhibitory activity of the Purkinje cells and subsequently, an increase in the neuronal activity in the DCN, evident by a higher rCBF. The results of the study suggested that the cerebellum was likely a candidate neural substrate for the adaptation of visuomotor tasks.

Diedrichsen et al. (2005) investigated the mechanisms underlying the CNS’s ability to segregate movement errors and utilize somatosensory information (error signals) from execution errors to adapt to the dynamics of an external environment. In their experiment, the subjects made reaching movements to targets while interacting with a robotic manipulandum. In one condition, the target location was shifted after the subjects had initiated the movement. The errors in this condition were termed target errors. In the other condition, the subjects had to compensate perturbing forces from the onset of movement trajectory. The errors in this condition were termed execution errors.
The psychophysical results indicated that the target errors did not attenuate with practice, while the execution errors decreased to a residual level after adaptation. BOLD analysis revealed increased activation of the basal ganglia when target errors occurred and increased cerebellar activity during early phases of learning due to execution errors (Diedrichsen et al. 2005). To move the hand accurately from a starting point to a final target, visual and proprioceptive information had to be integrated by the brain before a state space dependent motor command could be encoded. After movement onset, a change in the target position would result in a complete change of the state space dynamics. The torques produced at the joints according to the original motor plan would become inappropriate for the new target position. The constant change in the state space dynamics caused the brain to select new motor plans for each target position. Since the motor plans were different from trial-to-trial, the movement errors from one trial could not be utilized to update the motor plan on the next trial. These results were in agreement with other studies that suggested the basal ganglia as a neural substrate for the selection and switching of goal-dependent motor plans (Zink et al. 2003; Cools et al. 2004; Redgrave et al. 1999). In the force field condition, it was suggested that a single motor plan with appropriate state space dynamics was used. During early stages of learning, large movement errors occurred due to an inaccurate motor plan. However, with practice, sensory information from the movement errors was integrated to update the original motor plan, so that feedforward motor commands could directly counteract the perturbations. Results from the study posited the role of the cerebellum as a neural entity that
utilized sensory information (trial-to-trial execution errors) to update existing motor plans during motor adaptation (Diedrichsen et al. 2005; Imamizu et al. 2000; Seidler et al. 2004).

Using event-related fMRI, Tunik et al. (2007) examined the neural processes underlying the brain’s ability to adapt to distinct torque perturbations and how level of BOLD responses at the activated brain areas differed as a function of time. In their experiment, the subjects made bidirectional movements in a target-capture task while compensating randomly delivered position and velocity-dependent torque perturbations. With practice in the visuomotor task, the subjects significantly reduced movement errors in both conditions. Errors on catch trials indicated that the brain was able to learn the dynamics of the tasks and execute movements using feedforward control. The inclusion of ‘catch’ trials ruled out the possibility that impedance control mechanisms were used to counteract the perturbations. Standard subtraction of BOLD-contrast responses showed an activated network involving the basal ganglia, cerebellum, and frontal-parietal brain areas. Using these brain areas as regions of interest (ROIs), a BOLD coherence analysis was done to examine the functional interaction between the activated brain areas as a function of time. During early stages of learning, the spectral analysis of the BOLD signals at the ROIs revealed little coherence. However, during late stages of learning, distinct coherence patterns were observed. While adaptation to the position-dependent perturbations had a stronger coherence between cortical-cerebellar brain regions, learning the
dynamics of the viscous condition yielded stronger basal ganglia-cortical coherence. In line with the findings of previous studies, the authors suggested that the cortical-cerebellar network was likely involved in the processing of somatosensory signals and the updating of motor plan on a trial-to-trial basis (Desmurget and Grafton 2000; Imamizu et al. 2000, Milner et al. 2005), and the basal ganglia-cortical network was involved in neural processes related to selection and scaling of motor commands (Desmurget et al. 2003, 2004; Georgopulos et al. 1983; Turner et al. 2003; Vaillancourt et al. 2004; Wichmann et al. 1994a,b; Gentilucci and Negrotti 1999; Jueptner and Weiler 1998; Kimura et al. 2003; Menon et al. 2000).

Schmitz et al. (2004) examined the brain regions that were activated when the subjects were asked to lift the same object, which had two different weights (230 g or 830 g) with their index finger and thumb. As a baseline reference, the subjects lifted object that weighed either 230 g or 830 g. Subsequently, the two different weighted objects were lifted in alternation (regular condition) or in random permutation (irregular condition). The T2*-weighted contrast of the conditions minus baseline showed activations in the prefrontal cortex and parietal cortex, particularly in the region of the parietal operculum and the supramarginal gyrus. The authors suggested that the fronto-parietal neural network facilitated the update of sensorimotor memory representations and corrective reactions, which were necessary during object manipulation (Schmitz et al. 2004). Additionally, critical properties of the object stored in the memory representations
were recalled to set the parameters of the motor program so that forces generated were appropriate for the weight being lifted (Johansson and Cole 1992; Johansson 1998; Schmitz et al. 2004).

Suminski et al. (2006) investigated the neural correlates of wrist postural control in different mechanical environments. In their experiment, the subjects were instructed to stabilize the handle of a manipulandum at a desired angle while the device applied either a predictable constant extensor torque about the wrist, or an unpredictable, pseudo-random extensor torque drawn from a normal probability distribution. The BOLD-contrast responses of the wrist posture control task followed two distinct neural patterns: a cerebello-thalamo-cortical network and another that involved the prefrontal cortex, dorsal premotor areas, supplementary motor areas, and the parietal cortex. It was suggested that the former neural network served as a feedback control system that monitored the moment-by-moment changes in the position errors. When the fluctuation in the position errors exceeded a certain threshold, the latter neural network adjusted the gain of the feedforward control system so that new motor commands could attenuate the moment-by-moment position errors back to a reasonable baseline level.
Summary / Justification

The mechanisms underlying the CNS’s ability to incorporate somatosensory information of prior movement experience into predictive motor commands is not fully understood. Previous psychophysical studies suggested that through training, the CNS developed an *a priori* knowledge of the physical properties of the task, and utilized that information to compensate the mean perturbation of the probability distribution.

One of the goals of the present study is to investigate how the CNS incorporates *a priori* knowledge of movement experience into feedforward motor commands to compensate for the approximate mean torque pulse of a stochastic sequence, based on the work of Scheidt et al. (2001) and Kording and Wolpert (2004). To address the research question, a torque pulse will be introduced in the first half of a torque-matching task to perturb the hand from a neutral position. The subject will estimate the magnitude of the torque pulse and subsequently counteract an identical torque pulse in the second half of the trial. In this way, the subject will not be constrained to strategies for dealing with uncertainty as in previous studies where the magnitude of each perturbation was unpredictable (Takahashi et al. 2001; Scheidt et al. 2001; Suminski et al. 2006), but can use information about the magnitude of the first torque pulse to modulate the feedforward motor commands, in preparation for the second torque pulse (Kording and Wolpert 2004).
When identical torque pulses are presented during the task, it is suggested that the CNS maintains a specific internal model over time and updates it based on sensory information from the interaction with the torque pulses. Because sensory feedback is consistent, the CNS is able to develop an accurate internal model for the perturbations to reduce movement errors to a residual level. When torque pulses of varying amplitude are presented, the brain does not receive consistent error feedback that can be used to iteratively improve an internal model of the dynamics of the perturbations. Since the error varies from trial to trial, depending on the strength of the perturbation, it is not possible to form an accurate internal model that will be appropriate for the upcoming torque pulse. In this case, it is posited that the CNS combines *a priori* knowledge of movement experience and sensory information from previous and current trials to form an internal model that will be optimal in the sense that it produces the least error, on average. If sensory information were completely unreliable, i.e. torque pulse amplitude varies randomly then the expectation would be that the CNS would form a model of the mean torque pulse amplitude. On the other hand, if accurate sensory information about the impeding torque pulse magnitude is available then there should be adjustments made to the mean torque pulse magnitude, on a trial by trial basis, which could be predicted from Bayesian integration, i.e. the conditional probability of the response on a given trial given a priori knowledge about the torque pulse distribution and any additional available sensory information. Thus, on average the CNS would be expected to compensate the mean perturbation amplitude of the probability distribution, but
the actual response on a given trial would also depend on the magnitude of the torque pulse on the previous trial and any sensory information that could be used to predict the magnitude of the impending torque pulse. One way in which this process could be implemented is by iteratively retrieving the internal model that has been acquired through experience, maintaining it in working memory, and after estimating the strength of the first torque pulse, appropriately modifying the internal model for the current response. Previous studies of motor learning (Franklin et al. 2003; Milner and Franklin 2005) have indicated that the scaling compensates only for a portion of the error on any given trial. Consequently, it would be expected that there would be scatter in the response about the mean which would increase in proportion to the difference in the magnitude of torque pulses on successive trials.

The second goal of the present study is to examine the neural correlates of incorporating knowledge of prior movement experience into predictive motor commands. By contrasting the mean hemodynamic response of motor adaptation in both predictable and unpredictable environments, it is hypothesized that the activated brain areas represent the neural processes necessary for recursive updating of an internal model based on the prior error and current sensory information.

Drawing from the results of the reviewed fMRI studies, it is hypothesized that motor adaptation in unpredictable environment involves neural processes in
the premotor and parietal cortex. Specifically, areas within the 1) parietal cortex are involved in the retrieval of a neural representation from memory and 2) premotor areas are involved in the cognitive processing of the neural representation and optimization of the scaling parameters based on information conveyed by the cerebellum. To address the research question, whole-brain fMRI was used to measure condition-specific brain activity when the subjects performed the torque-matching task. To our knowledge, no previous studies have investigated the neural correlates of incorporating somatosensory information into predictive motor commands. Therefore, the proposed study is novel and its expected outcome will provide a better understanding of how the neural processes are executed in the CNS.
EXPERIMENTAL APPROACH

Objectives

1. To better understand how the central nervous system (CNS) processes somatosensory information of prior movement experience and utilizes that information to develop feedforward motor commands.

2. To investigate if the CNS uses Bayesian-like processes to estimate and compensate the torque pulses drawn from a normal probability distribution.

3. To determine regions of the brain that are activated when the CNS incorporates prior knowledge of movement experience into feedforward motor commands.

Research Hypotheses

Research Hypothesis #1

It is hypothesized that the CNS compensates the approximate mean torque pulse of the probability distribution.
Research Hypothesis #2

It is hypothesized that the neural correlates of Bayesian models in torque estimation involve a fronto-parietal network.

Methods

The study was conducted at Advanced Telecommunication Research International (ATR), Kyoto, Japan.

Subjects and general procedure

Twenty neurologically normal subjects (19-36 years of age; all males) participated in the study after having the experimental procedures explained. All the subjects were right-handed and the required task was performed only with the right hand, that is, movement at the wrist. On the first day of the experiment, the subjects trained and learned a torque-matching task to estimate and compensate torque pulses drawn from a normal probability distribution with a large standard deviation (s.d.). Immediately after the training session, the subjects took part in a psychophysical experiment that comprised 3 conditions. In one condition, torque pulses were drawn from a normal probability distribution with a large standard deviation (pulse*v condition). In another condition, torque
pulses were always equal to the mean of the original distribution (pulse*condition). In the third condition, the handle of the manipulandum was locked in place and the subjects were required to produce torque pulses that were appropriate for compensating the torque pulses experienced in the pulse*condition (push condition). On the following day, the subjects participated in a functional magnetic resonance imaging (fMRI) experiment using the same protocol as in the psychophysical experiment. In a supplementary experiment, the manipulandum handle was locked on 20% of the trials during the second half of the trial to measure the feedforward torque produced by the subjects.

On a particular trial, the subjects were first presented with a torque pulse of a specific strength. They were required to judge its magnitude and subsequently counteract its perturbing effect when the same torque pulse was presented again during the second half of the trial. During the training sessions and psychophysical experiments, the subjects sat in a chair that was approximately 0.75 m from a computer screen. The hand was positioned in a way that the axes of rotation of the wrist and the handle of the manipulandum (fMRI-compatible) were aligned. The elbow joint was flexed at approximately 90 degrees and the shoulder joint was in a slightly flexed and abducted position relative to the frontal and sagittal planes of the body, respectively. The subjects’ forearm was strapped to the frame of the manipulandum and the right hand was strapped to the handle in a position that was mid-way between pronation and supination with the fingers extended. This arrangement restricted forearm
movement and left only the hand mobile to flex or extend at the wrist joint (Figure 2). When asked after the training session, the subjects said that they had attended to the visual cues on the screen and did not pay much attention to the peripheral view of the hand.

Electrodes were attached to the forearm muscles to record electromyographic (EMG) data during maximum voluntary contraction (MVC) and the torque-matching task. During the fMRI experiment, the subjects performed the same protocol while lying in a supine position within the scanner bore of an imaging machine. Due to space constraints, the right arm had to be positioned beside the body in a way that the elbow and shoulder joints were slightly flexed.

Figure 2: Subject's position during torque-matching task. The subject sat in a chair positioned at approximately 0.75 m from a computer screen (left), the elbow joint was flexed at approximately 90 degrees, and the forearm and right hand was strapped to the frame and handle of the manipulandum in a semi-pronated position (right).
Experimental setup

A control computer with MATLAB / Simulink applications randomly selected magnitudes to generate sinusoidally shaped torque pulses according to the equation: $A/2 + A/2 \cdot \sin\left(\frac{2\pi t}{T} - \frac{\pi}{2}\right)$, where $A$, $t$ and $T$ represented torque magnitude, onset of torque pulse, and a constant value (320 ms), respectively. Information about the timing of the torque pulses and visual displays was sent to a target computer (xPC, MathWorks). The target computer computed commands that were then sent to a torque motor (Inland RBHR series) that moved a piston in the master cylinder of a hydraulic actuator (Z01.1-DK-20/10x100, Woodtli-Hydraulik AG, Switzerland). The displacement at the piston in the master cylinder was transmitted via hydraulic conducts to pressurize a slave actuator (fMRI-compatible). Pressure in the slave actuator of the 1 DOF manipulandum (Figure 3) created the desired torque (Gassert et al. 2006).

Figure 3: 1 DOF manipulandum (fMRI-compatible). The components comprise a control computer, motor rack with direct drive motor and master actuator, hydrostatic transmission, and slave actuator.
The torque at the center of the rotational axis of the handle was transduced with an optical sensor (Keyence FU-38) and the signals were relayed to the target computer via optical fibers. These signals were filtered at 100 Hz (low-pass), amplified, and captured by a data acquisition card (NI-PCI 6024E, National Instruments). Position was represented by the output of an encoder (APCI-1710) that was integrated into the torque motor, i.e. the position of the motor rather than the handle was recorded. The torque and position data were sampled at 1 kHz. The EMG was recorded with surface electrodes using a Delsys Bagnoli 16 system, which amplified and band-pass filtered the signals between 20 Hz (high-pass) and 450 Hz (low-pass). The contacts of the electrodes were silver bars 10 mm in length, 1 mm in width, and spaced 10 mm apart. The EMG signals were sampled at 1 kHz. The sampled data were stored for later analysis. During the fMRI experiment, the host computer, target computer, and the motor were positioned outside the imaging room to prevent interference of ferromagnetic materials with the fields of the scanner. Blood-oxygenation-level-dependent (BOLD) contrast functional images were obtained using a 1.5 T MRI scanner (Shimadzu-Marconi MAGNEX ECLIPSE Power Drive 250) in the ATR Brain Activity Imaging Center (Figure 4).
Protocol

In all the experiments, visual displays were presented to the subject on a computer screen. The subject was instructed to position the wrist at an angle that was neutral to flexion and extension. At the start of a trial, a red circle (diameter of 20 mm) with a number ‘1’ printed at its center appeared at the center of the screen for a duration of 320 ms. A vertical line, which represented the torque pulse, moved from the left side of the screen to the center of the circle (300 ms). When it reached the center of the circle, the subject experienced a sinusoidally shaped torque pulse that displaced the hand from its initial position. The subjects were not provided with visual feedback about the magnitude of the displacement. The time interval between the start of the first torque pulse to the end of second visual display was 1120 ms. During this time, the subject was instructed to reposition the hand to approximately the ‘neutral’ position so that he could
counteract the upcoming second torque pulse. In the second half of the trial, a green circle (diameter of 20 mm) with a number ‘2’ printed at its center was displayed. Similarly, a vertical line moving from the left side of the screen indicated the onset of the second torque pulse. The magnitude of the two torque pulses was the same (Figure 5). The time interval between the end of one trial to the start of the next trial was 1360 ms. Each trial lasted 3400 ms. The task for the subject was: 1) during the first half of the trial, to estimate the strength of the torque pulse when it displaced the hand and 2) during the second half of the trial, to produce an opposing torque that matched the first torque pulse. If the subject were able to counteract the torque pulse, the handle of the manipulandum would remain stationary.

*Figure 5:* Visual displays during the torque-matching task. The red circle with the number ‘1’ and the green circle with the number ‘2’ represent the start of the first and second half of each trial, respectively. The dotted arrows represent the transition of the cursor from the left side of the screen to the center of the circle. During each trial, the magnitude of the first and second torque pulse is always the same. The numbers between the blue dotted lines represent the duration of each phase of the trial.
The subjects practiced the task with torque pulses drawn from a normal probability distribution with mean 4.6 Nm and standard deviation 0.4 Nm (Figure 6). The practice session comprised of 4 blocks of 200 trials each, and between the blocks, the subjects were given a one-minute rest.

Figure 6: Normal probability distribution with mean 4.6 Nm and s.d. 0.4 Nm. Majority of the torque pulse magnitude were centered near the mean of the probability distribution. However, the subjects experienced occasional small (3.6 Nm) and large (5.6 Nm) torque pulses.

Psychophysical experiment

EMG activity was recorded during trials immediately after the training session from four muscles contributing to the torque at the wrist joint: flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), extensor carpi ulnaris (ECU), and extensor carpi radialis longus (ECRL). The muscles were located by palpation for electrode placement with reference to the Anatomical Guide for the Electromyographer – The Limbs and the Trunk (Perotto 2005). To locate the
FCU, the subject was asked to flex the elbow joint at 90 degrees, with the palm in a supinated position. In this position, the experimenter's left middle finger was placed along the ulnar bone of the subject, with the index finger lined up besides it. The site of electrode placement was the point of intersection between the axis along the index finger and a perpendicular line that was one-third the distance between the medial epicondyle of the humerus and the styloid process of the ulnar, distal from the elbow joint (Figure 7a). To locate the FCR, the subject was asked to extend the elbow joint with the palm in a supinated position. The midpoint between the medial epicondyle of the humerus and the biceps tendon (taken as superficially above the olecranon) was estimated. From this midpoint, a perpendicular projection of four-finger spacing distal to the elbow joint was the site of the electrode placement (Figure 7b). To locate the ECU, the subject was asked to flex the elbow joint at 90 degrees, with the palm in a supinated position. In this position, the experimenter's left index finger was placed along the ulnar bone of the subject, with his middle finger lined up besides it. The electrode placement was the point of intersection between the axis along the middle finger and a perpendicular line that was at the mid-point of the ulnar bone (Figure 7c). To locate the ECRL, the subject was asked to place the hand in a semi-pronated position. The subject was then asked to flex at the elbow joint so that the brachioradialis muscle could be palpated. Once determined, the experimenter placed his left index finger on the muscle, with the middle finger lined up beside it. The electrode placement was the point of intersection between the axis along the middle finger and a perpendicular line that was two-finger spacing distal from
the lateral epicondyle of the humerus (Figure 7d). To ensure that the palpated muscle was ECRL and not extensor digitorum communis, the subject was asked to wriggle his fingers continuously while the experimenter checked that the palpated muscle did not contract. The subjects had to perform a series of brisk test movements to confirm the site of the electrode placement. These movements were: ulnar deviation and wrist flexion for FCU, wrist flexion (fingers relaxed) for FCR, ulnar deviation and wrist extension for ECU, and wrist extension (fingers relaxed) for ECRL. MVC of the flexor and extensor muscles was obtained by instructing the subjects to maximally contract against an immobilized manipulandum handle.

Each subject was randomly assigned one of two protocols that consisted of five blocks of twenty trials with variable torque pulses drawn from a normal probability distribution (mean = 4.6 Nm, s.d. = 0.4 Nm [pulse*v condition]), five blocks of twenty trials with constant torque pulses (mean = 4.6 Nm, s.d. = 0 [pulse*c condition]), and five blocks of twenty trials where the subject had to push against an immobilized manipulandum handle with a torque that was equal to the mean of the original distribution [push condition]. The number of blocks and trials were the same for the EMG recording and fMRI sessions. The two protocols comprised different series of torque pulse magnitudes with identical mean and reverse order of the conditions. Therefore, the protocol was either of the sequence 1) pulse*v condition – pulse*c condition – push condition or 2) pulse*c
condition – push condition – pulse* v condition. In all cases, the pulse*c condition preceded the push condition (Figure 8).

Figure 7: Sites of electrode placement for electromyographic recording of muscle activity. (a) Flexor carpi ulnaris, (b) flexor carpi radialis, (c) extensor carpi ulnaris, and (d) extensor carpi radialis longus.
Figure 8: Experiment protocol. The subjects were randomly assigned protocol (a) or (b) and the same protocol was used in the psychophysical and fMRI experiments. For the ‘Push’ condition, there was no torque pulse during the first half of the trial and the subjects were required to push against an immobilized manipulandum handle with a torque that was equal to the mean of the original distribution (dotted arrows). The blue arrows indicate the transition between the conditions.

fMRI experiment

In the fMRI experiment, the subjects performed the torque-matching task while lying in a supine position within the scanner bore, using the same protocol that was assigned earlier. A custom-made bite bar and Velcro-strap were used to minimize head movements. The custom-made bite bar was attached to a birdcage volume coil and adjusted to fit the subjects when possible (n= 16/20 subjects) (Figure 9).
Figure 9: The custom-made bite bar was attached to the birdcage volume coil and adjusted to fit the subject.

A wedge-shaped stopper was placed against the scanner bed to prevent movements along the caudal-rostral direction (z-axis of the scanner’s coordinate system). The manipulandum was secured to a non-ferromagnetic frame and adjusted to complement the supine position of the subjects. The forearm and hand were strapped to the frame and handle of the manipulandum, respectively and the elbow and upper arm were supported with rubber pads (Figure 10). The experimenters communicated with the subjects via audio earphones. Visual displays were back-projected onto a screen, which the subject observed through a mirror placed in the subject’s line of sight.
Figure 10: Position of the manipulandum in the fMRI room. The manipulandum was secured to a non-ferromagnetic frame and adjusted to complement the supine position of the subject. The forearm and hand were strapped to the frame and handle of the manipulandum, respectively and the elbow and upper arm were supported with rubber pads.

The fMRI experiment was a block design and each condition comprised 5 blocks. Each block lasted 68 s and between blocks there was a 34 s rest. Visual cues were displayed on the computer screen to prepare the subjects for transition between conditions and rest. The visual cues were ‘Pulse’, which indicated the onset of pulse*v and pulse*c conditions, ‘Push’, which indicated the onset of push condition, and ‘Rest’. During the rest interval, the subjects were instructed to view the same visual display, i.e. identical to those presented during the movement conditions, but not move the handle of the manipulandum. The ‘Rest’ condition served as a baseline for detection of brain activity produced by movements at the wrist joint.
Scan Acquisition

Data were acquired on a 1.5 T Shimadzu-Marconi MRI scanner in the ATR Brain Activity Imaging Centre. High-resolution anatomical (structural) images were obtained with a $T_1$-weighted sequence for each subject. Functional images weighted with the apparent transverse relaxation time ($T_2^*$) were obtained with an echo-planar imaging sequence (repetition time [TR] = 3.5 s, echo time [TE] = 65ms, flip angle = 90 degrees). The spatial resolution was specified by three parameters: field of view (224 mm x 224mm), matrix size (64 x 64 voxels), and slice thickness (4 mm). 442 sequential whole brain volumes were acquired. Each session lasted 25 min 44 s.

Data Analysis

Psychophysical data

The difference between the magnitude of the preceding torque generated by the motor and the torque applied by the subject when the manipulandum was locked was termed torque error (torque error = torque generated by the motor – torque generated by the subject). Torque error during the blocked trials was plotted as a function of torque magnitude to determine if the CNS compensated the approximate mean torque pulse of the probability distribution.
During each trial, the purpose of the first torque pulse was to allow the subjects to experience the magnitude of the perturbation. Although EMG was recorded during the first torque pulse, it was not analyzed. The raw EMG recorded during the second half of a trial was quantified in terms of the root mean square (rms). Rms EMG was calculated under the MVC condition using a one-second block displaying the greatest activity. Condition-dependent rms EMG was normalized by representing it as a percentage of the subject’s rms EMG recorded during the isometric MVC trial. Specifically, the flexor and extensor muscle activity was expressed as a percentage of the flexor and extensor muscle activity on the respective MVC trials. To quantify muscle activity during the second half of the trial, feedforward muscle activity was first separated from activity that also included reflex responses. To do this, the time when the torque applied by the subject reached a peak value, i.e. $T_{\text{peak}}$, was determined. The onset of the interval for computing feedforward rms EMG was set at 350 ms prior to $T_{\text{peak}}$, and the end of the interval was set to the time when the torque exceeded a threshold of 0.1 Nm, relative to the baseline torque level at rest. The raw EMG recorded during this interval was classified as feedforward and quantified in terms of the root mean square. Baseline EMG was represented by the rms EMG during an interval displaying minimal muscle activity after the first torque pulse and before the start of the second torque pulse. It was subtracted from the rms EMG of the feedforward interval (Figure 11). To determine whether the subjects stabilized the wrist by means of cocontraction only during the second half of the trial, one-way ANOVA were used to compare the relative contribution of flexor and extensor
muscles under different conditions. An *a priori* significance level of 0.05 was used in the tests. When the assumption of sphericity was violated, the Greenhouse-Geiser or Huynh-Feldt correction was used (Howell 1997). The ANOVA was followed by a Tukey’s HSD to determine which differences in muscle activity were statistically significant.

![Graph](image.png)

**Figure 11.** Determining feedforward (FF) electromyographic (EMG) activity during the second half of a trial. (diagram is not to scale). A time index 350 ms prior to $T_{peak}$ was first determined (*bold black dotted* vertical line). The end of the time interval for FF EMG was a point in time when the applied torque exceeded a threshold of 0.1 Nm, relative to the baseline torque level at rest (*blue dotted* horizontal lines). The *bold black* and *bold green dotted* vertical lines represent the time interval for FF EMG. Subsequently, baseline rms EMG represented by the *red dotted* vertical lines was subtracted from FF rms EMG.
**fMRI data**

Functional imaging data were analyzed using Matlab (MathWorks, Natick, MA) and SPM 5 software (Wellcome Department of Cognitive Neurology, London, UK - [http://www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)). The first four image volumes were discarded to allow for longitudinal magnetization to approach equilibrium. The remaining 338 image volumes were preprocessed by correction of slice timing, realignment to the first image, coregistration of images, and normalization to the Montreal Neurological Institute (MNI; Montreal, Canada) reference brain. A 6 mm full width at half-maximum (FWHM) Gaussian kernel was used to spatially smooth the data, which were later high pass filtered with a cut-off frequency of 1/128 Hz to minimize slow varying trends. The preprocessed data from each subject were then analyzed within a general linear model to form statistical parametric maps (SPMs). At the 1st level analysis, SPMs were generated for all condition specific effects (pulse*v, pulse*c, Push, and rest). To increase the statistical power of the baseline condition in the analysis, the BOLD signals during resting conditions were concatenated into a single column in the design matrix (Tunik et al. 2007). In addition, statistical images corresponding to pulse*v – Push, pulse*c – Push, and pulse*v – pulse*c were computed. Using a random effects model, the contrast images obtained from level 1 were entered into a 2nd level analysis to create SPM {t} maps that addressed inter-subject variability in the group analysis. Anatomical regions were identified from normalized T1 structural images averaged across subjects, using the Automated Anatomical
Labeling (AAL) method of Tzourio-Mazoyer et al. (2002). MNI coordinates were transformed to Talairach-Tournoux coordinates according to Seitz et al. (2000) and Calder et al. (2001), and entered into the Talairach Daemon (Talairach and Tournoux 1988) to determine functional anatomy from the Brodmann Area (BA) map.
RESULTS

Psychophysical experiment

Torque data

To examine if the CNS compensated the approximate mean torque pulse of the probability distribution, torque error (torque generated by the motor – torque generated by the subject) during the blocked trials was plotted as a function of torque magnitude (Figure 12). On average, the subjects generated a mean torque pulse of 4.00 ± 0.66 Nm under pulse*v condition and 4.20 ± 0.50 Nm under pulse*c condition. The torque pulse generated under pulse*c condition was significantly greater than that under pulse*v condition (t (258) = 6.89, p <0.001) and the coefficient of variation (s.d. / mean) of the latter was significantly greater than that of the former (t (14) = 9.52, p < 0.001). When the motor generated torque pulses that were much lower or higher than the mean of the distribution, the CNS over- or under-compensated the perturbations, resulting in large torque errors. For subsequent statistical analysis, trials were classified into three main categories: 1) small [4.0 Nm], 2) mean [4.6 Nm], and 3) large [5.2 Nm] torque magnitudes. These lower and upper limits were chosen because there were relatively few trials for magnitudes below 4.0 Nm and above 5.2 Nm. Although the torque generated by the subjects tended to increase as a function of torque pulse magnitude (R² = 0.40, F (1,258) = 225.37, p < 0.001), the
differences across the three categories were not significant ($F(2,57) = 1.81, p = 0.17$). The mean torque pulse generated by the subjects was: 1) $M = 3.33, \text{s.d.} = 0.70$ at 4.0 Nm, 2) $M = 3.64, \text{s.d.} = 0.80$ at 4.6 Nm, and 3) $M = 3.79, \text{s.d.} = 0.87$ at 5.2 Nm.

![Figure 12. Torque error as a function of torque magnitude during blocked trials (under pulse*v condition). The dotted line on the plot represents a linear regression line ($R^2 = 0.40, F(1,258) = 225.37, p < 0.001$). The difference between the torque generated by the motor and the subjects was termed torque error. The point of intersection at the X-axis represents the approximate mean torque value compensated by the CNS.](image)

**EMG data**

During a typical trial, the CNS acquired sensory information about the first torque pulse, processed that information, and generated predictive motor commands to counteract the second, which was identical in magnitude. The pattern of muscle activation during the second half of the trials for one subject is shown in Figure 13. Averaged across torque magnitude, the normalized rms
EMG under pulse*v condition was: 1) 11.7% ± 3.38 for FCU, 2) 19.3% ± 6.11 for FCR, 3) 6.15% ± 1.61 for ECU, and 4) 6.56% ± 1.65 for ECRL. The muscle activity of FCR was significantly greater than that of FCU \( t(99) = 11.42, p < 0.001 \). Averaged across muscle type, the activity of the flexor muscles was significantly greater than that of the extensor muscles \( t(99) = 26.36, p < 0.001 \).

The pattern of muscle activation represented in terms of normalized rms EMG for all subjects is shown in Table 1.

![Figure 13. Normalized rms EMG of flexor and extensor muscles under pulse*v condition for one subject. Averaged across torque magnitude, the normalized rms EMG for flexor muscle activity was 11.7% ± 3.38 for FCU (top left) and 19.3% ± 6.11 for FCR (top right). For extensor muscle activity, the normalized rms EMG was 6.15% ± 1.61 for ECU (bottom left) and 6.56% ± 1.65 for ECRL (bottom right).](image-url)
Table 1: Normalized rms EMG of flexor and extensor muscles, averaged across subjects

<table>
<thead>
<tr>
<th>Movement condition</th>
<th>FCU</th>
<th>FCR</th>
<th>ECU</th>
<th>ECRL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse*v</strong></td>
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<td></td>
</tr>
<tr>
<td>Small (4.0 Nm)</td>
<td>15.2 ± 7.40</td>
<td>17.2 ± 3.85</td>
<td>6.16 ± 1.37</td>
<td>6.41 ± 1.50</td>
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<tr>
<td>Mean (4.6 Nm)</td>
<td>16.4 ± 10.3</td>
<td>18.0 ± 2.79</td>
<td>6.49 ± 1.45</td>
<td>6.62 ± 1.33</td>
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<tr>
<td>Large (5.2 Nm)</td>
<td>17.9 ± 11.8</td>
<td>18.2 ± 5.31</td>
<td>6.68 ± 2.12</td>
<td>6.70 ± 1.37</td>
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<tr>
<td><strong>Pulse*c</strong></td>
<td>16.3 ± 10.9</td>
<td>17.6 ± 3.07</td>
<td>6.45 ± 1.75</td>
<td>6.44 ± 1.70</td>
</tr>
<tr>
<td><strong>Push</strong></td>
<td>16.4 ± 1198</td>
<td>16.7 ± 5.38</td>
<td>6.60 ± 1.99</td>
<td>6.25 ± 1.86</td>
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</tbody>
</table>

* Muscle activity expressed as a percentage (%) of MVC.

Across movement conditions, the coefficient of variation, i.e. s.d. / mean, for muscle activity at FCU was highest compared to the other muscles (Table 1), i.e. 0.49 to 0.72 for FCU and 0.16 to 0.32 for the other muscles. For subsequent analysis of EMG data, the muscle activity of FCU and FCR were summed and the mean was calculated. The same was done for muscle activity of ECU and ECRL. The mean value of the combined EMG was subsequently used to represent the flexor and extensor muscle activity of the wrist joint (Table 2).

The pattern of muscle activation of the wrist flexors and extensors under pulse*v condition is shown in Figure 14. The muscle activity of the extensors was scaled to the corresponding percentage of the flexor MVC, i.e. rms extensor EMG multiplied by the ratio of maximum extensor torque (12.5 Nm) to maximum flexor torque (20.9 Nm) based on average values reported by Leger (1997). For
Table 2: Normalized rms EMG of combined muscle activity at the wrist flexors and extensors

<table>
<thead>
<tr>
<th>Movement condition</th>
<th>Normalized rms EMG*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wrist flexors</td>
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<tr>
<td><strong>Pulse*v</strong></td>
<td></td>
</tr>
<tr>
<td>Small (4.0 Nm)</td>
<td>15.73 ± 2.58</td>
</tr>
<tr>
<td>Mean (4.6 Nm)</td>
<td>15.48 ± 1.72</td>
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<tr>
<td>Large (5.2 Nm)</td>
<td>16.30 ± 3.85</td>
</tr>
<tr>
<td><strong>Pulse*c</strong></td>
<td>14.92 ± 1.81</td>
</tr>
<tr>
<td><strong>Push</strong></td>
<td>16.87 ± 3.06</td>
</tr>
</tbody>
</table>

* Muscle activity expressed as a percentage (%) of MVC.

Each category of torque magnitude, the relative muscle activity of the flexors was significantly greater than that of the extensors: 1) 4.0 Nm ($t(14) = 15.17, p < 0.001$), 2) 4.6 Nm ($t(14) = 20.76, p < 0.001$), and 3) 5.2 Nm ($t(14) = 9.60, p < 0.001$). Across torque magnitude, the muscle activity of the flexors ($F(2,42) = 0.35, p = 0.71$) and extensors ($F(2,42) = 0.32, p = 0.73$) was not statistically different. Although muscle activity under pulse*v condition at 4.6 Nm tended to be higher than under pulse*c and Push conditions, it was not significantly different for either the flexors ($F(2,42) = 2.87, p = 0.07$) or extensors ($F(2,42) = 1.55, p = 0.23$). Extensor activity prior to the onset of the second torque pulse was significantly greater ($t(14) = 18.58, p < 0.001$) than during the period with the lowest muscle activation under the Push condition.
Figure 14. Percentage of flexor MVC as a function of torque magnitude. For each category of torque magnitude, there was significantly greater muscle activity of the flexors (blue) compared to the extensors (red), indicated by the asterisks. Across torque magnitude, the muscle activity at the flexors and extensors was not significantly different, indicated by N.S.

fMRI experiment

Realignment parameters were checked for all subjects, and it was noted that translation in the X-Y-Z dimension was less than 2mm. Averaged across subjects, translation in the X, Y, and Z direction was 1.49mm ± 0.26, 0.66mm ± 0.16, and -0.98mm ± 0.12 respectively. Pitch, roll, and yaw were of the order of -0.49 deg ± 0.17, 0.36 deg ± 0.09, and 0.13 deg ± 0.05 respectively. The result of the image realignment for one subject is shown in Figure 15. Subsequently, preprocessed functional images of all the subjects were analyzed. Using the
general linear model, 1st level SPM $t$ maps corresponding to condition specific effects (pulse*v, pulse*c, Push, and rest) were constructed at a significance level of $P<0.05$, applying a family-wise error (FWE) $P$-value correction and an extent threshold of 12 voxels. Contrast images obtained from level 1 were entered into a 2nd level analysis using the random effects model. 2nd level SPM $t$ maps corresponding to the contrasts: pulse*v – Push, pulse*c – Push, and pulse*v – pulse*c were constructed at a significance level of $P<0.001$ (uncorrected).

![Figure 15](image1.png)

**Figure 15:** The result of image realignment for one subject.
Brain activation: all movement conditions minus resting baseline

Several brain regions showed stronger activity when the subjects performed the three movement conditions, relative to the resting baseline \((P<0.05, \text{FWE-corrected}; \text{Table 3, Table 4, and Figure 16})\). Under the pulse*v condition, the strongest activation was located in the left pre- and post-central gyrus, i.e. primary motor cortex (M1; BA 4) and primary somatosensory cortex (S1). In the anterior lobe of the right cerebellum, significant activation occurred medially in the culmen and laterally in lobule VI. Under the pulse*c condition, the strongest activation was also located in the left pre- and post-central gyrus, i.e. BA 3 and BA 4. Significant activation again occurred in the anterior lobe of the right cerebellum, medially in the culmen and laterally in the dentate nucleus. Under the Push condition, the strongest activation was located in the left precentral gyrus. A large cluster of activated voxels, which was not contiguous with the site of peak activation, was located in the left pre- and post-central gyrus. Significant activation also occurred in the left medial frontal gyrus, i.e. SMA. Across movement conditions, the contrast against resting baseline yielded a common anatomical region of strongest activation, i.e. left pre and post-central gyrus. Under the pulse*v and pulse*c conditions, the contrast revealed significant cerebellar activity \((P<0.05 \text{ corrected})\). In contrast, there was no statistically significant activity anywhere in the cerebellum under the Push condition. However, under this condition, significant brain activity occurred in the SMA \((P<0.007 \text{ corrected})\).
<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>MNI Coordinates</th>
<th>Peak z Score</th>
<th>Cluster Size*</th>
<th>P Value†</th>
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<td><strong>Pulse*v versus baseline</strong></td>
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<tr>
<td>Left central gyrus</td>
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<tr>
<td>(S1 / M1-BA 4**)</td>
<td>-34 -26 58</td>
<td>6.35</td>
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<td>Right cerebellum</td>
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<tr>
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<td>(Lobule VI)</td>
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<td><strong>Pulse*c versus baseline</strong></td>
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<tr>
<td>Left central gyrus</td>
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<tr>
<td>(S1-BA 3** / M1-BA 4**)</td>
<td>-30 -28 54</td>
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<td>Right cerebellum</td>
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<td>(Lobule IV / V- dentate nucleus**)</td>
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<td><strong>Push versus baseline</strong></td>
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<td>Left precentral gyrus</td>
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<td>Left central gyrus</td>
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<tr>
<td>(Supplementary motor area**)</td>
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<td>5.37</td>
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*Number of 8 mm³ voxels in cluster. †FWE corrected P values using small volume correction.

** Functional anatomy from the Brodmann Area map (Talairach and Tournoux 1988).
Table 4: Results of cluster labeling for movement tasks versus resting baseline†

<table>
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<tr>
<th>MNI Coordinates</th>
<th>Anatomical label</th>
<th>Percentage (%) cluster</th>
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<td><strong>Pulse*v versus baseline</strong></td>
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<tr>
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<tr>
<td>-8</td>
<td>-2</td>
<td>56</td>
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</tbody>
</table>

†Cluster labeling using AAL method (Tzourio-Mazoyer et al. 2002).
Figure 16: BOLD contrast signals of movement tasks minus resting baseline. Top row: the design matrix and SPM \( \{t \} \) maps corresponding to condition specific effects, which were significant at the level of \( P < 0.05 \), applying a family-wise error (FWE) \( P \)-value correction and an extent threshold of 12 voxels. Activated brain regions were superimposed on a glass brain. 2\textsuperscript{nd} row: brain region with the highest BOLD signals superimposed on a normalized \( T_1 \) structural image: \textit{pulse*v minus baseline} and \textit{pulse*c minus baseline} – left central gyrus; \textit{Push minus baseline} – left precentral gyrus. 3\textsuperscript{rd} and 4\textsuperscript{th} rows: other brain regions with significant BOLD signals: \textit{pulse*v minus baseline} – right cerebellum (lobule IV / V / VI); \textit{pulse*c minus baseline} – right cerebellum (lobule IV / V); \textit{Push minus baseline} – left central gyrus and SMA.
Using the false discovery rate (FDR) \( P \) value correction, additional brain regions were found to have significant activation in the contrasts with the resting baseline \((P < 0.05, \text{FDR-corrected}; \text{Table 5})\). These regions were: 1) under pulse*\( v \) condition- left pallidum and left/right putamen, 2) under pulse*\( c \) condition- left/right thalamus, and 3) under Push condition- left/right hippocampus, left parahippocampal gyrus, right caudate nucleus, and left putamen.
Table 5: Movement tasks versus resting baseline (P value FDR corrected)

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>MNI Coordinates</th>
<th>Peak z Score</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
</tr>
<tr>
<td><strong>Pulse*v versus baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left central gyrus</td>
<td>-34</td>
<td>-26</td>
<td>58</td>
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<tr>
<td>Right cerebellum</td>
<td>10</td>
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<tr>
<td>Right cerebellum</td>
<td>26</td>
<td>-46</td>
<td>-28</td>
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<tr>
<td>Left pallidum**</td>
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<tr>
<td>Left thalamus**</td>
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<td>-16</td>
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</tr>
<tr>
<td>Left putamen**</td>
<td>-26</td>
<td>-6</td>
<td>4</td>
</tr>
<tr>
<td>Right putamen**</td>
<td>24</td>
<td>12</td>
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</tr>
<tr>
<td><strong>Pulse*c versus baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left central gyrus</td>
<td>-30</td>
<td>-28</td>
<td>54</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>10</td>
<td>-52</td>
<td>-16</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>22</td>
<td>-46</td>
<td>-24</td>
</tr>
<tr>
<td>Left thalamus**</td>
<td>-16</td>
<td>-14</td>
<td>12</td>
</tr>
<tr>
<td>Right thalamus**</td>
<td>20</td>
<td>-14</td>
<td>16</td>
</tr>
<tr>
<td><strong>Push versus baseline</strong></td>
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<td></td>
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<tr>
<td>Left precentral gyrus</td>
<td>-28</td>
<td>-16</td>
<td>56</td>
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<td>Left central gyrus</td>
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<tr>
<td>Left postcentral gyrus</td>
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<td>-20</td>
<td>60</td>
</tr>
<tr>
<td>Right hippocampus**</td>
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<td>-36</td>
<td>-4</td>
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<tr>
<td>Right caudate nucleus**</td>
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<td>Left putamen**</td>
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<td>-20</td>
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<tr>
<td>Left parahippocampal gyrus**</td>
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<td>Left hippocampus**</td>
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<td>-38</td>
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<tr>
<td>Left thalamus**</td>
<td>-10</td>
<td>-16</td>
<td>-6</td>
</tr>
</tbody>
</table>

*Number of 8 mm³ voxels in cluster. †FDR corrected P values using small volume correction.

** Additional brain regions activated (P< 0.05, FDR corrected)
Brain activation: pulse*v - Push, pulse*c - Push, and pulse*v - pulse*c

The between-task contrasts showed statistically significant brain activity at $P<0.001$ uncorrected (Table 6, Table 7, and Figure 17). For pulse*v - Push contrast, the strongest activation was located in the left pre- and post-central gyrus, i.e. BA 3 and primary motor cortex. There was also significant activation of the right cerebellum laterally in lobule IV / V and medially in lobule IX. Clusters of active voxels, which were not contiguous with the site of peak activation, were located in the left precentral gyrus and left postcentral gyrus, i.e. inferior parietal lobule. For pulse*c - Push contrast, the strongest activation was also located in the left pre- and post-central gyrus, i.e. BA 4 and primary sensory cortex. Significant activation also occurred laterally in the right cerebellum in lobule IIX and lobule IV / V and medially in lobule IV / V and at lobule VI, i.e. right vermis. Significant activation also occurred in the left thalamus. For pulse*v - pulse*c contrast, the strongest activation was located in the right middle frontal gyrus, i.e. BA 6. The right superior parietal lobule, i.e. BA 7 and left postcentral gyrus, i.e. BA 2 were also significantly activated.
Table 6: Tasks specific activations

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>MNI Coordinates</th>
<th>Peak z Score</th>
<th>Cluster Size*</th>
<th>P Value†</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
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<tr>
<td><strong>Pulse*v versus Push</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Left central gyrus</td>
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<td>-26</td>
<td>58</td>
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<tr>
<td>(S1-BA 3** / M1)</td>
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<tr>
<td>Right cerebellum</td>
<td>20</td>
<td>-48</td>
<td>-22</td>
<td>3.55</td>
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<tr>
<td>(Lobule IV / V)</td>
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<tr>
<td>Left precentral gyrus</td>
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<td>-17</td>
<td>72</td>
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<td>Left postcentral gyrus</td>
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<td>60</td>
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<tr>
<td>(Inferior parietal lobule**)</td>
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<tr>
<td>Right cerebellum</td>
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<td>(Lobule IX)</td>
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<tr>
<td><strong>Pulse*c versus Push</strong></td>
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<td>Left central gyrus</td>
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<tr>
<td>(S1 / M1-BA 4**)</td>
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<td>Right cerebellum</td>
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<td>(Lobule IIX)</td>
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<td>Right cerebellum</td>
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<tr>
<td>(Lobule IV / V)</td>
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<tr>
<td>Left thalamus</td>
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<td>Right vermis</td>
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<td>-18</td>
<td>3.12</td>
</tr>
<tr>
<td>(Lobule IV / V)</td>
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<td></td>
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<td>Right vermis</td>
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<td>(Lobule VI)</td>
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<td><strong>Pulse<em>v versus Pulse</em>c</strong></td>
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<tr>
<td>Right precentral gyrus</td>
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<td>(BA 6**)</td>
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<td>Right superior parietal lobule</td>
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<td>3.41</td>
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<td>(BA 7**)</td>
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<td>Left postcentral gyrus</td>
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<td>-22</td>
<td>56</td>
<td>3.14</td>
</tr>
<tr>
<td>(BA 2**)</td>
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</table>

*Number of 8 mm³ voxels in cluster. †Uncorrected P values.
** Functional anatomy from the Brodmann Area map (Talairach and Tournoux 1988).
Table 7: Results of cluster labeling for task specific activations†

<table>
<thead>
<tr>
<th>MNI Coordinates</th>
<th>Anatomical label</th>
<th>Percentage (%) cluster</th>
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<tr>
<td>-34</td>
<td>-26</td>
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<tr>
<td>14</td>
<td>-54</td>
<td>-50</td>
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<tr>
<td><strong>Pulse*c versus Push</strong></td>
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<td></td>
</tr>
<tr>
<td>-34</td>
<td>-26</td>
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<td>-60</td>
<td>-22</td>
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<tr>
<td><strong>Pulse<em>v versus Pulse</em>c</strong></td>
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<td>0</td>
<td>48</td>
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<td>-64</td>
<td>66</td>
</tr>
<tr>
<td>-52</td>
<td>-22</td>
<td>56</td>
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</tbody>
</table>

†Cluster labeling using AAL method (Tzourio-Mazoyer et al. 2002).
Figure 17: BOLD contrast signals of task specific activations. Top row: the design matrix and SPM \( t \) maps corresponding to task specific effects, which were significant at the level of \( P<0.001 \) (uncorrected). Activated brain regions were superimposed on a glass brain. 2nd row: brain region with the highest BOLD signals superimposed on a normalized T1 structural image: pulse*\( v \) minus Push and pulse*\( c \) minus Push – left central gyrus; pulse*\( v \) minus pulse*\( c \) – right precentral gyrus. 3rd and 4th rows: other brain regions with significant BOLD signals: pulse*\( v \) minus Push - right cerebellum and left postcentral gyrus; pulse*\( c \) minus Push – right cerebellum and left thalamus; pulse*\( v \) minus pulse*\( c \) – right superior parietal lobule and left postcentral gyrus.
Region of interest (ROI) analysis: pulse*v - pulse*c

ROI masks were created for the anatomical regions in which the local maxima were located when brain activity under pulse*c condition was subtracted from that under pulse*v condition. Three atlases were used to create the ROIs: 1) Talairach-Tournoux Brodmann Areas, i.e. right BA 6 and right BA 7, 2) Talairach-Tournoux labels, i.e. right middle frontal gyrus and right superior parietal lobule, and 3) shape generation implemented in the WFU pick atlas (spheres, 10mm radius with center located at MNI coordinate [52 0 48] and [14 -64 66]). No brain activation was observed when the $P$ value was FWE or FDR corrected. The descriptive statistics from the ROI analysis were identical to those when the $P$ value was uncorrected.
DISCUSSION

Consistent with the hypotheses of the present study, the CNS combined a priori knowledge of movement experience and sensory information to compensate approximately for the mean torque pulse amplitude of the probability distribution (Figure 12). When brain activity under pulse*c condition was subtracted from that under pulse*v condition, the neural correlates of Bayesian processing revealed a fronto-parietal network.

Behavioral study

Results from the present and previous studies (Kording et al. 2004; Scheidt et al. 2001; Takahashi et al. 2001) consistently showed that the CNS underestimated the true mean of the probability distribution. When the magnitude of the torque pulses deviated significantly from the mean of the probability distribution, the CNS over- or under-compensated the perturbations, resulting in negative or positive torque errors, respectively. Since subjects appeared to underestimate the mean of the probability distribution, the minimum torque error occurred for torque pulses somewhat below the mean of the distribution. Under pulse*c condition, where the magnitude of the torque pulse was consistent, the
CNS utilized the sensory information arising from the interaction with the first torque pulse to better compensate the perturbation, i.e. 4.20 ± 0.50 Nm. This was a more accurate estimation because the torque generated under pulse*c condition was significantly greater than that under pulse*v condition, 4.20 Nm was closer to the true mean of the probability distribution, and the coefficient of variation under pulse*c condition was significantly less than that under pulse*v condition.

Since the muscle activity of the extensors under Push condition was not statistically different from that under pulse*c condition or from that at 4.6 Nm under pulse*v condition (Table 2, Figure 14), the possibility that the subjects compensated the perturbations exclusively by cocontraction could be ruled out. However, across movement conditions, there was still residual cocontraction because extensor activity prior to the onset of the torque pulse was significantly greater than during the period with the lowest muscle activation.
fMRI study

Brain activity related to movement condition minus resting baseline

$P<0.05$, FWE corrected and extent threshold of 12 voxels

Although the site of peak activation was relatively similar under pulse*v and pulse*c conditions, the cluster size and distribution of active voxels were different (Table 3). Under the pulse*v condition, the cluster of activated voxels was larger and more equally distributed between the motor and sensory cortex than under the pulse*c condition (Table 4). The higher neural activity under the pulse*v condition is probably due to the greater variation in afferent information related to torque pulse amplitude, which required a greater degree of neural processing in the primary somatosensory cortex (S1). Since no significant difference was found in the level of muscle activation across conditions, it is unlikely that differences in activation of primary motor cortex were related to motor output. They may also have reflected processing of incoming afferent information. The activity in the cerebellum was centred in lobule IV/V of the anterior lobe, which has been implicated as a key structure for timing control in repetitive hand movements (Kawashima et al. 2000; Ivry 1996). This activity may have been related to coordination of the timing of muscle activation with the movement of the cursor across the screen.

Under the pulse*c condition, the dentate nucleus was activated whereas this was not found under the pulse*v condition. However, since there was no task specific activation of this region or any other part of the cerebellum, it does not
appear that this reflects a difference in the role played by the cerebellum under the two conditions.

Under the Push condition, statistically significant brain activity was observed in the primary motor and supplementary motor areas (Table 3). In agreement with previous studies, the neural network connecting M1, SMA, and other cortical areas has been shown to be active during motor actions that are under internal control (Debaere et al. 2003; Jenkins et al. 2000). In the present study, the subjects generated torque pulses that were equal to the mean of the original probability distribution based on recollection of previous movement experience. Statistically significant activity was not observed in the cerebellum because sensory feedback from the interaction with the first torque pulse was not available, i.e. the manipulandum was locked. Without sensory error signals, the cerebellum could not compare the consequences of the intended and achieved motor action.

\[ P < 0.05, \text{False Discovery Rate (FDR) corrected} \]

Using the FDR \( P \) value correction method, activity related to movement conditions minus resting baseline could be shown for additional regions of the brain (Table 5). Under the pulse*v condition, these regions included the thalamus, pallidum and putamen. The pallidum and putamen are parts of the
subcortical nuclei that make up basal ganglia. Previous studies have suggested that the basal ganglia play a role in scaling processes (Bergman et al. 1994; Turner et al. 2003; Vaillancourt et al. 2004; Wichmann et al. 1994a, b; Desmurget et al. 2004). Activation of the basal ganglia may reflect a tendency to scale motor commands, according to the size of the torque pulse. Activity in the thalamus was expected since it acts as a relay for all inputs to the cerebral cortex. The only additional region of activation under the pulse* condition revealed by the FDR P value correction method was the thalamus which is consistent with afferent information being relayed to the cortex.

Under the Push condition, additional regions of activation included the putamen, caudate nucleus, thalamus, hippocampus, and the parahippocampal gyrus. Under this condition, the manipulandum was locked and the subjects were instructed to generate torque pulses with a magnitude equal to that experienced under the pulse* condition. Due to the absence of proprioceptive feedback the subjects had to rely on information stored in working memory to generate the appropriate torque pulses. The memory processes utilized by the CNS likely activated the hippocampus and parahippocampal gyrus. These areas have been shown to play important roles in both working and long-term memory.
Brain activity related to tasks specific activations

For the pulse*v – Push and pulse*c – Push contrasts, significant activation ($P < 0.001$, uncorrected) occurred in the left sensorimotor areas and right cerebellum (Table 6). Under the Push condition, there was no position feedback because the manipulandum was locked. This would reduce the afferent feedback to all three regions of the brain and would lead to an expectation of greater activation under the pulse*v and pulse*c conditions than the Push condition. The absence of error information under the Push condition would have prevented the cerebellum from comparing the consequences of the intended and achieved motor action. Therefore, greater activation of the cerebellum would have been expected under the pulse*c and pulse*v conditions.

Evidence from a previous study in our laboratory showed that under both pulse*v and pulse*c conditions, greater displacement is produced by the first pulse than the second (Chapman et al. 2007). In that study, it was shown that responses to pulses of random amplitudes, selected from a Gaussian probability distribution, followed the principles of a Bayesian probability model based on prior experience. To examine the neural correlates of this hypothesized Bayesian probability model for torque pulse amplitude estimation, the BOLD signal under pulse*c condition was subtracted from that under pulse*v condition. The result of the contrast revealed significant activation ($P < 0.001$, uncorrected) of the right precentral gyrus (BA 6) and the right superior parietal lobule (BA 7), i.e. a fronto-
parietal neural circuitry (Table 6). A small cluster of active voxels in the left postcentral gyrus suggested that sensory processing under pulse*v condition was greater compared to pulse*c condition. The pulse*v-pulse*c contrast did not show significant cerebellar activation, suggesting that the cerebellum was performing the same function under both conditions, e.g. assessing the error signals produced by the first force pulse to govern the motor command to counteract the second torque pulse. The activation in the ipsilateral parietal cortex, i.e. right BA 7, could not be due to differences in visuomotor information processing because the visual displays and motor task were the same under both conditions. Furthermore, previous studies have shown that visually directed reaching movements in extrapersonal space are subserved by neural activity in the contralateral posterior parietal cortex when movements are directed to targets in the peripheral visual field and bilaterally when directed to the centre of the visual field (Andersen 1987; Hyvarinen 1982; Stein 1989; Clower et al. 1996; McKay 1992). Kawashima et al. (1995) suggested that there were at least two different functional fields in the posterior part of the superior parietal lobule of humans; one related to maintaining a representation of target positions in working memory and another related to the retrieval of neural representations from long-term memory. They suggested that activation in the right superior parietal lobule could be related to processes associated with the use of visuo-spatial information retrieved from long-term memory.
Comparison with previous studies

In the Schmitz et al. (2005) study, the subjects lifted an object under conditions where the weight (230g or 830g) was either constant, changed regularly (alternated between the two) or changed pseudo randomly on consecutive trials (irregular). The results from their experiment showed significant brain activity in the inferior frontal gyrus, parietal operculum, and supramarginal gyrus in the irregular versus constant contrast, which we did not find. However, only activation of the inferior frontal gyrus was found in the irregular versus regular contrast, suggesting that this activation could be related to the uncertainty or randomness of the irregular condition. Because there were a number of differences between their study and our study many explanations for our failure to find significant activation of the inferior frontal gyrus are possible. A primary difference is that their task involved online correction for errors in the initial forces applied during object lifting, i.e. subjects could adjust their motor commands during the lifting. In our experiment, the torque pulses were too brief to perform any type of online correction. However, our protocol allowed subjects to determine the required response beforehand by providing two identical force pulses. In this way, the entire response could be performed as a feedforward command based on prior information.
The neural mechanisms underlying functions of Bayesian models in torque estimation would be expected to involve processes related to maintaining and updating neural representations in working memory based on prior knowledge and current sensory information. In the present study, the subjects had trained prior to the start of the fMRI experiment. After intensive training, i.e. 800 trials, it was likely that the temporal features of the torque pulse were learned and stored in memory, as well as cumulative information about the torque pulse magnitudes. A number of previous studies have indicated that a region in the superior parietal cortex at approximately the same location as our activation maximum in BA 7 is involved in visuo-spatial memory tasks that require the use of working memory (Kawashima et al. 1995; Olesen et al. 2003; Wendelken et al. 2007). However, in these studies there was bilateral activation of BA 7. One of these studies (Wendelken et al. 2007) has also shown activation of right SMA (BA 6) in a working memory task, although a number of other regions in the left and right hemispheres were also found to be activated. In a study that examined the neural correlates of motor memory consolidation, significant activation occurred in the left BA 6 and left parietal cortex when brain activity corresponding to late learning of an internal model was subtracted from the recall of that internal model at a later time (Shadmehr and Holcomb 1997). However, the sites of the neural activity were on the contralateral (left) side of the brain and may have been related to consolidation of the internal model. Other studies have attributed the role of the right BA 7 to the storage component of visual memory (Fink et al. 1996, Ungerleider et al. 1998) and left BA 7 to phonological memory (Mottaghy et
Other evidence that supports the involvement of SPL in storage processes comes from lesion studies. In the Wolpert et al. (1998) study, it was reported that a right-handed patient with a large cyst in the left SPL showed profound fading of tactile sensation and concomitant inability to maintain constant force output with the right hand. It was posited that the lesion prevented the maintenance of an accurate estimate of the state of her right limbs over time. It was postulated that the state estimate was perpetually decaying over time and that the proposed recursive mechanism for updating the state estimate would consequently become increasingly erroneous which led to deficits in perception and action (Wolpert et al. 1998). It has also been reported that patients with unilateral left or right parietal lobe lesions were found to be impaired in a visually-guided pointing task and a separate task that required them to predict the time needed to perform differentiated finger movements via mental imagery. Although the exact mechanisms underlying the impairments remained unclear, it was postulated that the SPL lesions damaged the mechanisms required to iteratively activate the stored neural representation, thus, preventing other brain regions involved in the neural process from being entrained to achieve the task goals (Sirigu et al. 1996). In another study, it was reported that patients with right SPL lesions were impaired in the formation of motor imagery (Danckert et al. 2002). Taken together, the results from functional imaging and lesion studies suggest that the right SPL is a candidate substrate for storage of neural representations and/or limb's state estimate in working memory. The posterior parietal cortex has also been implicated in visually guided reaching or pointing movements (Goodale

al. 1999).
and Milner 1992; Desmurget et al. 1999; Connolly et al. 2003) and in maintaining attention to visual or tactile stimuli (Posner et al. 1984). However any visual guidance or attention to sensory stimuli should have been similar in the pulse*v and pulse*c conditions so activity related to either of these functions would not explain our task specific findings. A more relevant finding is that the posterior parietal cortex is more highly activated on the first than on subsequent movements either from a new posture to a fixed target or from a fixed posture to a new target (Pellijeff et al. 2006). Under the pulse*c condition, there is only one new pulse amplitude (target) out of 20 trials where as under the pulse*v condition every trial presents a new target. However, in the Pellijeff et al. (2006) study activation of the posterior parietal cortex was bilateral.

Under the pulse*v condition, the CNS had to assess the sensory information arising from the perturbations and determine how to use it for error reduction. This may explain the involvement of BA 6. Several studies have described activation of BA 6 and BA 7 related to verbal, numerical or spatial mental operations (Hanakawa et al. 2002; Tanaka et al. 2005). However, none of these studies have found activation restricted to the right hemisphere. The activity is either bilateral or confined to the left hemisphere. Nevertheless, these studies provide convincing evidence that BA 6 and BA 7 are involved in tasks that require manipulation of information in working memory. It should be noted that in the studies involving mental operations required conscious manipulation of
information as opposed to manipulation of sensory information for updating an internal model, which takes place subconsciously.

The results of a previous study (Chapman et al. 2007) suggest that an internal model is kept in working memory and updated according to the error on a given trial and the amplitude of the first torque pulse, given the prior history of torque pulses (prior knowledge of the distribution). Thus, sensory information would be used to modify the neural representation (internal model) being held in working memory. It was proposed that working memory involves short-term maintenance of an active representation of information so that it is available for cognitive functions such as planning and problem solving (Baddeley 1986; Shallice et al. 1988). Previous studies consistently reported the activation of BA 6 and BA 7 in tasks that required spatial (Jonides et al. 1993; Anderson et al. 1994) and non-spatial (Grasby et al. 1993; Paulesu et al. 1993) working memory. A review of studies related to spatial and non-spatial working memory provides evidence that activation is localized in the medial BA 6 and lateral BA 7 (D'Esposito et al. 1998). The mean coordinates of activations in BA 6 and BA 7 across all studies reported in the review were [28 -4 52] and [28 -61 44], respectively. The focus of activation in BA 6 and BA 7 are not near to the local maximum found in the present study, i.e. [52 0 48] and [14 -64 66], suggesting that neural activity under pulse*v – pulse*c contrast was not simply related to working memory processes. It is certainly possible that working memory was involved in the present study. However, because the neural processes involved
in the working memory were likely similar under both conditions, activity related to working memory, particularly in BA 7, may have cancelled out.

To optimize torque estimation under the different conditions, the CNS had to compare the sensory consequences of the intended and achieved motor act. Although the magnitude of the perturbations was different under the pulse*v and pulse*c conditions, the sensory signals were essentially of the same modality. Therefore, the neural pathway to the cerebellum should have been the same, i.e. the cerebellum received peripheral sensory feedback via the inferior olive. The cerebellum received cortical projections from the motor, sensory, premotor, and parietal cortices. By integrating these neural signals, the cerebellum could compute the discrepancy between the intended and achieved motor act. Under the pulse*c condition, the required response did not change so the sensory information could be utilized to iteratively reduce error in the torque estimation. Over time, it was posited that the CNS formed a neural representation that approximated the response needed to compensate for the perturbation. This representation could have been maintained in working memory and iteratively modified based on recent sensory information to reduce error during learning. Under the pulse*v condition, the sensory information arising from the perturbations would also be processed in the cerebellum. However, because the errors would have varied both in magnitude and direction from trial to trial the neural signals conveyed by the cerebellum to the motor-related cortices could not be directly used to iteratively reduce error in the torque estimation. In this case, it
is suggested that the right premotor area, upon receiving signals from the cerebellum, engaged in a computational process that was guided by the statistical properties of the perturbation amplitude and led to the determination of an optimal response based on the accumulation of prior knowledge, i.e. formation of an internal model representing the mean response. This would then be adjusted from trial to trial based on the size of the error of the previous trial and current sensory information from the first torque pulse.

Limitations

The choice of non-ferromagnetic materials used for the construction of the fMRI-compatible manipulandum and the long hydraulic lines resulted in friction that affected the response of the manipulandum. A portion of the torque generated by the motor was required to overcome friction. For this reason, the torque pulse applied to the hand was inevitably smaller than the commanded torque. Although the controller implemented compensation for friction, it was not perfect. This may explain why subjects' mean response was less than the mean of the commanded torque. It was not possible to determine the exact magnitude of this effect because of its complex nature. The only position signal available was from the output of an encoder that was integrated into the torque motor, instead of the displacement at the handle of the manipulandum. Because there was considerable backlash between the motor and the manipulandum this signal
did not accurately represent the motion of the manipulandum. Consequently, it was not possible to determine the position error. For this reason, we did not provide subjects with any visual representation of position error. The estimate of hand position was either based on peripheral vision of the hand or proprioception.

In the present study, no EMG was recorded during the training session. Hence, information about pattern of muscle activation during initial exposure to the task dynamics was not available. Without this information, it was not possible to determine to what extent the CNS reduced cocontraction under the pulse*v condition.

Although three atlases were used to create the masks for the ROI analysis, the statistical power for the pulse*v – pulse*c contrast did not improve and the descriptive statistics from the analysis were identical to that when the P value was uncorrected. To this end, an event-related analysis of the hemodynamic response between the end of the second torque pulse of a particular trial to the end of the first torque pulse of the next trial could improve the statistical power of the contrast between pulse*v and pulse*c. Another possibility is to parcelate the right BA 6 and BA 7 of each subject at the 1st level analysis to localize the areas of activation. The contrast images from the 1st level analysis could then be entered into a 2nd level region of interest analysis to address the statistical power of the task specific contrast. Using coherence
analysis, future research could examine how parametrical manipulation modulates the hemodynamic response at the voxel level.
CONCLUSION

The results from the present study indicated that the CNS was capable of learning and adapting to both predictable and unpredictable environments. When the dynamics of perturbing environments remained constant over time, the CNS utilized the sensory signals from the interaction with the perturbations to code accurate compensatory motor commands. When the dynamics of perturbing environments changed randomly from time to time, the CNS discriminated the sensory information and took into account previously acquired knowledge of movement experience, to optimally compensate the varying perturbations. Albeit not a ‘mirror-image’ compensation, the strategy of coding for the approximate mean of the random perturbations reduced spatial errors according to the probabilistic properties of the environment. Consistent results from the present and previous studies showed that the CNS underestimated the true mean of the perturbing environment so that metabolic cost would be minimized (Kording et al. 2004; Takahashi et al. 2001; Scheidt et al. 2001). The results from functional imaging suggested that a fronto-parietal network subserve the neural processes inherent in Bayesian models of torque estimation.
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