Linking Error, Passage of Time, the Cerebellum and the Primary Motor Cortex to the Multiple Timescales of Motor Memory

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ABSTRACT

Recently, our laboratory proposed that a single model could account for a large body of behavioral data in numerous motor adaptation paradigms. The idea was that motor memory is supported by at least two interacting processes: a fast process that learns quickly from motor error but rapidly forgets, and a slow process that only gradually learns from error but has long-term retention. The main purpose of this research is to uncover the time and error-dependent properties of these putative processes and to ask whether there is a link between these processes and the functions of the cerebellum and primary motor cortex.

How does passage of time affect retention of motor memories? The typical approach is to learn a task, and then look at retention as a function of time. However, if motor memories are supported by multiple processes, then a better way to reveal their timescales is to adapt, reverse adapt, and then quantify retention. The prediction of our theory is that there should be spontaneous recovery of the initial adaptation with passage of time. Because theory predicts that reverse adaptation will primarily engage the fast system, this experimental design allowed us to quantify how retention changed as the fast and slow processes decayed with passage of time. The different rates of decay in these putative processes resulted in a time-dependent pattern of spontaneous recovery, as well as a time dependent stabilization of the fast memory process.

Previous work by Huang and Shadmehr demonstrated that the statistics of the environment during adaptation altered the time constant of the putative processes that support memory (Huang and Shadmehr 2009). When the perturbation was presented abruptly, the memory decayed quickly, suggesting engagement of the fast process. When

the perturbation was presented gradually, the memory was decayed slowly, suggesting engagement of the slow process. We hypothesized that the role of the cerebellum is to respond to large errors, thus supporting the fast process of motor memory. To test for this, we trained cerebellar degeneration patients in both the abrupt (large errors) and gradual (small errors) conditions. Severely affected patients showed improved adaptation in the gradual condition and upon sudden removal of the perturbation the motor memory that was acquired showed a strong resistance to change, exhibiting after-effects that persisted much longer than in healthy controls. Therefore, cerebellar degeneration impairs the ability to learn from large magnitude errors, but has a lesser impact on learning from small errors.

Finally, we hypothesized that the role of the primary motor cortex is to support the late phase of adaptation, during which error is small, motor output has reached a plateau, and the slow process dominates net adaptation. We employed three behavioral conditions, abrupt, gradual and uber to vary the size of the error, the number of trials where the perturbation was at steady state, and the phase of learning. A single pulse TMS paradigm was applied to the primary motor cortex. Disruption of the primary motor cortex caused an impairment in performance when the errors were small and the environment at steady state, independent of the phase of the learning. We conclude that the primary motor cortex contributes to motor learning when the training environment and motor output have reached steady state for an extended number of trials.

Advisor: Dr. Reza Shadmehr

PREFACE

To be added.

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CHAPTER 1
INTRODUCTION

1.1 Neural Basis of Motor Learning

To better understand the relationship between declarative and motor memory, an amnesic patient, H.M., performed a reach adaptation task that required him to compensate for a force perturbation (Shadmehr et al., 1998). Not only did H.M. learn, as evidenced by 'catch' trials in which the force perturbation was turned off, but upon returning the next day he showed large aftereffects, indicating retention from previous training. This observation, as well as those seen in mirror-tracing and other motor learning tasks, suggests that there are two distinct neural systems for declarative and motor memory formation (Milner, 1962; Gabrieli et al., 1993; Tranel et al., 1994; Yamashita, 1993). While it is believed that the formation of motor memories depends on neural plasticity that allows for the association of motor commands and sensory consequences, the neural basis and regions where these changes occur are not well understood.

Investigators have long hypothesized that many of the tasks that H.M. learned were forms of "habit learning", and that this learning was crucially dependent on the basal ganglia (Mishkin et al., 1984). However, recent experiments have overturned this idea. Patients with cerebellar degeneration demonstrated marked impairment when given extended exposure in the force field adaptation paradigm (Smith, 2005; Smith and Shadmehr 2001). Patients with mild to moderate Huntington's disease were able to adapt

to the perturbations, using the error in a given trial to improve performance in the next (Smith et al., 2000). Similarly, Parkinson's disease patients were able to adapt to the perturbations (Krebs et al., 2001). Together, these studies of the force field reach adaptation in patients suggested that the cerebellum, and probably not the basal ganglia, was a crucial site for adapting motor output to compensate for reach inaccuracies.

During this same period, a number of laboratories began using the paradigm in neurophysiological experiments. The Bizzi laboratory discovered that after extensive training, task-related cells in M1 and the ventral premotor cortex changed their preferred directions, rotating in the direction of the field and sometimes maintaining that rotation despite removal of the field (Li et al., 2001). However, the Ebner laboratory discovered that with training, despite large changes in motor output (EMG) there was little change in the discharge of Purkinje cells in the cerebellum (Pasalar et al., 2006). These results were puzzling for two reasons. First, in terms of the neural basis of motor memory, it was unclear why integrity of the cerebellum was crucial for patient acquisition of the task, while training did not result in lasting neurophysiological changes in monkeys. Second, while there were no studies in humans that directly investigated the role of the motor cortex in reach adaptation, it was unclear why training should result in lasting neurophysiological changes there and not in the cerebellum.

1.2 Multiple Timescales of Motor Memory: The Two-State Model

While the role of the cerebellum and primary motor cortex in motor learning were unresolved, in 2006 a new model of motor learning was proposed that appeared to account for a number of behavioral observations in reach and saccade adaptation (Smith

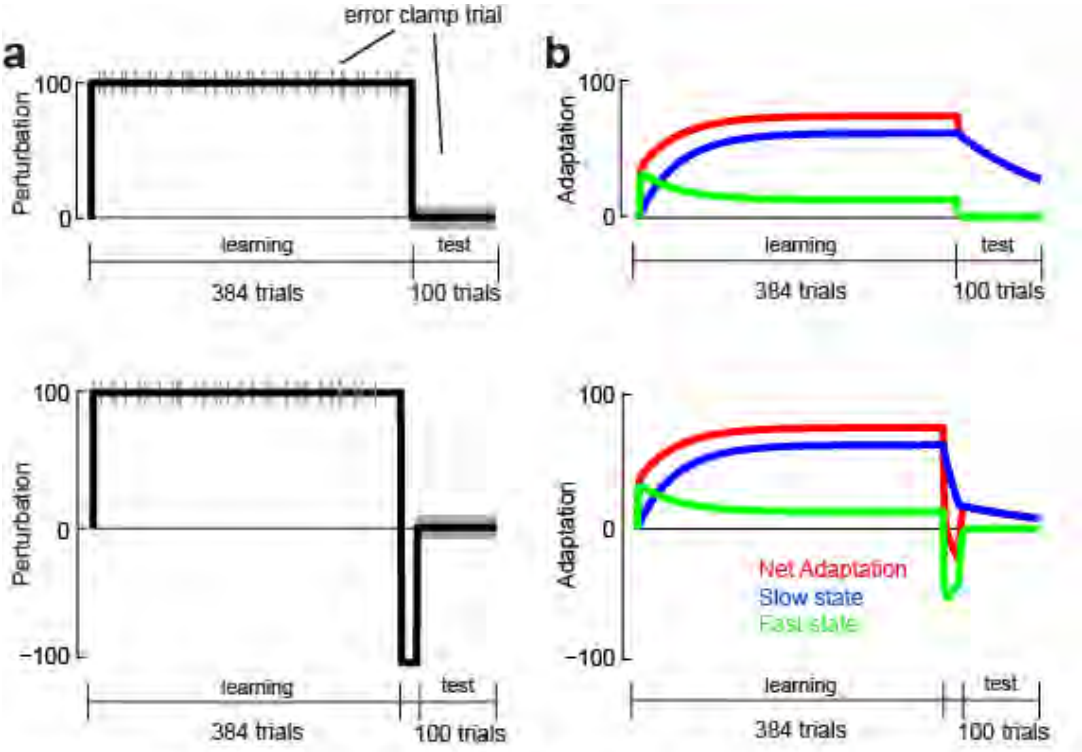

Figure 1.1 The two-state model. a. The paradigm for an error-clamp experiment. The gray bars schematically represent 'error-clamp' trials, during which performance error is minimized. The learning block (384 trials) is followed by an error-clamp test block (100 trials) (top). The learning block (384 trials) is followed by an unlearning block (20 trials) and an error-clamp test block (100 trials) (bottom). b. During initial learning, the fast state adapts quickly in response to large errors, while the slow state adapts gradually. In the error-clamp trials that follow, the fast state forgets quickly, while the slow state forgets gradually (top). When the initial learning is followed by a brief period of unlearning, the fast state unlearns rapidly, while little unlearning occurs for the slow state. In the error clamp trials that follow, the fast state once again forgets quickly. Since the net adaptation is the sum of the fast and slow states, this results in spontaneous recovery (bottom).

et al., 2006). The behavioral data in these tasks produced two important results. First, when adaptation was followed by extinction training, the animal still exhibited savings when re-tested in the same task (Kojima et al., 2004). Second, when extinction was followed by a period when movements were denied error feedback, their motor output reverted to the initial adapted state, resulting in "spontaneous recovery" of the motor memory. This new model explained these results by suggesting that motor memory was

supported by at least two functional states: a fast state that was highly sensitive to error and learned quickly, but had poor retention and could not sustain its memory for long periods of time; and a slow state that was less sensitive to error and learned slowly, but had good retention and could sustain its memory for longer periods. The two-state model highlighted the possibility that motor memory was not a single entity, but rather a "sum" of multiple processes, each with its own sensitivity to motor errors and passage of time (Figure 1.1).

On a given trial, the participant learns from the sensory prediction error $\mathbf{e}^{(n)}$, which is the difference between the predicted and observed outcome:

$$\mathbf{e}^{(n)} = y^{(n)} - \mathbb{y}^{(n)} \tag{1.1}$$

The contributions from both the fast and slow processes are updated on each trial:

$$\mathbb{y}^{(n)} = x_f^{(n)} + x_s^{(n)} \tag{1.2}$$

$$x_f^{(n+1)} = \mathrm{A}_f\, x_f^{(n)} + \mathrm{B}_f\, \mathrm{e}^{(n)} \tag{1.3}$$

$$x_s^{(n+1)} = \mathrm{A}_s\, x_s^{(n)} + \mathrm{B}_s\, \mathrm{e}^{(n)} \tag{1.4}$$

where x represents the internal states, A is the forgetting factor, and B is the learning rate.

Is there a way to tilt the balance between the fast and slow systems in healthy people? That is, is there a way to preferentially engage the fast or slow systems? A number of studies demonstrate that manipulating the schedule of behavioral training alters the properties of a memory. When a perturbation is presented abruptly, the learner initially produces large performance errors and is keenly aware of the disturbance. Yet, if a perturbation is presented gradually, performance errors remain small and the learner is unaware of the disturbance. Learning in either an abrupt or gradual training environment

produces motor memories that can be recalled upon revisiting the task (Klassen et al., 2005). However, in prism and reach adaptation tasks gradual introduction produces longer-lasting after effects (Kagerer et al., 1997; Hatada et al., 2006) and better retention (Klassen et al., 2005; Huang and Shadmehr, 2009). That is, small errors during learning appear to engage the slow process and encourage more resistant motor memories while large initial errors appear to engage the fast process and encourgage less resistant motor memories.

1.3 The Consolidation Controversy

Our lab recently attended the Society for Neuroscience Conference. Professor Shadmehr and I decided to attend different lectures, but planned to meet for lunch. Knowing that I would not remember his phone number a few hours later, I saved the number in my cell phone. Interestingly, I can still recall the phone number of my childhood best friend (317) 283-2453, even though I have not called the number in over 15 years. While a declarative memory like the phone number of a friend is susceptible to forgetting, it can be remembered indefinitely through recall and rehearsal. This process where a memory transitions from a fragile to a stable state is called consolidation.

From personal everyday experience, it is evident that both declarative and motor memories can be consolidated. For instance, at the age of eight I learned to figure skate. My warm-up routine at the beginning of each practice session consisted of front and back crossovers around the rink. During the past 6 years, I have only figure skated five times, yet each time I was able to execute my warm-up routine effortlessly. Yet, experimental evidence of the consolidation of motor memories has proven controversial.

In 1996, Brashers-Krug and colleagues provided compelling evidence that the passage of time allows motor memories to transition from a fragile state that is susceptible to interference to a stabile state that is resistant to interference (Brashers-Krug et al., 1996). When initial learning in force field A was immediately followed by performance in force field B, participants demonstrated naïve levels of performance in field A 24 hours later. However, if four hours elapsed between the learning of field A and field B, the passage of time protected field A from interference from field B. A second set of experiments confirmed that if the learning of the two skills was separated by approximately six hours then two motor maps could be formed and retained for extended periods of time (Shadmehr and Brashers-Krug, 1997). While some attempts to replicate these results have shown that as much as 24 hours is still insufficient to protect field A from interference from field B (Caithness et al., 2004), other studies observed that passage of time and increased training produced a less vulnerable memory (Krakauer et al, 2005). Krakauer and colleagues hypothesized that naïve performance in task A was not due to unlearning caused by task B, but was instead a result of anterograde interference that masked retrieval of the memory of task A.

Can memories be unlearned, or is unlearning a form of acquiring a new memory that competes with the old, effectively masking it? In Chapter 2, we probed the error and time dependent correlates of the fast and slow timescales of motor memory. In previous experiments, participants performed a comparable number of trials in both field A and field B. If both memories were present and competing, then evidence of each memory would be masked by the other memory. Thus, extensive training in field A (slow memory) was immediately followed by brief training in field B (fast memory). We

examined both the magnitude and resistance to change of the memories of A and B. We observed that learning of B did not cause unlearning of A, but rather installed a competing memory. Additionally, memories with a fast timescale gained stability with the passage of time.

1.4 Cerebellar Contributions to Motor Learning

The cerebellum plays a key role in motor learning. Purkinje cells receive input from climbing fibers, which are capable of initiating numerous action potentials but fire infrequently, and parallel fibers, which are weak individually but are a strong collective force. Early computational theories hypothesized that the climbing fiber input strengthens the parallel fiber – Purkinje cell synapses, serving as a teaching signal (Marr, 1969). In 1971, Albus provided an alternative view, positing that the climbing fiber input weakens the parallel – Purkinje cell synapses, serving instead as an error signal (Albus, 1971). While the precise role of climbing fibers has proven controversial, there is extensive experimental evidence of cerebellar involvement in motor learning.

The contribution of the cerebellum in adaptation is most clearly demonstrated by animal and human degeneration and lesion studies. For example, laterally displacing prism glasses shift the view of the world. When a participant puts on the glasses and attempts to point to a target, they initially make errors and miss the target. With practice, participants adapt to the visual perturbation and upon removal of the glasses they demonstrate after-effects. In a lesion study, healthy macaque monkeys adapted to prism perturbations, but ablation of the areas of the cerebellar cortex receiving mossy fiber input abolished adaptation (Baizer et al., 1999). Patients with lesions of the olivocerebellar systems are also impaired in prism adaptation (Martin et al., 1996).

Similarly, learning impairments in cerebellar degeneration patients are seen in force field reaching (Smith and Shadmehr, 2005) and splitbelt treadmill walking (Morton and Bastian, 2006) adaptation paradigms.

What is the driving force in cerebellar dependent motor adaptation? Animal studies have shown that during rapid reaching movements ~200 ms to a target (Kitazawa et al., 1998) and tracking in a circular manual task (Roitman et al., 2009), error is encoded by Purkinje cells. Imaging studies have also demonstrated increased cerebellar activation in response to tracking (Imamizu et al., 2000) and execution errors (Diedrichsen et al., 2005). More specifically, saccade (Wallman and Fuchs, 1998) and reaching (Tseng et al., 2007) adaptation studies have shown that prediction error, the difference between predicted and actual outcome of motor commands, not motor correction, is the driving force of motor learning.

We know the cerebellum is necessary for error dependent learning. Yet, small errors may affect the process of learning in a fundamentally different way than large errors. More specifically, small errors during learning appear to encourage more resistant motor memories while large initial errors appear to encourgage less resistant motor memories (Huang and Shadmehr, 2009). Are distinct neural mechanisms engaged in response to large vs. small errors? If the cerebellum is particularly important for fast adaptation to large errors, would cerebellar ataxia patients have an easier time learning if we preferentially engage the slow process, allowing them to rely more on alternative neural structures?

In Chapter 3, we considered a group of patients with cerebellar degeneration. We hypothesized that if the cerebellum is equally important in supporting adaptation in

response to small as well as large magnitude errors, then these patients should be equally impaired in reach adaptation in response to abrupt vs. gradually imposed force perturbations. However, patients showed improved adaptation when errors were minimized in the gradual paradigm and exhibited after-effects that persisted much longer than in healthy controls. The neural basis of learning from small and large magnitude movement errors appears to be distinct.

1.5 Primary Motor Cortex Contributions to Motor Memory

Production of a voluntary arm movement requires target localization, motor planning and motor execution. While the role of the primary motor cortex in the execution of movements is well understood, the precise contribution to motor learning is less clear. Damage to the primary motor cortex is known to cause severe impairments in the execution of reaching movements (Castro, 1972; Whishaw et al., 1991; Gharbawie et al., 2005). It has also been shown that stroke may not only impair motor execution, but also motor planning, due to an increase in neuromotor noise (MrCrea and Eng, 2004). Interestingly, a TMS study in humans revealed that the primary motor cortex is activated during observation of motor actions, indicating involvement beyond just execution (Hari et al., 1998). Further evidence for the involvement of the primary motor cortex in learning was seen in a study where hemiparetic stroke patients with intact full range of motion of their paretic arm were impaired in adaptation in a force field reaching task (Takahashi and Reinkensmeyer, 2003).

Recently, the potential for linking the timescales of motor memory with the primary motor cortex was demonstrated when a repetitive transcranial magnetic

stimulation (rTMS) study produced the remarkable result that disruption of M1 prior to reach adaptation in force fields resulted in no behavioral consequences during learning, i.e., subjects acquired the task as well as subjects who had not been stimulated (Richardson et al., 2006). However, the rTMS subjects displayed markedly reduced recall when they were tested at 24 hours. This raised the interesting possibility that M1 may have played a crucial role in consolidation and retention of the motor memory, but possibly a lesser role in its acquisition. Recently, we our laboratory found that a single pulse of TMS applied to M1, timed to the arrival of motor error feedback, did not affect motor output and learning rates during adaptation, but produced a motor memory that was more susceptible to subsequent errors (Hadipour-Nikitarash et al., 2007). Together, these TMS results suggested that M1 may play a more important role in forming memories that are less susceptible to motor errors and passage of time. These are characteristics of the slow state of motor memory.

Neurophysiology experiments have also implicated the primary motor cortex in motor learning. Recall that the Bizzi laboratory found that the cells of the primary motor cortex experienced a long lasting change in their preferred direction following extensive training (Li et al., 2001). In 2003, Paz and colleagues demonstrated that changes in M1 lag behind performance improvements (Paz et al., 2003). Together, results from TMS and neurophysiology studies implicate the primary motor cortex during the later phase of learning and consolidation. Coincidentally, the prediction errors are small and the perturbation is at steady state during this late phase of training. Does engagement of the primary motor cortex depend on the size of prediction error, the number of trials that the perturbation is at steady state and/or the phase of the learning?

In Chapter 4, we varied the size of error and number of trials at which the perturbation was at steady state during a force field reach adaptation task. We utilized three training paradigms: 1.) abrupt (290 trials step) 2.) gradual (45 trials ramp, 245 step) and 3.) uber (240 trials ramp, 50 step). We hypothesized that if the primary motor cortex supported adaptation when errors are small and it is the late phase of learning, then TMS over M1 should cause an impairment in all three conditions. However, we observed that TMS impaired performance when the errors were small and the perturbation was at steady state for an extended period of time in the abrupt and gradual conditions. The lack of impairment in the uber condition indicates engagement of the primary motor cortex once the motor output has reached a plateau.

CHAPTER 2

CONSOLIDATION PATTERNS OF HUMAN MOTOR MEMORY

2.1 INTRODUCTION

One of the defining characteristics of primates is the ability to use tools. Learning to use a tool requires practice, and the result of this practice is a motor memory that allows the user to display skilled performance the next time the tool becomes available. Classic texts on memory hypothesized that motor memory differed from cognitive or declarative memories because it did not appear to include a short-term phase in which the memory was fragile (Squire, 1987). This picture changed when it became clear that motor memories exhibited a phenomenon termed spontaneous recovery (Kojima et al., 2004;Smith et al., 2006;Ethier et al., 2008). For example, after people learned to use a novel tool (a robotic arm) that exhibited dynamics A, they could quickly 'unlearn' that behavior if the tool's dynamics suddenly changed to B. However, in the subsequent 'error-clamp' trials in which motor output could be assayed while minimizing error-dependent learning, behavior reverted back toward A (Smith et al., 2006). This suggested that during motor learning, changes in behavior were due to two processes: a fast learning process that was highly sensitive to error but had poor retention, and a slow learning process that had poor sensitivity to error but had robust retention. Learning of B installed a fast memory that decayed rapidly after acquisition. Extensions of this simple

idea appeared to account for a range of behaviors in motor learning (Kording et al., 2007;Chen-Harris et al., 2008).

If motor memory is supported by a fast and a slow process, what are their characteristics? For example, do these processes show different sensitivities to passage of time? Are the processes independent of each other, or does passage of time transform one process into another? Finally, can motor memories be unlearned, or is 'unlearning' merely learning of a new memory that competes with the old? These questions are of fundamental importance because they deal with consolidation patterns of motor memory, a topic that despite years of research in various laboratories has produced a large body of apparently conflicting results. While some have found that passage of time increases resistance of the memories to 'unlearning' (Shadmehr and Brashers-Krug, 1997;Krakauer et al., 2005;Overduin et al., 2006), others have seen no evidence for a temporal gradient (Caithness et al., 2004;Mattar and Ostry, 2007).

Here, we assayed the effects of time on motor memory through 'error-clamp' trials, trials in which the memory was re-activated but error-dependent learning was minimized (Scheidt et al., 2000). The crucial advantage of this approach was that it allowed us to simultaneously measure both the magnitude of the re-activated memory and its resistance to change. We found that the large errors subjects experienced during de-adaptation did not produce unlearning of A, but rather installed a competing memory of B. However, in contrast to predictions of the fast/slow model, with passage of time after A+B training, B did not rapidly fade away. Rather, when subjects stopped performing the task, the initially fragile memory gained stability. These results together suggest a new memory model in which learning not only engages processes that adapt at multiple

timescales, but that once practice ends, the fast states can be partially transformed into slower states. We suggest that this framework can account for much of apparently conflicting results in motor memory consolidation research.

2.2 METHODS

One hundred and seven neurologically intact right hand dominant participants were involved in this study. Fifty-six volunteers (24 male, 32 female) were recruited for Experiment 1 (average age, 26.0 years; SD, 4.3 years). Fifty-one different volunteers (26 male, 25 female) were recruited for Experiment 2 (average age, 28.5 years; SD, 9.1 years). All volunteers were naïve to the purpose of the experiment. Experimental procedures were approved by the Johns Hopkins University School of Medicine Institutional Review Board and all participants signed a consent form.

2.2.1 Behavioral Training

The volunteers were trained in the standard force field reach adaptation paradigm (Shadmehr and Mussa-Ivaldi, 1994). They held a two-joint robotic manipulandum with their right hand and made point-to-point reaching movements from a center starting position to a single one centimeter square target positioned at 10 cm directly along the body midline. Once at the target, the robot brought the subject's hand back to the center. Subjects were rewarded with an 'explosion' for completing the movement within a 50ms window centered at 0.5sec after movement start time. The subject's hand was covered by a horizontal screen, onto which a small cursor (5x5 mm) representing hand position was projected at all times. We recorded force at the handle, hand position, and hand velocity at a rate of 100Hz.

The experiment (Figure 2.1) began with training in a null field (no forces, 192 trials) followed by training in a curl field in which forces were dependent on hand velocity $\mathbf{f} = A\dot{\mathbf{x}}$, in which A=[0 13; -13 0] N.sec/m. This adaptation phase consisted of 384 trials. One subject was excluded from the analysis because of failure to adapt to the force field during the training session.

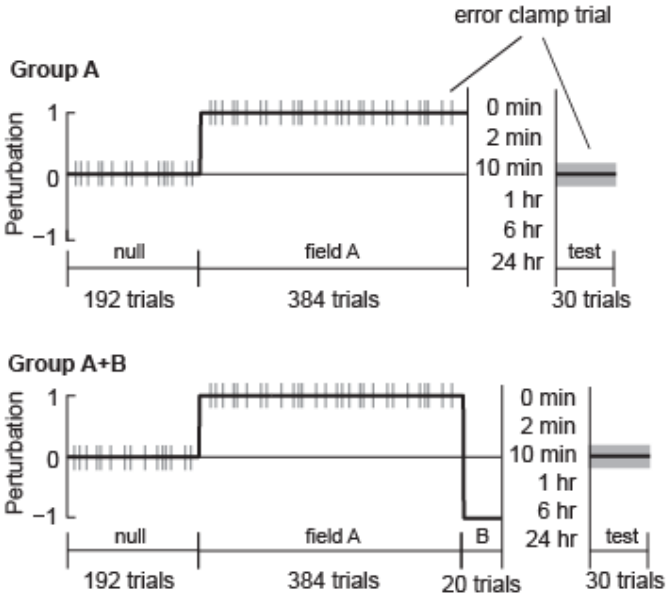

Figure 2.1. Experimental paradigm. Volunteers were divided into two groups (Group A and Group A+B). They held the handle of a light weight robotic arm and reached to a target. In the first 192 trials the robot produced a null field (no forces). In the subsequent 384 trials, a curl force field was introduced (Field A), perturbing the hand perpendicular to its direction of motion. In Group A+B, the force field was reversed in sign for 20 additional trials. The gray bars schematically represent 'error-clamp' trials, trials in which the robot produced a stiff channel that allowed us to measure the subject's motor output perpendicular to the direction of motion. After a break of variable length, subjects returned and were asked to hold the robotic tool and perform the task. We quantified the strength of the re-activated memory through 30 error-clamp trials.

Experiment 1: Group A. This experiment assayed the sensitivity of the motor memory to passage of time. After completion of adaptation, subjects were re-examined once at 0 min, 2 min, 10 min, 1 hr, 6 hrs, or 24 hrs. The re-examination consisted of 30 error-clamp trials only.

Experiment 2: Group A+B. In this experiment, volunteers who had completed their training in field A were immediately exposed to 20 trials of field B (viscosity matrix

[0 -13; 13 0] N.sec/m). This small number of trials was sufficient to bring the motor output back to baseline. However, according to our theory, the trials set up a competition between a 'fast' memory acquired in response to training in B and a 'slow' memory acquired in response to training in A. As a result, we expected to see spontaneous recovery of A immediately after completion of the 20 trials in B. We were interested in quantifying the sensitivity of this spontaneous recovery to passage of time after completion of training in B. Therefore, after completion of training in B, subjects were re-examined once at 0 min, 2 min, 10 min, 1 hr, 6 hrs, or 24 hrs. The re-examination consisted of 30 error-clamp trials only.

We accounted for the time that passed between end of training and start of the test session in all subjects. In the 0, 2, and 10min groups, all subjects remained seated in front of the robot. In the 1, 6, and 24 hr groups, all subjects left the chair during the break and were instructed to proceed throughout their day normally. Subjects in the 24 hr group were required to sleep a minimum of 6.5 hrs between day one and day two.

2.2.2 Error-clamp trials

We placed error-clamp trials randomly in the baseline and adaptation phases with $1/8^{th}$ probability (no error-clamp trials were present during the exposure to field B). During the error-clamp trials, the motion of the hand was constrained to a straight line to the target by a stiff one-dimensional spring (spring coefficient = 2500 N/m; damping coefficient = 25 N·s/m) that counteracted any forces perpendicular to the target direction. Error-clamp trials, however, were no different than regular trials in the type of feedback that the subject receives: they were rewarded with an 'explosion' for completing the movement within a 50ms window centered at 0.5sec after movement start time. Because

the curl field perturbed the hand perpendicular to the direction of motion, the forces that the hand produced against the 'channel' wall in error-clamp trials served as a proxy of adaptation, i.e., the change in the motor output. Previous work has shown that after training, forces in error-clamp trials faithfully represent the ideal force trace that one should produce to cancel the robot forces, whether in velocity dependent (Scheidt et al., 2000;Smith et al., 2006;Hwang et al., 2006b) or acceleration dependent fields (Hwang et al., 2006a).

2.2.3 Data Analysis

Performance was measured via the force that subjects produced against the channel wall of the error-clamp trials. Our performance measure, termed force output as a percent of perturbation, was simply the ratio between this force as measured at the maximum velocity and the ideal force in field A. That is, regardless of whether the block of trials was in field A or null, the ideal force was described as $\mathbf{f} = A\dot{\mathbf{x}}$, where $\dot{\mathbf{x}}$ is hand velocity on that trial. In this way, in the null field we assayed motor output with the same yard-stick as in subsequent training trials in field A. Note that there were no error-clamp trials during exposure to field B. Repeated measures ANOVA and post-hoc Tukey tests were used to quantify effects of time passage and differences between groups. All analyses were done using Matlab and SPSS.

When subjects were using the robot, the memory was "active" and it changed as a function of time/trial. When subjects were not using the robot, the memory was "inactive" but it still continued to change as a function of time. To assay the sensitivity of the active memory to time/trial, we focused on the rate of decay of the force output during the error-clamp trials of the test period. This rate was estimated by fitting a single

exponential of the form $f(n) = a\exp(-bn)$ to the data set during the test period for each subject. In this equation, f is force and n is trial number. This continuous-domain equation can be well approximated in the discrete domain: $f^{(n+1)} = (1-b)\, f^{(n)}$ in which $(1-b)$ is an estimate of sensitivity of the memory to trial. Therefore, b is fraction of the force that is lost from one trial to the next. This measure quantifies the fragility of the memory as assayed at a particular time after its acquisition.

We performed a boot-strapping procedure to estimate strength of memory for B at each time point after A+B training. To do so, we had two subject groups to choose from: one group of subjects who had learned A and was then tested at time point t for 30 trials, and another group of subjects who had learned A+B and was then tested at the same time point t for 30 trials. We picked one subject at random (with replacement) from group A, and another subject at random (with replacement) from group A+B, and then subtracted performance of subject in group A from subject in group A+B, i.e., $\hat{B} = (A+B) - A$. We then repeated this procedure 50 times to arrive at a distribution for the motor output at each trial during the test period at time t. This produced the data for $\hat{B}$ shown in Fig. 4.

When the subjects were not reaching with the robot, the memory was "inactive". The sensitivity of the inactive memory to passage of time was estimated using a boot-strapping procedure. We selected at random one subject (with replacement) from each group and calculated the average of the first two error-clamp trials of the test session. We then took the six data points (one for each time delay) and fitted it to a single exponential of the form $f(t) = a\exp(-t/\tau)$. We repeated this procedure 50 times.

2.2.4 Active-Inactive State Model of Motor Memory

Previous models of motor memory assumed that during learning, the observed state of the environment was assigned to one of two general states: a fast state and a slow state. Learning was a procedure in which one tried to estimate the state of the environment (Kording et al., 2007). With passage of time, the fast state decayed rapidly while the slow state decayed gradually. Here, one of our main observations was that effect of time was not merely a decay in the states, but rather a transformation of the fast state into a slow state. In particular, when the subject was not performing the task (the inactive state of the memory), passage of time produced a partial transformation of the fast state into a slow state. To represent this idea, we considered a generative model in which the environment was sometimes observable and sometimes unobservable. In the observable condition, the generative model was identical to our previous model (Kording et al., 2007). However, in the inactive state, the state transitions allowed some transformation of the fast states into slow states.

The graphical representation of the model is shown in Figure 2.5a. The measured variables are filled circles while the estimated variables are unfilled circles. When the environment is observable (active memory), measurements are simply the sum of the fast and slow states, with equal weight, i.e., $y^{(t)} = \mathbf{c}^T \mathbf{x}^{(t)} + \varepsilon_y$ where $\mathbf{c}^T = \begin{bmatrix} 1 & 1 \end{bmatrix}$ and $\mathbf{x}^T = \begin{bmatrix} x_s & x_f \end{bmatrix}$. Time affects the states in both the active and inactive conditions. When the environment was observable, we assumed $\mathbf{x}^{(t+\Delta)} = A_a \mathbf{x}^{(t)} + \boldsymbol{\varepsilon}_a$, where A_a was diagonal, representing the state transition for the active memory. When the environment was unobservable, we assumed $\mathbf{x}^{(t+\Delta)} = A_i \mathbf{x}^{(t)} + \boldsymbol{\varepsilon}_i$, where A_i was not diagonal, representing the state transition for the inactive memory. To fit the model to the data, the only

relevant variables are A_a (two parameters) and A_i (three parameters) because the noises play no role in the decay rates in error-clamp trials (as long as we assume that there are no errors in error-clamp trials, and the noises are Gaussian). We assume that by end of training in A, 83% of the memory was due to the slow state and 17% was due to the fast state. Training in B introduced a competing memory that was 83% fast and 17% slow. These values were found to be the optimal initial condition proportions for the fast and slow states for the memory of A and the memory of B. We estimated the five parameters of the model by fitting it to the average data using nonlinear optimization.

2.3 RESULTS

We imagined that practice resulted in a motor memory that had at least two functional states: a fast state, and a slow state. To assay the sensitivity of the hypothetical slow memory to passage of time, we trained subjects for a long period of time (384 trials, Figure 2.1) on a reach adaptation protocol (field A), and then divided them into 6 groups and tested each group at a single time point after completion of practice (Experiment 1). To assay the sensitivity of the hypothetical fast memory to passage of time, we performed an adaptation/de-adaptation experiment in which the same training in A was followed by a brief period of training in B (20 trials) until performance reached naïve levels (Experiment 2). While A+B training produced apparent extinction, we hypothesized that the training in fact produced a fast memory of B that competed with the slow memory of A. We divided the subjects into 6 groups and tested each group at a single time point after completion of A+B. By comparing A vs. A+B at various time points, we quantified how passage of time affected the hypothetical slow memory of A and fast memory of B.

Performance was measured via the force that subjects produced against the channel wall of the error-clamp trials. Adaptation in A produced performance measures that had the familiar initial fast rise followed by a period of gradual increase (Figure 2.2). We found no significant differences in the performance measures of the 12 groups during adaptation in A (repeated measures ANOVA, $F(11,95)=0.683$, $p=0.752$). A one way ANOVA on the average of the last five trials showed no differences between groups ($F(11,95)=0.174$, $p=0.999$).

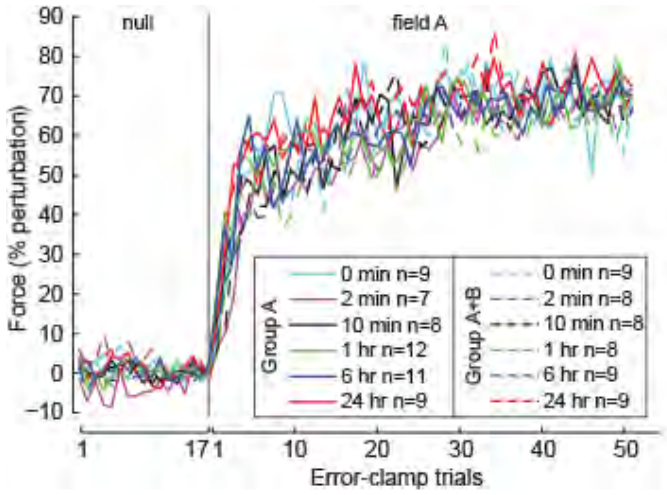

Figure 2.2 Force output (mean for each group for each trial) during the error-clamp trials in the baseline and learning periods (Field A only). Learning of A was similar among the groups, exhibiting the classic double exponential pattern: rapid initial learning followed by slow, gradual learning. Bin size is one trial.

2.3.1 Memory of A decayed as a function of time, but when re-activated, remained resistant to trial

After completion of 384 trials in A, subjects were assigned to one of six groups and waited 0 min, 2 min, 10 min, 1 hr, 6 hrs, or 24 hrs. In the 0, 2, and 10 min groups the subjects remained seated in front of the robot. In the 2 and 10 min groups, subjects released the handle of the robot during the delay period. The subjects in other groups left

the room and returned at their scheduled time. Upon return, they were asked to hold the handle and reach to the target. In these movements, the robot always produced a 'channel'. Therefore, the test period consisted of only error-clamp trials, allowing us to assay the memory without contamination from further re-learning.

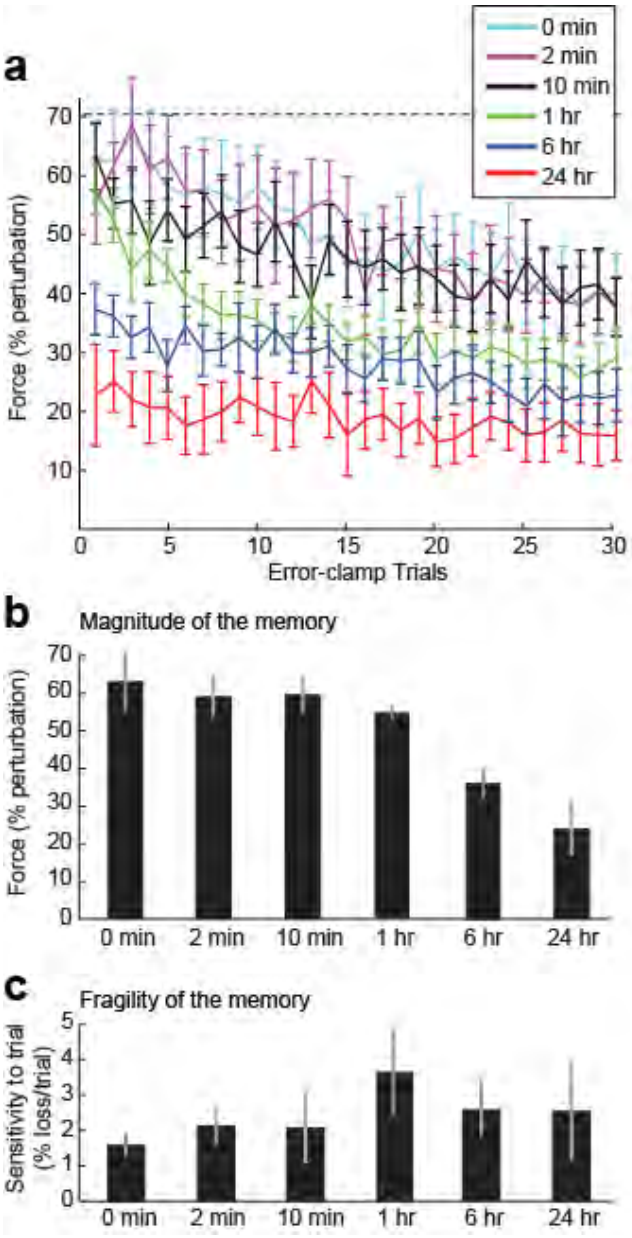

Figure 2.3 Performance during test of recall in Group A. a. Force output (mean±SEM) for each sub-group following completion of training in A. The dashed line represents the force output at end of training (average of last 5 error-clamp trials across all sub-groups). The output started higher for subjects that acquired the task recently, and decayed slowly during test of recall in all sub-groups. Bin size is one trial. b. Magnitude of the memory as a function of time since acquisition. Each bar plot represents the initial force output (bin size is two trials) averaged across subjects in each subgroup (error bars are SEM). c. Fragility of the memory. Force output as a function of trial for each subject was fitted to a single exponential. The decay rates, shown here as mean±SEM, did not change with passage of time.

The performance of each group during the test phase is shown in Figure 2.3a. During the time between end of training and start of testing, the memory decayed as a function of time, as reflected in the force that subjects produced in the first two trials (Fig. 2B, $F(5,50)=8.469$ $p<0.05$). A Tukey post hoc test revealed differences between the 24 hr group and the 0, 2, 10 min, and 1hr groups and the 6 hr group and the 0 min and 10 min groups ($p<0.05$ in all cases). A repeated measures ANOVA suggested that groups that waited a longer period of time produced smaller forces during the course of the entire test session than those that waited a brief period (main effect of wait period, $F(5,50) = 3.773$, $p<0.01$).

Suppose that we consider the memory 'active' when the subject is using the tool, and 'inactive' during the period that the subject is not holding the handle of the tool (i.e., time between training and testing). The effect of passage of time is a measure of decay of the 'inactive' memory. To estimate the sensitivity of the inactive memory to passage of time, we used a boot-strapping procedure to select at random one subject from each group in Figure 2.3b and fitted their data to a single exponential. The result suggested that the strength of the inactive memory decayed with a time constant of 18.5±3.89 hrs (SEM).

Once the test trials began, the activated memory decayed as a function of time/trial. Intriguingly, this resistance did not appear to change with the passage of time. Figure 2.3c illustrates the distribution of time-constants when a single exponential was fitted to the force output of each subject during the error-clamp trials in the test period. A one-way ANOVA found no significant effect of passage of time on sensitivity to trial

$F(5,50) = 0.562$, $p = 0.729$. A Tukey post-hoc analysis revealed no significant differences between individual groups.

When the memory was re-activated (Figure 2.3c), trial dependent loss was distributed between 1 to 3% per trial, which translates into a time constant of 200-600 seconds. In contrast, when the memory was inactive, the time constant was about 18.5 hours (Figure 2.3b). Therefore, decay of the activated memory was about two orders of magnitude faster than the inactive memory.

In summary, after a long period of training in A the resulting inactive memory decayed when the subject was not in the context of the task with a time constant of 18.5 hrs. Once the memory was re-activated in the test session, it further decayed as a function of time/trial with a loss of between 1-3% per trial (time constant of 200-600 seconds). This sensitivity of the re-activated memory did not change despite the fact that time caused decay in the inactive memory.

2.3.2 A+B training did not alter the memory of A, but produced a competing memory of B

After 384 trials in A, subjects were exposed to 20 trials of B (Experiment 2). The small number of trials in B was sufficient to drop the performance to naïve levels (Figure 2.4a), producing an apparent extinction. Subjects then waited 0 min, 2 min, 10 min, 1 hr, 6 hrs, or 24 hrs. In all but the 0 min group, subjects released the handle. In the 0, 2, and 10 min groups the subjects remained seated in front of the robot. The subjects in other groups left the room and returned at their scheduled time. Upon return, they were asked to hold the handle and reach to the target. The testing was always in error-clamp trials.

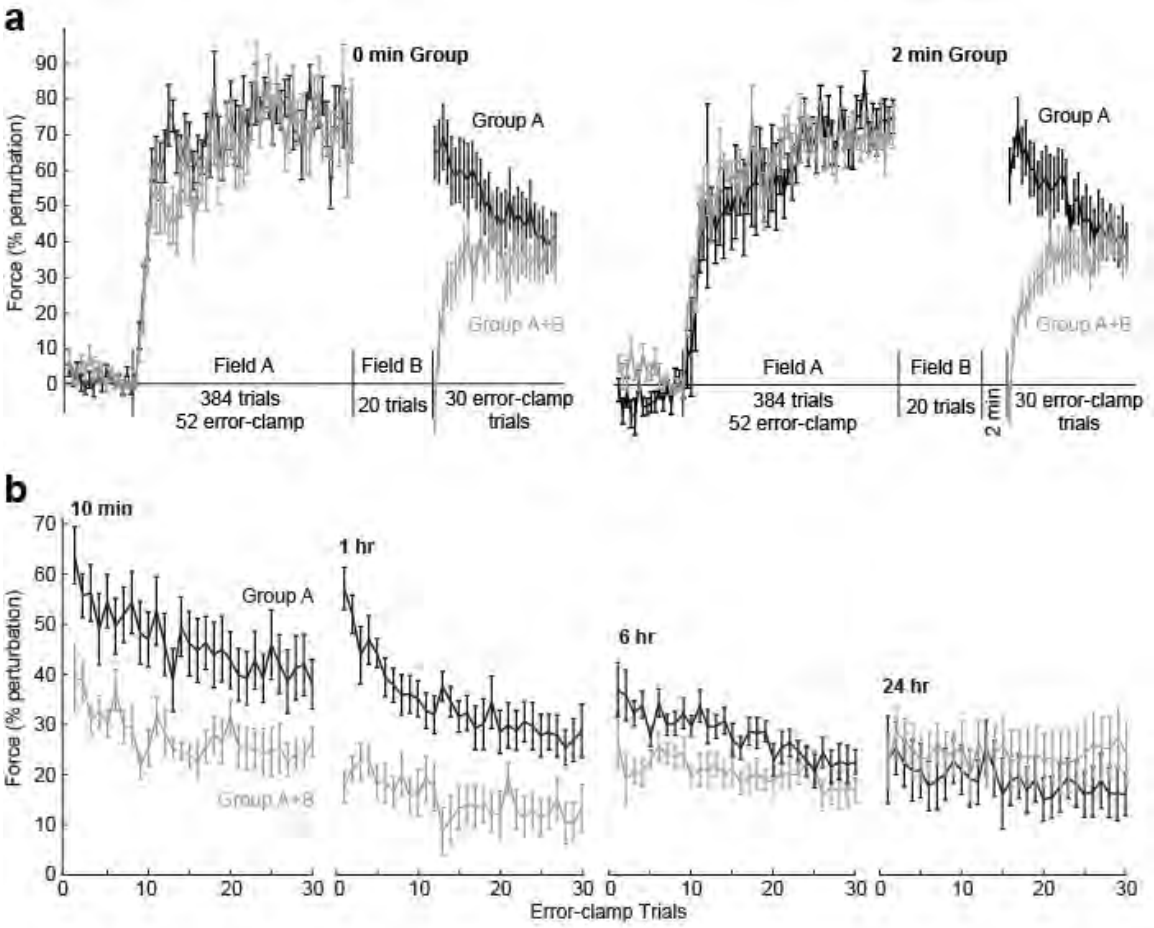

Figure 2.4 The patterns of spontaneous recovery. a. In the A+B group, the 20 B trials were sufficient to bring the motor output to baseline, as assayed at 0 or 2 minutes. Yet, in the subsequent error-clamp trials output spontaneously rose and precisely converged to the output of Group A. b. At 10 minutes after A+B acquisition and for all subsequent time intervals, motor output no longer started at zero and no longer rose during the error-clamp trials. All data points are mean±SEM. Bin size is one trial.

By comparing performance of subjects who learned A with subjects who learned A+B we can answer a fundamental question: does learning of B produce any destructive effects in the memory of A? At 0 or 2 minutes after A+B training, the force output for the first error-clamp trial was at zero (Figure 2.4a). Trial by trial, the force output increased and converged to the output observed in subjects who had only learned A (Figure 2.4a). This rise is a form of spontaneous recovery and has been reported

previously (Smith et al., 2006). However, the crucial new result is that the rise is so strong as to precisely converge to the falling memory of A. A repeated measures ANOVA on the last four trials of the test session for the 0 min A and A+B groups revealed no significant differences ($F(1,16)=0.186$, $p=0.672$). Similarly, there were no significant differences in the last four trials for the 2 min A and A+B groups ($F(1,13)=0.052$, $p=0.824$). If learning of B produced any destructive effects on A, this rise would have fallen short of A. Therefore, the data for the 0 and 2 minute groups suggested that the long-term training in A produced a memory that was essentially unaffected by the brief training in B, despite the fact that this brief training brought performance down to baseline.

A repeated measures ANOVA on the last four trials of the test session revealed no significant differences between the A and A+B groups for the 6 hr ($F(1,18)=0.686$, $p=0.418$) and 24 hr groups, ($F(1,16)=1.074$, $p=0.315$). The A and A+B group were different for the 10 min ($F(1,14)=5.37$, $p=0.036$) and 1 hr ($F(1,18)=5.69$, $p=0.028$) wait periods.

The 20 trials in B produced a memory that competed with A, effectively learning a force that was equal in magnitude but opposite to A. However, at 0 or 2 min post acquisition, the memory of B washed-out to zero within 30 error-clamp trials, whereas the same 30 trials after A did not washout A (Fig. 2.3a). Therefore, whereas A decayed slowly as a function of time/trial, at 0 or 2 min post acquisition B decayed nearly completely within 30 trials. The memory of B was extremely fragile at 0 and 2 minutes after it was acquired.

2.3.3 B starts out as a fast motor memory, but with time becomes slow-like

If at 0 or 2 minutes after acquisition, B starts out with a magnitude equal to A but decays away within 30 trials (these trials took a total of 1.85±0.02min), does passage of time alter the characteristics of this memory? That is, at 10 minutes and beyond, what is the strength of the B memory and what is its sensitivity to trial? We found that as we waited a longer period of time after A+B training, the motor output changed considerably. Whereas at 0 and 2 minutes after A+B training the motor output rose from zero to meet A, at 10 minutes and beyond the force output started out significantly higher than zero (Figure 2.4b): first trial was not significantly different than zero at 0 min (t-test, $p=0.595$), and at 2 min (t-test, $p=0.451$). However, force output was significantly higher than zero for all other test periods (t-test, $p<0.005$). Whereas at 0 and 2 minutes after acquisition, A+B converged onto A, at 10 minutes and 1 hr performances no longer converged: A repeated measures ANOVA on the last four trials of the test session revealed a significant difference between A and A+B groups at 10 minutes ($F(1,14)=5.37$, $p=0.036$) and 1 hr ($F(1,18)=5.69$, $p=0.028$). Therefore, the patterns of 'spontaneous recovery' changed drastically within minutes after A+B training.

The change in the pattern of spontaneous recovery could not have been due to the effects of time on memory of A, as data in Exp. 1 suggested that fragility of A did not change significantly with passage of time. It is likely that the changes were due to effects of time on memory of B. To estimate how the passage of time affected the magnitude and sensitivity of B, we used a bootstrapping procedure to estimate B at each time point and each trial after A+B training. We selected a subject at random from each of the A

and A+B groups and subtracted their force output for each trial, i.e. $\hat{B} = (A+B) - A$ (see Methods 2.2).

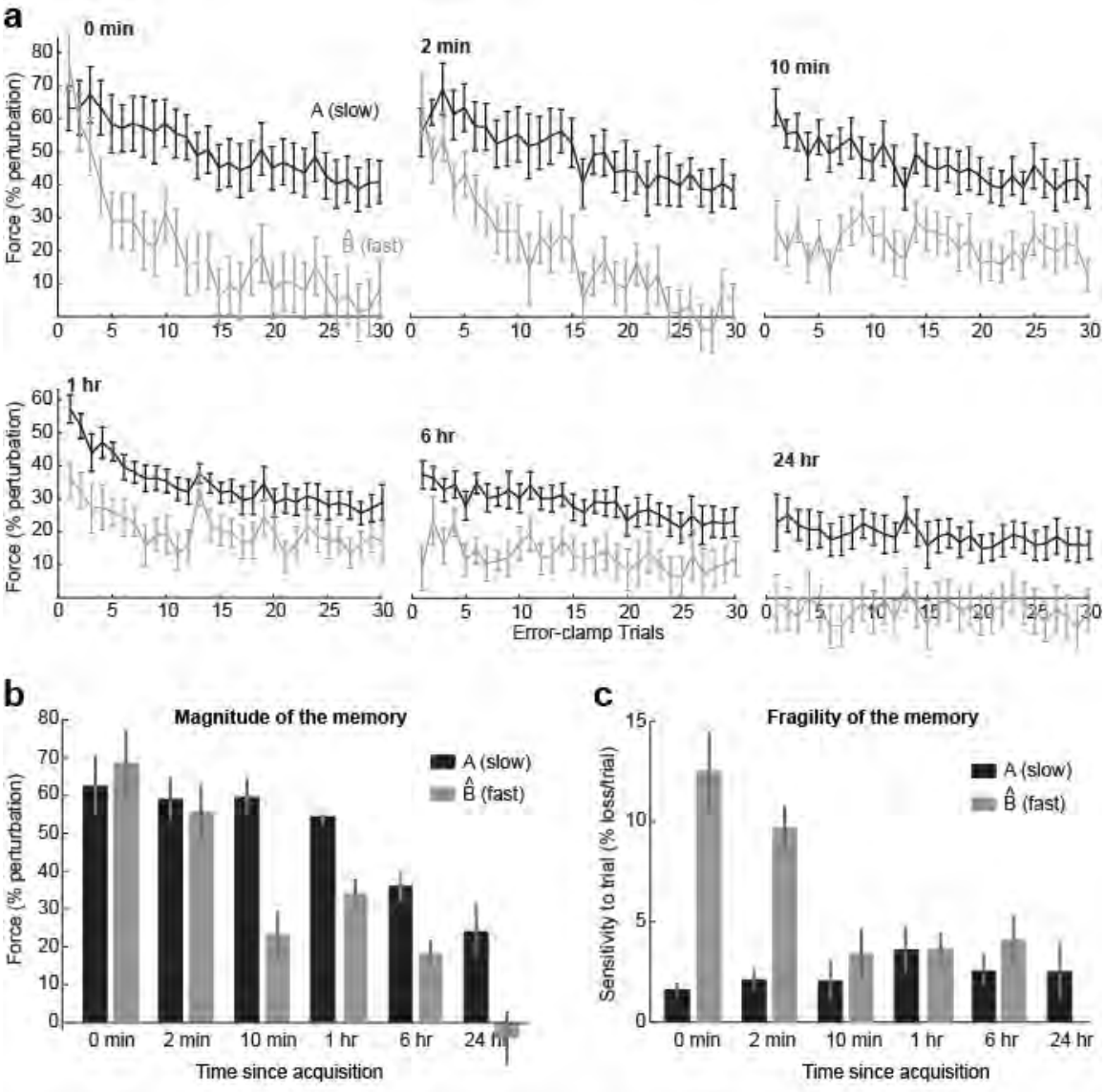

Figure 2.5 The effect of re-activation of memory as a function of time since acquisition. a. Force output as a function of trial after acquisition of A vs. after acquisition of B. To estimate the memory of B, we used a boot-strapping procedure to subtract performance of the A group from the A+B group. The memory of B is a result of only 20 training trials. This memory at 0 and 2 minutes after acquisition is fragile, in the sense that when activated in error-clamp trials it decays rapidly to baseline. However, at 10 minutes and beyond it acquires an increased resistance to trial. By 24 hours, the memory of B is no longer measurable. b. Magnitude of memories of A and B as a function of time since acquisition. Each bar plot represents the initial force output (bin size is two trials) averaged across subjects in each subgroup (error bars are SEM). With passage of time, the memory of A declines gradually, whereas memory of B declines rapidly. c. Fragility of the memory. Force output as a function of trial for each subject was fitted to a single exponential (shown as mean±SEM). Within minutes after acquisition, the memory of B became more resistant to trial.

The results, plotted in Figure 2.5a, illustrate two points. First, when subjects were away from the task (what we termed inactive memory), passage of time caused forgetting. However, the rate of this forgetting was much faster for memory of B than memory of A (Figure 2.5b). For example, the two memories appeared to be equal in magnitude at 0 and 2 minutes, yet B was significantly smaller at 10 minutes, 1 hr, and 6 hrs (0 min: $F(1,57)=0.009$, $p=0.924$, 2 min: $F(1,55)=0.176$, $p=0.676$, 10 min: $F(1,56)=30.692$, $p<0.05$, 1 hr: $F(1,60)=58.244$, $p<0.05$, 6 hrs: $F(1,59)=11.401$, $p<0.05$. Second, when subjects were brought back to the task (what we termed re-activated memory), immediately after acquisition the reactivated memory of B was far more fragile than A, but with passage of time, it gained stability. For example, at 0 and 2 minutes after acquisition, the re-activated memory of B displayed a decay (loss per trial) that was five times the rate of decay of memory of A (Figure 2.5c). However, at 10 minutes, the memory of B had a decay rate that was no different than A. This increased resistance was maintained for as long as the memory of B could be assayed (6 hrs). Therefore, memory of B started out fragile (large loss per trial), but then appeared to be transformed with passage of time to a more stable memory (small loss per trial).

Together, these two observations suggest that at 0 and 2 minutes post acquisition, the re-activated memory of B was fragile, as it decayed rapidly as a function of time/trial. However, if that memory was not activated, it lost much of its content within 10 minutes, but the remaining content gained stability.

2.3.4 A model of motor memory consolidation

We observed that: 1) after long-term training in A, brief exposure to B produced apparent extinction, but at 0 and 2 minutes error clamp trials produced spontaneous

recovery; 2) the rate of decay of an active memory (i.e., reaching with the robot) was two orders of magnitude greater than that of an inactive memory (i.e., simple passage without reaching with the robot); and 3) in the inactive state, over time the initially fast memory of B was partially transformed into a more stable memory. The first observation is a fundamental prediction of a multi-state memory model (Smith et al., 2006;Kording et al., 2007). This model is illustrated by the graphical representation in Figure 2.6a: the learner assumes that the environment has multiple states (here represented by a fast and a slow state), and that his/her observations are a sum of these states. However, to account for the 2nd and 3rd observations, we need to make a distinction between the condition in which the learner can observe the environment (learning from the environment through observations, active memory), and the condition in which the learner is outside the context of the environment (passage of time, inactive memory).

The simplest generative model that best accounted for our data had a state transition matrix in the active state that was diagonal: $A_a = [0.984, 0; 0, 0.855]$, and a non-diagonal transition matrix in the inactive state $A_i = [0.9999, 0.0043; 0, 0.983]$, where $\mathbf{x}^{(t+\Delta)} = A\mathbf{x}^{(t)} + \boldsymbol{\varepsilon}$ and Δ=6sec (typical inter-trial interval in the test period). The non-diagonal transition matrix in the inactive condition is essential to re-produce the result that with passage of time, the initially fast memory of B gains stability. However, the change in the model from the active to inactive condition is a bit unsettling, as it raises the possibility that even in the activated state, the fast memory states may be transformed into slow states. Our experiment had no power to detect this possible transformation during the active state of the memories, and therefore we stayed with the simplest approach and kept the transition matrix in the active state diagonal. However, we noted

the possibility of the transformation of the fast to slow states in the active condition with a dotted arrow in Figure 2.6a.

In Figure 2.6b, the data is re-plotted with the resulting curves from the model (we estimated the goodness of fit of the model to all of the data with an omnibus R^2=0.83, p<0.001). The model provided a reasonable fit to the data at 0 min, 2 min, 10 min, 1 hr and 6 hr groups. However, forgetting rates for the inactive state were smaller than expected for the 24 hr group. This raises the possibility that sleep may play a role in further stabilizing the motor memories, something that would be consistent with some

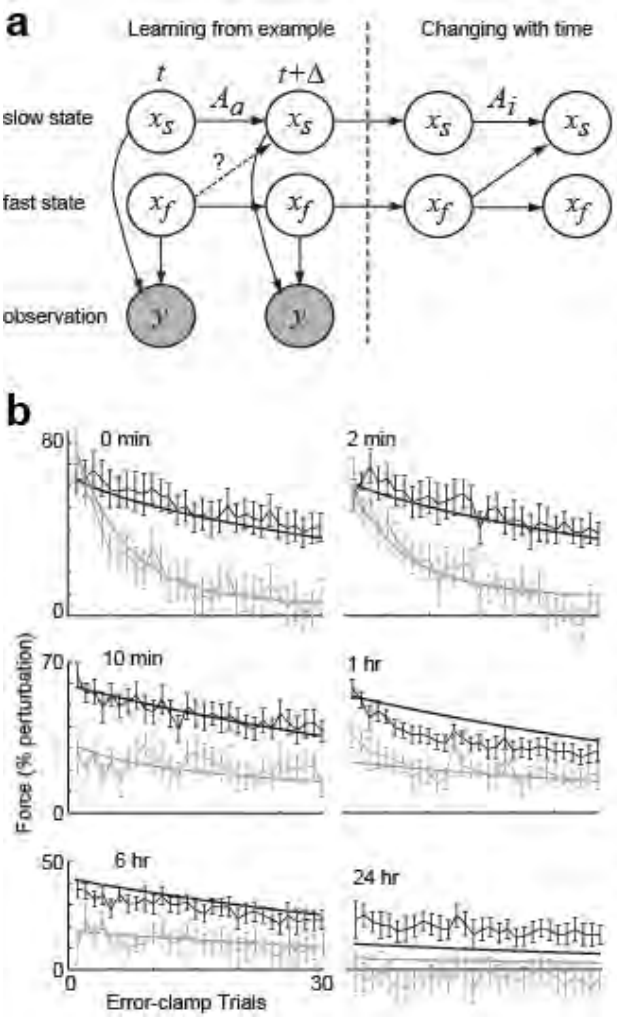

Figure 2.6. Active/inactive multi-state model of motor learning. a. A generative model, describing the learner's hypothesis about the task. As in earlier generative models (Kording et al., 2007), the learner assumes that the environment is composed of states with multiple timescales (two timescales are considered here, labeled fast and slow), and the problem of learning is state estimation. In the active condition (left panel), the learner can sample the environment (i.e., subject is using the tool) and learns from observation. In the inactive condition (right panel), the learner is not in the context of the task and therefore cannot sample the environment. Passage of time affects the two conditions differently, as specified by the state transition matrices and , referring to the active and inactive conditions. We assumed that is diagonal but allows for transformation of a portion of the fast states into the slow states. In total, there were five parameters in this model (components of the two matrices). b. Model's output as compared to the measured data. [0.984, 0; 0, 0.855] and [0.9999, 0.0043; 0, 0.983]

(Huber et al., 2004) but not all previous results in reach adaptation (Donchin et al., 2002).

2.4 DISCUSSION

In this chapter, we trained people to reach with tool A until performance approached an asymptote (~400 trials in a single direction). We then quantified properties of this memory as it was re-activated in error-clamp trials, i.e., trials in which error-dependent learning was minimized. We made three observations. 1) With passage of time (24 hrs), memory of A gradually declined, but when re-activated it remained resistant to trial. This resistance did not change with passage of time. 2) When dynamics of the tool were suddenly changed to B for 20 additional trials, the large performance errors brought the motor output back to baseline, demonstrating an apparent unlearning or extinction. When we assayed performance at 0 or 2 minutes after A+B training, we found that within 30 error-clamp trials (about 3 minutes) the motor output increased from baseline until it converged to that of subjects who had trained in A only. The magnitude of the spontaneous recovery suggested that the large performance errors introduced by B could not have produced any unlearning of A. Rather, it installed a memory that competed with A. This competing memory, termed memory of B, was initially fragile in the sense that when re-activated, it decayed to zero within 30 trials. 3) Within 10 minutes after A+B training, re-activation produced a changed pattern of spontaneous recovery. The nature of these changes suggested that with passage of time, the memory of B gained stability.

To encapsulate these results, we suggested a new model of motor memory (Figure 2.6). Acquisition of a motor memory not only depends on processes that have multiple timescales, as has been proposed before (Smith et al., 2006;Kording et al., 2007), but that

during the inactive state, i.e., when time passes outside the context of the task, the fast states partially transform to slower states.

Our conclusions depend crucially on the assumption that memory of B can be assayed through mathematical subtraction of A from A+B. This assumption was tested at 0 and 2 minutes post A+B training, in which we observed that performance of A+B group rose from zero and converged to A. The convergence is a strong hint that there is super-position of the two memories. The convergence could not occur unless learning of B left memory of A virtually untouched.

If we now hypothesize that performance errors can produce unlearning in only the fast memory and not the slow memory, the resulting theory may explain a large set of apparently conflicting results. We had initially reported that if task A was followed by task B, subjects exhibited naïve performance when re-tested on task A some days later (Shadmehr and Brashers-Krug, 1997). However, inserting a few hours between tasks A and B allowed for recall of A. Caithness et al. (2004) and Mattar and Ostry (2007) performed a similar experiment but observed that despite 24 hours between A and B, there was no recall of A. Overduin et al. (Overduin et al., 2006) reproduced both results and explained that the key difference was the presence of 'catch-trials', i.e., trials in which the dynamics were unexpectedly returned to null, causing occasional large errors, especially near the end of training. The important questions are: why should learning of A with catch trials make it more vulnerable to B at 0 minutes than 6 or 24 hours? Why should removal of catch trials fundamentally alter this time-dependency?

Our theory explains that learning with catch trials produces a memory of A that contains a significant amount of the fast component (because of the large errors that catch

trials produce). Learning of B probably destroys the fast memory at 0 minutes, but with passage of time, the fast memory of A is transformed to slow, becoming less vulnerable to B. This explains results of Brashers-Krug et al. (1996) and Shadmehr and Brashers-Krug (1997), as both studies employed catch trial. However, if learning of A is without catch trials, then extended training in A produces a memory that is slow, making it resistant to B at all times. In that scenario, learning of B always installs a competing memory. No matter when the task is assayed, both memories are present and will compete, explaining results of Caithness et al. (2004), Mattar and Ostry (2007), and Overduin et al. (2006). Indeed, Krakauer et al. (2005) showed that when training is without catch trials, there is robust recall of A if subjects are provided with washout trials before test of recall. As they noted, naive performance is not because A is gone, but because both A and B are present and competing.

Our theory also explains why a relatively small amount of training in A produces a memory that is vulnerable to B at 0 minutes but less vulnerable at 24 hours, yet a longer amount of practice produces a memory that is invulnerable both at 5 minutes and at 24 hours (Krakauer et al., 2005). A small amount of training installs a fast memory, making it vulnerable to B at 5 minutes, whereas longer training installs a slow memory, making it invulnerable to B at all times.

The fundamental prediction of our theory is that once training installs a 'slow' motor memory, it may not be possible to unlearn it through performance errors. Our current understanding of the biology of memory supports this idea. Retention of a motor skill (Bracha et. al 1998, Luft et. al 2004, Luft et. al 2004) requires synthesis of new proteins. If unlearning is the formation of a new memory trace and not erasure of the

original learning, then it should also require de novo protein synthesis for its long term retention. A number of paradigms have examined this question. In inhibitory avoidance training (Vianna et al., 2001), conditioned taste aversion (Berman & Dudai 2001, Burgos-Robles et. al 2007), and classical conditioning of eyelid response (Inda et. al 2005), unlearning is termed extinction. In all cases, retention of the 'extinction' memory (what we termed memory of B here) requires new protein synthesis, suggesting that 'unlearning' is spawning of a new, competing memory, not erasure of the existing memory.

Our finding that memory of B is a fast memory that over time is transformed into a slow, stable memory closely parallels the conclusions of studies that have attempted to disrupt the extinction memory. Berman and Dudai (Berman and Dudai, 2001) found that while injection of anisomycin at ten minutes following extinction training disrupted later recall of the extinction memory, at thirty minutes the drug had no effect on consolidation of the extinction memory. From our point of view, the extinction memory is analogous to the memory of B, which starts as a fast, vulnerable memory. Berman and Dudai (2001) found that within minutes following acquisition, this extinction memory gains resistance. In our data, we see that within 10 minutes after exposure to B, the resistance of memory of B to trial has more than doubled.

Because all of our conclusions are based on measurements in error-clamp trials, it is important to consider how this method of assaying memory differs from traditional approaches in which testing is either via after-effects, or in the same type of trials as the original learning. In error-clamp trials, we can measure both the magnitude of the re-activated memory via motor output, and its resistance to change via the derivative of the

motor output with respect to trials. Whereas in a catch trial we would be assaying an after-effect, in an error-clamp trial we are measuring the after-effect but minimize the error-dependent change that is caused by the after-effect. In the traditional approach, retention is assayed via 'savings' in which trials provide error feedback, resulting in faster re-learning. Therefore, the motor output in error-clamp trials can be viewed as the bias from which the re-learning curve would start in the traditional savings experiment.

Consolidation of motor memory has now been investigated in the reaching paradigm for more than 10 years, with sometimes conflicting results. Our results here provide a way to account for much of that data. Motor memory can exist in two functional states, a fast and a slow state. With passage of time away from the task, some of the fast state may be transformed into a slow state. Furthermore, once a slow motor memory has been established, large performance errors may not be able to change it.

Is the neural circuit for the fast and slow motor memories the same? We recently reported that brief disruption of M1 during adaptation did not affect rates of adaptation, but produced a memory that decayed more rapidly than normal (Hadipour-Niktarash et al., 2007). It is possible that M1 has a particularly important role for the 'slow' human motor memory (Richardson et al., 2006), though the question of whether the neural basis of the fast memory is distinct has yet to be approached.

It appears that a typical long period of training (without catch trials) is sufficient to produce a slow motor memory, and subsequent performance errors do not erase his memory, but install a competing memory. The general implication of our work is that once a motor skill has been well learned, all further learning may be instantiation of

competing memories. This suggests that in biology, the cost of unlearning may be much higher than learning.

CHAPTER 3

SIZE OF ERROR AFFECTS CEREBELLAR CONTRIBUTIONS TO MOTOR LEARNING

3.1 INTRODUCTION

In Chapter 2, we explored the error and time dependent correlates of the fast and slow putative processes. In this chapter, we alter the training environment to encourage formation of fast and slow like memories respectively. Here, we examine the contributions of the cerebellum to the fast and slow process of motor learning by varying the size of prediction errors in a cerebellar degeneration patient study.

Prediction error—the difference between predicted and actual outcome of motor commands—is a driving force of motor learning (Wallman and Fuchs, 1998;Noto and Robinson, 2001;Tseng et al., 2007). Yet, the specific aspects of error, including its size, can fundamentally change how the learning process occurs. For example, in a motor adaptation task one can train a subject with a perturbation that is suddenly introduced in full, versus one that is introduced gradually over many trials. The sudden introduction exposes the learner to many trials with large errors. In contrast, gradual introduction produces learning that is driven by only small errors, often in the absence of subject's awareness. There appear to be three main differences in how people and other animals adapt their motor output in response to large vs. small errors:

1. In young people, the two types of training result in comparable changes in motor commands, and produce motor memories that can be recalled upon revisiting the task (Klassen et al. 2005). Yet, the memories appear to have distinct properties. In prism adaptation and reach adaptation tasks, gradual introduction (i.e. small errors) produces longer-lasting after-effects (Kagerer et al., 1997;Hatada et al., 2006) and better retention (Klassen et al., 2005;Huang and Shadmehr, 2009).

2. In older people and other animals, the ability to adapt to gradual visuomotor perturbations is often better than the ability to adapt to abrupt, large perturbations (Buch et al., 2003;Linkenhoker and Knudsen, 2002).

3. The patterns of generalization following gradual perturbations are distinct from sudden perturbations (Malfait and Ostry, 2004;Michel et al., 2007). For example, when force fields perturb reaching movements (Shadmehr and Mussa-Ivaldi, 1994), sudden perturbations produce internal models that generalize to the un-trained arm (Criscimagna-Hemminger et al., 2003), whereas gradual perturbations have no such generalization properties (Malfait and Ostry, 2004). On the other hand, gradual perturbations can lead to more robust generalization when the trained arm is used in a different context (e.g. reaching in free air after reaching with a robot), whereas this generalization is smaller if the training is in response to a sudden perturbation (Kluzik et al., 2008).

Because generalization may be a reflection of the activation fields of neurons that participate in the encoding of an internal model (Poggio and Bizzi, 2004;Shadmehr, 2004), the distinct generalization patterns suggest that gradual and sudden perturbations do not engage the same neural structures or mechanisms of plasticity. The cerebellum is perhaps the single most important structure for motor learning, as damage to this

structure generally produces severe impairments in the capabilities of humans to adapt in response to a perturbation (Martin et al., 1996;Baizer et al., 1999;Maschke et al., 2004;Smith and Shadmehr, 2005;Morton and Bastian, 2006;Rabe et al., 2009). There is evidence that cerebellum-dependent mechanisms that support formation and retention of motor memories are distinct for small versus large errors. One study in monkeys demonstrated that inactivation of the cerebellar dentate nucleus impaired adaptation to gradual perturbations, yet spared adaptation to sudden perturbations (Robertson and Miall, 1999). In the cerebellar cortex, plasticity related to motor learning is thought to be primarily due to long-term depression (LTD) of parallel fiber-Purkinje cell synapses. In a recent motor learning study in knockout mice, the ability to maintain LTD over time was disrupted (Boyden et al., 2006). The animals could learn a motor skill in response to either large or small errors (as the formation of LTD was not disrupted), but could maintain the skill only if it was acquired via small errors. That is, disruption of LTD maintenance in the cerebellar cortex affected retention of memories acquired via large magnitude errors, but not small errors.

Here, we asked whether cerebellar dependent adaptation in humans depends on the size of the error. Previous work had shown that damage to the human cerebellum produced profound deficits in reach adaptation to force fields (Smith and Shadmehr, 2005;Maschke et al., 2004;Rabe et al., 2009). However, to our knowledge all previous adaptation experiments in cerebellar patients have utilized an abrupt perturbation (i.e. large errors). We considered a within subject design to quantify the cerebellum's contributions to learning from large vs. small errors.

3.2 METHODS

3.2.1 Cerebellar Degeneration Patients

Thirteen individuals with cerebellar ataxia and thirteen neurologically healthy age-matched controls participated in this study (Table 3.1). Seven of our patients were diagnosed with spinocerebellar ataxia type 6 (SCA6), one patient had both SCA6 and SCA8, one had SCA 8, and one had SCA14. These are autosomal dominant diseases where clinical symptoms of ataxia tend to manifest in mid adulthood. SCA6 is usually a pure cerebellar syndrome. SCA8 also tends to be a pure cerebellar, disease, though in the minority of cases can include sensory neuropathy and spasticity. Likewise, SCA14 is often only a cerebellar disease, with a minority of cases showing myoclonus and some cognitive changes. All of our patients showed purely cerebellar signs in the arms on clinical examination, as described below. Other patients had either sporadic ataxia or autosomal dominant cerebellar ataxia type III (i.e. pure cerebellar syndrome with unknown genetics).

Table 3.1: Characteristics of cerebellar degeneration patients

Identifier	Gender	Age	Handedness	Diagnosis	ICARS
1	M	54	R	SCA6 and SCA8	63
2	F	72	R	SCA6	58
3	F	67	R	ADCA III	55
4	M	75	L	SCA6	54
5	F	54	R	Sporadic	52
6	F	40	R	SCA6	50
7	M	61	R	SCA14	47
8	M	37	L	SCA8	46
9	F	53	R	SCA6	35
10	F	56	R	SCA6	33
11	F	67	R	Sporadic	27
12	F	57	R	Sporadic	24
13	F	67	R	SCA6	5

SCA=spinocerebellar ataxia; ADCA= autosomal dominant ataxia

The severity of ataxia was rated using the International Cooperative Rating Scale (Trouillas et al., 1997). For the purpose of data analysis, cerebellar degeneration patients were divided into two groups, mild (ataxia score<40, n=5) and severe (ataxia score ≥40, n=8). This division was somewhat arbitrary, but based on the natural separation of the ataxia scores in our sample. Clinical examination showed no evidence of hypertonia, sensory loss (proprioception and fine touch via monofilament), or extrapyramidal features in the arms of these individuals. Experimental procedures were approved by the Johns Hopkins University School of Medicine Institutional Review Board and all subjects signed a consent form.

3.2.2 Behavioral Training

Subjects performed arm movements while holding the handle of a robotic device. They were asked to reach toward a target but did not have to stop at the target. Rather, a virtual 'pillow' was placed behind the target and they were asked to punch it. In this way, the subject was a boxer who was given a target by a trainer. The trainer held a soft glove in hand (simulated by the virtual pillow). The task for the subject was to accurately punch the soft glove of the trainer.

A crucial feature of our task was that we did not require the subject to stop their reach at the target. This was done for a few reasons: First, our task design reduced the effect of cerebellar intention tremor, which can be marked at the end of a reaching movement at a time when the individual is attempting to stop their hand near a target. Individuals attempt to compensate by making slower movements (Bastian et al. 1996), making it difficult to perturb their reach with forces that are speed dependent. Second, movements without the virtual pillow take cerebellar patients longer than normal to

complete. This added effort could contribute to a mental fatigue, making it difficult to study patients in protocols that involve many hundreds of trials. Finally, an earlier experiment demonstrated that in our punching task, cerebellar patients produced movements that were nearly as fast as healthy controls (Tseng et al., 2007).

Subjects held the handle of a two-joint robotic manipulandum with their dominant hand and made ballistic 'punching' movements from a center starting position through a 5x5mm target. The hand was covered by a horizontal screen, onto which a small cursor (5x5 mm) representing hand position was projected at all times. The target was presented at 10 cm from the center at either 121.5^o (toward the right shoulder, 0^o is at 12 o'clock) or 301.5^o (random with equal probability). The target position was reflected in the sagittal axis for left handed subjects (58.5^o and 238.5^o). Once through the target, the hand hit a robot-generated virtual pillow. The robot then brought the hand back to the center start position. If the movement duration was 150-400 ms, subjects were rewarded with an 'explosion'. The size of the explosion and the number of points assigned were dependent on the end point accuracy of the movement, which was displayed as a yellow dot at the point where the hand crossed the 10 cm radius. Color feedback indicated whether the movement speed was too slow or too fast. We recorded force at the handle, as well as the position and velocity of the hand at a rate of 100Hz.

Experimental protocol. The experiment (Figure 3.1) began with training in a null field (no forces, 170 trials), followed by an adaptation phase (240 trials) in which subjects trained in a curl field in which forces were perpendicular to hand velocity $\mathbf{f} = A\dot{\mathbf{x}}$. The force field was either a counter-clockwise curl $A = \{0, -11; 11, 0\}$ N·s/m or a clockwise curl field $B = \{0, 11; -11, 0\}$ N·s/m. Following the adaptation trials, we

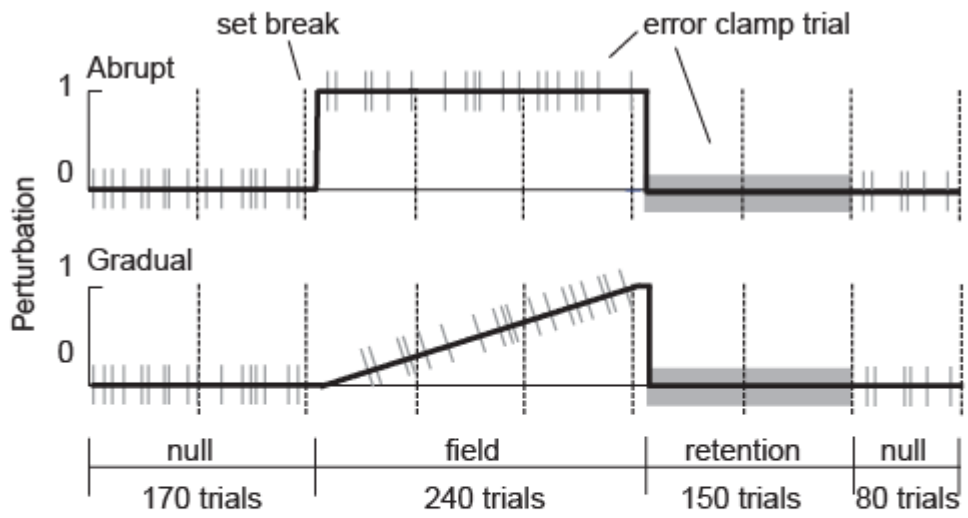

Figure 3.1 Study protocol and performance during adaptation. Subjects participated in two experiments: Abrupt and gradual introduction of a force field. They held the handle of a light-weight robotic arm and made shooting movements to a target. In the first 170 trials the robot produced a null field (no forces). In the subsequent 240 trials, a curl force field was introduced (field A or field B), perturbing the hand perpendicular to its direction of motion. The gray bars schematically represent 'error-clamp' trials during which the robot produced a stiff channel that allowed us to measure the subject's motor output perpendicular to the direction of motion. Vertical dashed lines indicate brief set breaks.

measured the rate of decay of the memory via a long sequence of error-clamp trials (150 trials). The session ended with a washout phase in which a null field was re-introduced (80 trials). We placed error-clamp trials randomly in the baseline, adaptation, and washout blocks ($1/5^{th}$ probability). During the error-clamp trials, the motion of the hand was constrained to a straight line to the target by a stiff one-dimensional spring (spring coefficient = 2500 N/m; damping coefficient = 25 N·s/m) that counteracted forces perpendicular to the target direction. Error-clamp trials, however, were no different than regular trials in the type of feedback that the subject received: they were rewarded with an 'explosion' for completing the movement within the specified time window. Because

the field perturbed the hand perpendicular to the direction of motion, the forces that the hand produced against the 'channel' wall in error-clamp trials served as a proxy for the change in the motor output.

The two experimental sessions. The subjects were tested on two sessions, separated by an average of 17 days [range of 1.05 hrs – 105 days, as patient visit schedule permitted]. Ten of the 13 patients were tested within 24 hours. The two sessions for the healthy controls were separated by a maximum of 96 hours, median of 24 hours [range of 1.1-96 hrs]. On one of these sessions they were tested on an abrupt version of the perturbation (Figure 3.1), and on the other session they were tested on a gradual version. In the abrupt protocol, the field was presented on trial one and remained at full strength for 240 trials. In the gradual protocol, the field was linearly increased during the first 232 adaptation trials. The last 8 trials of the adaptation phase (6 fielded, 2 error-clamp) were performed at full field strength. Three severe patients performed an additional 20 trials at the end of adaptation at full field strength. The order of the two sessions was counterbalanced.

3.2.3 Data Analysis

In field trials, our performance measure was the endpoint error (distance between center of target and hand position as it crossed the 10cm boundary of the trial). In error-clamp trials, our performance measure was the forces that subjects produced against the channel wall. The average force profile in the null block of error clamp trials for each target served as a baseline. We subtracted this baseline from the force that we recorded in the adaptation and retention block of error clamp trials. We represented the result as a percent of perturbation, i.e., the ratio between the actual force produced and the ideal

force, where the idea force is the velocity dependent force that should be produced to counteract the field.

The post-adaptation retention period was composed entirely of a sequence of error-clamp trials for which we examined the rate of decay of the force output. The decay was estimated by calculating the percent loss in the force output during the 150 error clamp trials. The difference in the average force during the first six and last six error clamp trials was calculated for each subject.

3.3 RESULTS

We compared performance of individuals with cerebellar damage in two protocols (Figure 3.1): one in which the perturbation was introduced abruptly (resulting in larger errors), vs. one in which the perturbation was introduced gradually (resulting in generally small errors).

3.3.1 Severe cerebellar patients learned better in the gradual protocol

Representative trajectories from the end of null, and the beginning and end of the adaptation periods are plotted in Figure 3.2 for individual subjects from the control, mild, and severe groups. By the end of the adaptation period (trials 233-240), during which the magnitude of the force field was equal in the abrupt and gradual protocols, the subject in the control group performed equally well in the abrupt and gradual protocols (endpoint errors, two-tailed t-test, $p>0.30$). Similarly, the mildly affected cerebellar patient performed equally well in the two protocols (two-tailed t-test, $p>0.30$). However, the

severely affected cerebellar patient had smaller endpoint errors at the end of the gradual protocol than the end of the abrupt protocol (two-tailed t-test, $p<0.05$).

Across our sample population, there was indeed a tendency for the severely affected patients to benefit from the gradual training protocol. A repeated measures ANOVA on the adaptation trials (192 field trials, bin size = 16) revealed a main effect of group ($F(2,48)=8.857$, $p=0.001$), a main effect of condition ($F(1,48)=89.625$, $p<0.001$) and a main effect of trial ($F(1,11)=16.855$, $p<0.001$). There was also a group by trial interaction ($F(2,22)=1.689$, $p=0.026$) and a condition by trial interaction ($F(1,11)=10.189$, $p<0.001$).

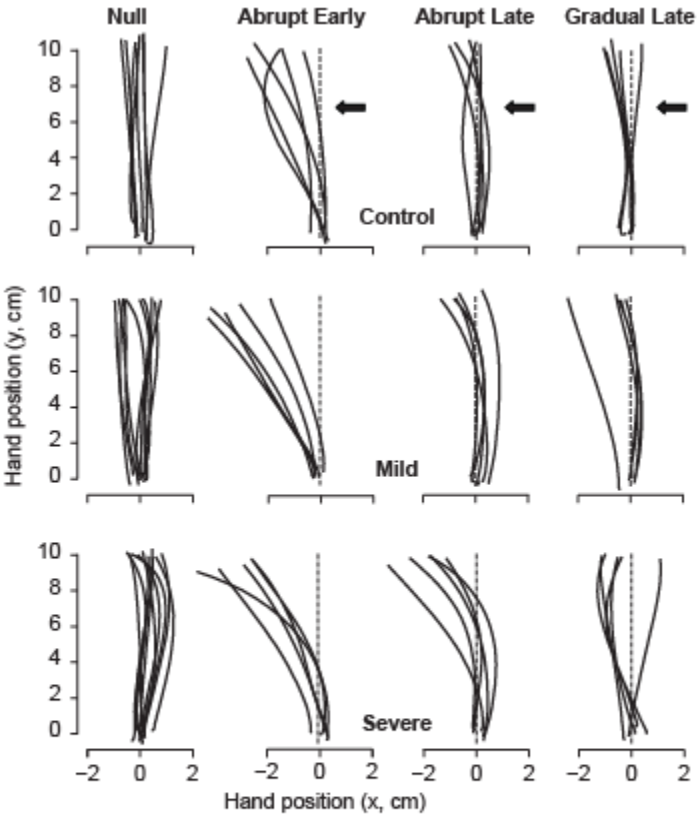

Figure 3.2 Representative trajectories from the end of the null, and the beginning and end of the adaptation periods for an individual subject from the control, mild (#9) and severe (#6) groups.

In the abrupt protocol, patients from the severe group were clearly impaired in adapting to the field (Figure 3.3a). A repeated measures ANOVA on the abrupt adaptation trials confirmed a main effect of group ($F(2,23)=33.627$, $p<0.001$), a main effect of trial ($F(1,11)=18.584$, $p<0.001$), but no group by trial interaction ($F(2,22)=1.166$, $p>0.28$). Post hoc analysis (Tukey's test) indicated a significant difference between the severe and control groups ($p<0.001$) and the severe and mild groups ($p<0.001$), whereas the mild and control groups performed comparably ($p>0.30$). That is, adaptation was significantly impaired in the severe group in the abrupt condition. In contrast, when the same force field was introduced gradually (Figure 3.3b), a repeated measures ANOVA revealed no main effect of group($F(2,23)=2.330$, $p=0.120$), but a main effect of trial ($F(1,11)=19.075$, $p<0.001$), and a group by trial interaction ($F(2,22)=2.907$, $p<0.001$). Post hoc analysis (Tukey's test) showed no significant differences between the severe and control groups ($p>0.12$), the severe and mild groups ($p>0.30$) or the mild and control groups ($p>0.30$). Therefore, between group comparisons suggested that whereas the individuals in the severe group were impaired in the abrupt protocol, they were not different from the mild and control groups in the gradual protocol.

To further test whether the cerebellar patients adapted better to the sequence of small errors, we compared their performance as measured by endpoint error during the trials in which the force field was at full strength in the abrupt and gradual protocols (average of adaptation trials 233-240). A two-way ANOVA revealed a main effect of group ($F(2,23)=22.484$, $p<0.001$), and a group by condition interaction ($F(2,23)=6.172$, $p=0.007$), but no main effect of condition ($F(2,23)=1.254$, $p>0.25$). A post hoc Tukey's

test revealed that the severe patients performed worse than both the mild patients (p<0.01) and the control groups (p<0.001). The mild group performed comparably to the control group (p>0.25). More specifically, in the abrupt condition the severe patients were impaired as compared to the control subjects (p<0.001) and mild patients (p=0.001), while the controls subjects and mild patients performed comparably (p>0.69). A within-subject planned comparison confirmed that the patients in the severe group had

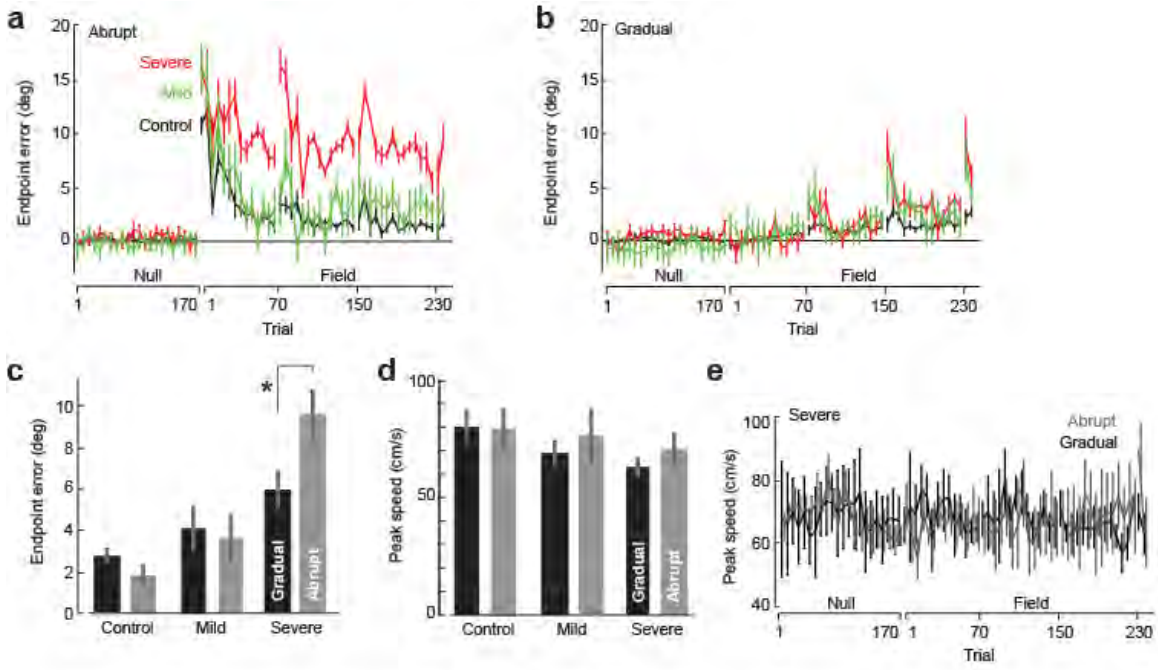

Figure 3.3 Performance during the adaptation block. a&b. Angular error at the end of the movement (mean+SEM) for each sub-group during abrupt and gradual training. Bin size is 2 trials for the trials immediately following set break and 6 trials for the remainder of the block. c. Average angular error at the end of the movement (mean+SEM) during the last six field trials when the force field was at full strength in both the abrupt and gradual conditions. Control and mild patients perform comparably in the two conditions. Severe patients showed an improvement in performance in the gradual versus the abrupt condition. d. Average peak speed (mean+SEM) during the last six trials when the field was at full strength in both the abrupt and gradual conditions. e. Average peak speed (mean+SEM) for the severe patients during abrupt and gradual training. Bin size is 2 trials for the trials immediately following set break and 6 trials for the remainder of the block.

significantly larger angular errors at the end of adaptation in the abrupt protocol as compared to the gradual protocol (two-tailed t-test, $p<0.05$, Figure 3.3c). However, the subjects in the control group performed equally well in these two conditions (two-tailed t-test, $p>0.15$ Figure 3.3c). Similarly, the performance of the patients in the mild group did not differ in the two training protocols (two-tailed t-test, $p>0.30$, Figure 3.3c).

Because the perturbations were velocity dependent, it was important to determine whether movement speeds were comparable during the two protocols. Figure 3.3d displays the average peak speed in trials at the end of the adaptation block, and Figure 3.3e displays the peak movement speeds for the null and adaptation blocks. For the data shown in Figure 3.3d, a two-way ANOVA found no effect of condition, no effect of group and no interaction (all $p>0.20$). For the data shown in Figure 3.3e, repeated measures ANOVA during adaptation trials (bin size = 16) in the abrupt and gradual conditions for severe patients revealed no main effect of condition ($F(1,14)=0.792$, $p>0.38$), no main effect of trial ($F(1,14)=1.108$, $p>0.35$) and no interaction ($F(1,14)=1.333$, $p>0.21$). Despite these similar movement speeds, performance of the severely affected patients was significantly improved in the gradual protocol (Figure 3.3c).

In the original protocol, there were only eight full strength trials in the gradual condition. To test the robustness of our results, three of the patients in the severe group (#4, #5, and #6) were tested in a modified protocol in which we added 20 extra trials (16 field and 4 channel) to the adaptation block. In this way, for these three severely affected patients the fields in the abrupt and gradual protocols were of equal strength for 28 trials. A within-subject planned comparison once again indicated that the individuals in the

severe group benefited from the gradual protocol: endpoint errors were significantly smaller in the gradual protocol (abrupt: 0.154±0.02 rad, gradual: 0.059±0.03, mean±SEM, two-tailed t-test, $p<0.05$). In summary, movement trajectories indicated that with severe cerebellar degeneration, there was a greater impairment in adapting to large errors vs. small errors.

3.3.2 The gradual protocol enhanced predictive adaptive control in severe patients

In principle, the improved performance in response to a force perturbation during reaching can be attributed to two mechanisms: one may get better at reacting to a perturbation as the movement unfolds (e.g., increased stiffness), or one may get better at predicting that perturbation and producing motor commands that compensate for it. One way to dissociate these two possibilities is via the forces that the subjects produced in error-clamp trials. During an error-clamp trial there are no perturbations. Rather, a 'channel' constrains the movement to a straight line to the target, eliminating the need to correct for an error. Thus, we can view the forces that the subjects produced against the channel walls as a proxy for the forces that they expected from the external perturbation.

The force profiles for the last two error-clamp trials of training are plotted in Figure 3.4a. The time at which the movement crossed the target is shown in the top subplot of Figure 3.4b. A two-way ANOVA on the average peak force during these error-clamp trials showed a main effect of group $F(2,23)=11.141$, $p<0.001$, and group by condition interaction $F(2,23)=3.566$, $p=0.045$ (Figure 3.4b bottom subplot). Indeed, the maximum force produced by the severe patients was smaller than controls in the gradual (one-way ANOVA, $F(2,23)=5.586$, $p<0.05$; post hoc Tukey's test, severe v. control

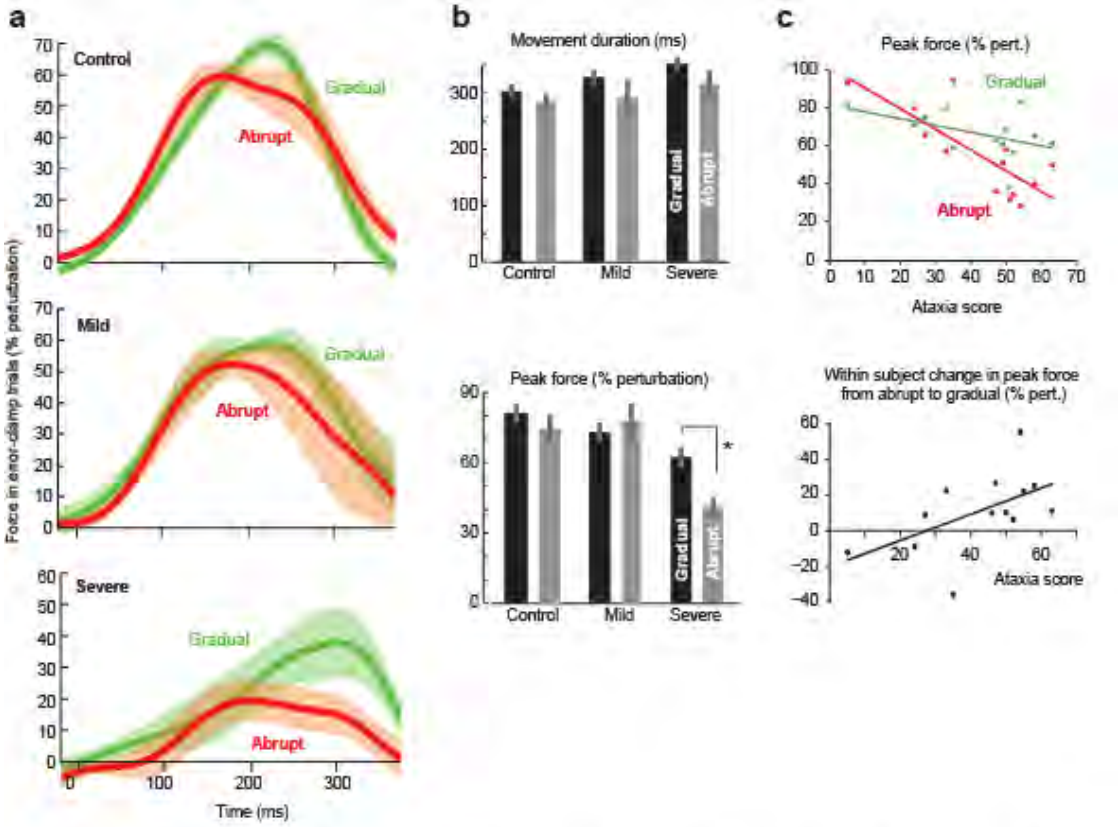

Figure 3.4 Motor output in error-clamp trials at end of adaptation. a. Force output, represented as percent of perturbation (which normalizes for movement speed), during the last two error-clamp trials of the adaptation phase for the control, mild and severe groups. b. Average movement duration and peak force (% perturbation) during the last two error-clamp trials of training. c. Peak force (% perturbation) during the last two-error-clamp trials of the adaptation phase plotted as a function of ataxia score for mild and severe patients, (top: abrupt and gradual, bottom: within subject difference between abrupt and gradual). In the abrupt condition, severity of the disease predicts performance in the error-clamp trials.

$p<0.01$, severe v. mild $p>0.25$, mild v. control $p>0.30$) and smaller than controls and mild patients in the abrupt protocols (one-way ANOVA, $F(2,23)=10.286$, $p=0.001$; post hoc Tukey's test, severe v. control $p=0.001$, severe v. mild $p=0.004$, mild v. control $p=0.935$). Importantly, for the severe patients a within-subject comparison of the peak forces showed a significant improvement in performance in the gradual versus the abrupt protocols ($p=0.007$), but no difference for mild patients ($p>0.30$) or controls ($p>0.15$).

Therefore, the severe cerebellar patients were better able to predict the force perturbation after training in the gradual protocol vs. the abrupt protocol.

The average peak force during the last two error-clamp trials of the adaptation phase is plotted for the mild and severe patients in both the abrupt and gradual conditions (Figure 3.4c top). In the abrupt the condition, patients with greater severity produced less force (R^2=0.64, p=0.001). However, in the gradual condition severity of ataxia was not a clear predictor of performance (R^2=0.24, p=0.09). The within subject difference in the abrupt and gradual conditions is plotted in Figure 3.4c bottom). The data suggests that patients with increased severity tended to benefit the most from the gradual presentation of the perturbation (R^2=0.30, p=0.05).

3.3.3 In the severely affected patients, the gradual protocol produced motor memories that resisted change

The adaptation block was followed by a long series of error-clamp trials in which we assayed the rate of decay of the adapted response. The maximum force during the post-adaptation retention block is shown for the control, mild, and severe groups in Figure 3.5. We calculated the percent loss as the difference between the average force during the first six and last six error clamp trials for each subject (Figure 3.5d). A two-way ANOVA showed a main effect of group ($F(2,23)=7.444$, $p=0.003$) and no group by condition interaction ($F(2,23)=0.658$, $p>0.50$) or main effect of condition ($F(2,23)=1.450$, $p>0.24$). This main effect of group appeared to have been driven by the decreased rate of decay in the severely affected patients in the gradual condition (one-way ANOVA, $F(2,23)=7.228$, $p=0.004$). A post hoc Tukey's test confirmed that the gradual training in the severely affected patients produced a motor output that decayed more slowly than

those observed in the control (p=0.005) and mildly affected (p<0.02), while the mild and control groups decayed at comparable rates (p>0.97). This same result was arrived at when we quantified the decay by fitting an exponential to the individual data. In the gradual condition, the severe patients had slower decay rates in their motor output than the mild and control groups.

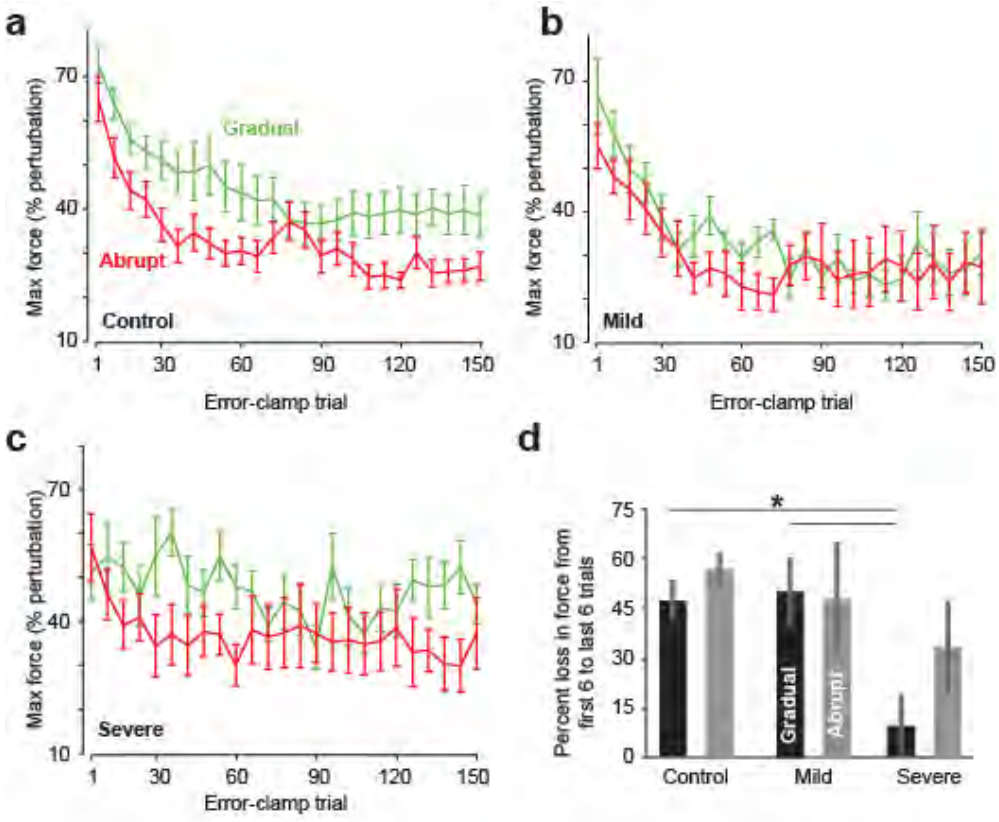

Figure 3.5 Motor output in post-adaptation error-clamp block. a, b & c. Maximum force output during the error-clamp trials in the post-adaptation retention block (mean+SEM) for the control (a), mild (b), and severe (c) groups. Bin size is six trials. d. Fragility of the memory. The change in force output from the beginning to the end of the post-adaptation block, expressed as percent reduction from the first 6 trials to the last 6 trials. The changes are shown as mean+SEM. In the gradual condition, the severe patients had less percent loss of motor output than control and mild patients.

After completion of the retention block, all subjects were provided with a brief break, and then they returned to the reaching task (Figure 3.1). However, now the robot motors no longer produced a force perturbation (i.e., null field). This allowed us to ask two questions: first, would the severe cerebellar patients show after-effects of the prior training? And second, would these after-effects washout more slowly than in healthy controls?

To test whether the cerebellar patients had aftereffects of prior training, we examined the endpoint error in each movement during the final null block (Figure 3.6, a

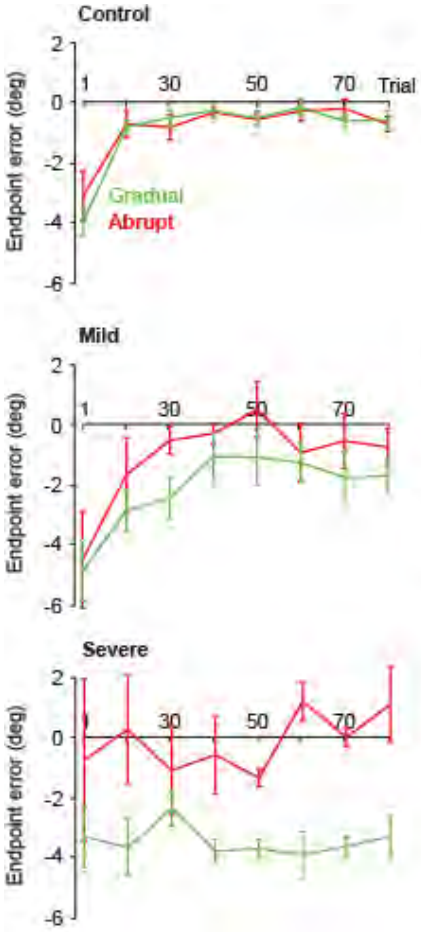

Figure 3.6 Aftereffects during the final null block of trials. Angular error at the end of the movement (mean+SEM) during the null washout trials for the control, mild, and severe groups. Bin size is eight trials. The control and mild groups demonstrate aftereffects in both the abrupt and gradual conditions. The severe group only shows significant aftereffects in the gradual condition. (The total number of trials does not add up to 80 because there were also error-clamp trials in this data set, which are not shown.)

negative value indicates an after-effect). Aftereffects were seen in the control group, as demonstrated by the negative average endpoint error (significantly different from zero, two-tailed t-test, abrupt, $p<0.004$, gradual, $p<0.001$). While the average endpoint error was negative for the mild and severe groups, the large variability in the abrupt condition resulted in aftereffects that were significantly different than zero only in the gradual condition (two-tailed t-test, mild: abrupt $p>0.17$, gradual $p<0.01$, severe: abrupt $p>0.65$, gradual $p<0.015$). Furthermore, we observed that the after-effects of the severe group following the gradual condition showed little or no evidence of washout in the 80 null trials. Thus, the motor memory formed by the severely affected patients not only decayed more slowly than normal in the error-clamp block of trials, it produced after-effects that washed out more slowly in the null block of trials.

3.3.4 A missing component of adaptation in the cerebellar patients

Elsewhere we reported that during adaptation to a velocity dependent force field, the optimal trajectory to the target is not a straight line, but a trajectory that overcompensates early into the movement (when the forces are weak), allowing the robot to bring the hand back toward the target when velocities are higher and the field is strong (Izawa et al., 2008). Such a trajectory would bring the hand to the target with minimum effort (sum of forces exerted). Here, we found that while this ability to optimize the adaptive response was present in the control subjects, it was clearly missing in the severely affected patients in both the abrupt and gradual conditions.

The overcompensation pattern is demonstrated by a perpendicular displacement that becomes negative early into the movement (Izawa et al. 2008). To quantify this

pattern, we measured the perpendicular displacement at 100ms (Figure 3.7). In the abrupt protocol, patients from the severe group did not show a pattern of overcompensation. A repeated measures ANOVA on the 240 abrupt adaptation trials (192 field trials, bin size =16) showed a main effect of group ($F(2,23)=9.774$, $p=0.001$).

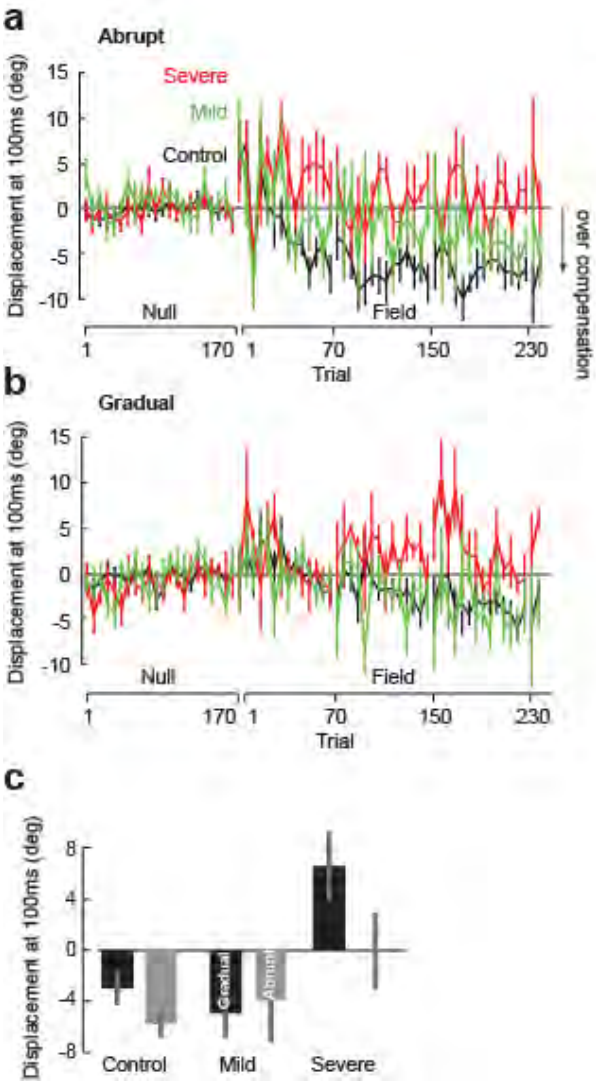

Figure 3.7. a&b. Angular error at 100 ms (mean+SEM) for each sub-group during abrupt and gradual training. Bin size is 2 trials immediately following set break and 6 trials for the remainder of the block. c. Average angular error at 100 ms (mean+SEM) during the last six trials when the field was at full strength in both the abrupt and gradual conditions. Controls showed overcompensation in both conditions. The severe patients did not show significant overcompensation in either condition.

A post hoc Tukey's test indicated a significant difference between the severe and control groups (p=0.001), whereas the severe and mild groups (p=0.157) and the mild and control groups performed comparably (p>0.20). Likewise, when the same force field was introduced gradually, there was a main effect of group (repeated measures ANOVA, $F(2,23)=6.761$, p=0.005). A post hoc Tukey's test showed that the severe group showed less overcompensation than the mild (p<0.05) and control (p<0.01) groups, but there were no significant differences between the mild and control groups (p>0.30). Thus, while the performance of the severe patients was better in the gradual protocol, they were unable to learn the optimal adaptive response in both the abrupt and gradual conditions.

To test whether the cerebellar patients learned optimally when the sequence of errors was small, we examined whether the average perpendicular displacement was negative (i.e. subjects overcompensated) during trials in which the magnitude of the force field was at full strength in both protocols (Figure 3.7c). Overcompensation was seen in the control group, as demonstrated by the negative average perpendicular displacement (significantly different from zero, two-tailed t-test, abrupt, p<0.001, gradual, p<0.05). While the average overcompensation was negative for the mild group, the large variability resulted in overcompensation that was not significantly negative (two-tailed t-test, gradual p=0.066, abrupt p>0.30). The severe patients not only failed to overcompensate in the abrupt condition (p>0.5), they had a positive perpendicular displacement at 100 ms in the gradual condition (p<0.05). We also compared the performance of the groups with each other at the end of adaptation. A two-way ANOVA revealed a main effect of group ($F(2,23)=9.887$, p=0.001), but no main effect of condition ($F(2,23)=2.235$, p=0.149) or group by condition interaction ($F(2,23)=1.187$,

p>0.30). Post hoc analysis (Tukey's test) showed that the severe patients did not overcompensate comparably to the mild (p=0.008) or control (p=0.001) groups, but the mild patients did overcompensate comparably to the control group (p>0.5). The ability to find the optimal trajectory (i.e., over-compensate) was clearly absent in the severe group in both the abrupt and gradual conditions.

3.4 DISCUSSION

Damage to the cerebellum generally produces profound impairments in the ability of the brain to learn from movement errors. Results from previous experiments are unequivocal: cerebellar patients are impaired in their ability to alter their motor output to compensate for a predictable perturbation (Martin et al., 1996;Smith and Shadmehr, 2005;Lang and Bastian, 1999;Nowak et al., 2007). Our results change this perspective by demonstrating that motor learning impairment is not a general phenotype of cerebellar damage. Rather, cerebellar degeneration has a significant effect on the ability to learn from large errors but has a lesser effect on the ability to learn from small errors. Therefore, the neural bases of learning from large and small errors are likely distinct.

The patients that we studied suffered from cerebellar atrophy. We divided our population into a mild and a severe group based on their ataxia score and then tested them in a reaching task in which a force field pushed the hand perpendicular to the direction of motion. Previous work had demonstrated that the greater the severity of the cerebellar disease, the greater the learning impairment in response to an abrupt perturbation (Maschke et al., 2004). Indeed, we found that there was a trend of increasing endpoint error corresponding to degree of impairment (Figure 3.3c).

Our volunteers were tested under two conditions: abrupt introduction of the perturbation in a single trial, and gradual introduction over many trials. When the two perturbations were of equal strength, the severely affected patients had smaller endpoint errors in the gradual vs. the abrupt protocol. This improved performance may have been due to learning of an internal model that better predicted the perturbing forces, as evidenced by the greater forces that the patients produced in the gradual protocol.

After the adaptation period, the stability of the acquired memory was tested in a long-sequence of error-clamp trials, i.e., trials in which movement errors were eliminated. This assayed the sensitivity of the acquired memory to passage of time and/or trial. Following gradual training, the acquired motor memory decayed more slowly in the severe group than in the control and mild groups. When the force field was unexpectedly removed, in the severe group the resulting after-effects persisted for nearly 80 trials, whereas the after-effects washed out within 10 trials in healthy controls. Thus, the severely affected patients not only learned better from small errors, this learning produced a motor memory that was more resistant to change as compared to healthy controls.

The observation that the adaptation in the severe patients appeared to produce a motor memory that had a slower rate of decay than controls is consistent with observations in another adaptation experiment. Earlier, we examined the ability of cerebellar degeneration patients to adapt the gain of their saccadic eye movements (Xu-Wilson et al., 2009). We found that while the patients (8 of whom were also in the current study) were impaired in their ability to adapt their saccades, the learning that did take place produced motor memories that exhibited little forgetting as a function of time.

If we assume that there are fast and slow adaptive processes that support motor memory in healthy people (Smith et al., 2006), the ability to learn better from the gradual protocol and the resulting slower decay of motor output suggest that cerebellar degeneration has a particularly significant impact on the fast process.

One way to explain these results is to hypothesize that learning from large and small errors normally requires the integrity of the cerebellum, but there are other brain structures that contribute to motor learning and these structures are primarily engaged in response to small errors. For example, Boyden et al. (2006) reduced the capacity of Purkinje cells to maintain LTD and found that this affected retention of a VOR motor skill, but only if the adaptation was due to a perturbation that introduced large errors (high frequency rotation). It is possible that our patients were less impaired in the gradual condition because they could utilize generally spared neural structures outside the cerebellum to learn from small errors.

The trouble with this line of thinking is that it implies that the cerebellum is specialized for learning from large errors, something that is inconsistent with at least one neurophysiological experiment. Soetedjo et al. (2008) recently quantified encoding of movement errors in a saccade adaptation protocol. They noted that while there were Purkinje cells in the oculomotor vermis that were sensitive to only small errors (i.e., complex spikes occurred with high probability for small errors but low probability for large errors), the Purkinje cells that were sensitive to large errors were often equally sensitive to small errors. That is, in the healthy subject, small errors had a greater probability of producing complex spikes in the Purkinje cells of the vermis.

It is important to point out that as cerebellar degeneration takes place (particularly in SCA6 patients), the disease tends to have a differential effect on the hemispheres vs. the vermis (Schulz et al., 2010). The generally spared ability to learn from small errors may indicate that different regions of the cerebellum are engaged in response to large and small errors.

The rationale for this idea is that large perturbations produce conscious awareness of the error, which coincides with activity in prefrontal cortical regions (Shadmehr and Holcomb, 1997), whereas small perturbations often preclude this awareness. Prefrontal regions project to and receive inputs from parts of the cerebellum (Crus II) that are distinct from those regions (lobule IV-VI) that connect to the motor cortex (Kelly and Strick, 2003). In principle, it is possible that large errors that produce conscious awareness not only engage non-motor structures in the cortex, but also produce learning in regions of the cerebellum that are distinct from regions that may be connected to the motor cortical structures. Therefore, the improved performance with small errors may not be a reflection of specialization of cerebellum for large errors, but rather an indication of specialization of large and small errors within the cerebellum along with a differential rate of damage associated with degeneration.

While our data does not allow us to dissociate between these possibilities, it uncovers an unexpected and important fact: despite severe cerebellar damage, there is a latent ability in the brain to learn form small errors, and the motor memory that this learning produces has a greater resistance to change. When damage to the brain affects one form of learning but not another, it generally suggests that the neural bases of the two forms of learning are distinct. Our results raise the possibility that the multiple

computational processes that are thought to support motor adaptation, i.e., the so-called fast and slow processes (Smith et al., 2006), are neurally distinct.

From a practical standpoint, gradual introduction of a perturbation may be an effective method for training of patient or elderly populations. For example, in a visuomotor rotation paradigm, healthy elderly people have smaller errors at the end of a gradual training protocol as compared to a abrupt protocol (Buch et al., 2003). The longer lasting after-effects of gradual training (Kagerer et al., 1997;Hatada et al., 2006) coupled with its generalization to movements outside the training apparatus (Kluzik et al., 2008) suggest that this method of training might be more advantageous for rehabilitation.

Despite this ability to learn to predict the pattern of forces in a gradually imposed perturbation, the motor memory formed by cerebellar patients was missing a fundamental component: their motor output did not exhibit an over-compensation of the perturbation early in the movement. This specific feature of reaching movements in force fields has been linked to a process of optimization (Izawa et al., 2008), i.e., a process in which the brain finds the motor commands that do not merely compensate for the perturbation, but do so with minimum effort. This optimization process appears to be lost with cerebellar damage in both the mild and severe patients.

What does the current result suggest about the function of the cerebellum in motor control? Elsewhere we have proposed that the general problem of motor control is twofold (Shadmehr and Krakauer, 2008): 1) to learn to predict the sensory consequences of motor commands, and 2) to find motor commands that bring the maximum amount of reward at a minimum effort. From a theoretical standpoint, the first problem is one of learning a forward model, whereas the second problem is learning an optimal control

strategy. Importantly, the two steps are not independent, but need to take place in sequence. That is, one cannot form an optimal control strategy unless one already has formed an accurate way to predict the consequences of motor commands. An influential idea is that the cerebellum is a site for learning of forward models (Miall and Wolpert, 1996;Pasalar et al., 2006). However, our results here suggest that cerebellar damage impairs one of the adaptive processes that are involved in learning a predictive model of the perturbation (the process that depends on large errors), but there are other mechanisms, perhaps in different regions of the cerebellum or outside the cerebellum, that may contribute to learning from small errors. Furthermore, even when learning is driven by small errors, cerebellar damage prevents formation of a predictive model that has an optimal timing property. This raises the possibility that the contributions of the cerebellum go beyond formation of sensory predictions, i.e., forward models, but also play a role in the programming of motor commands that optimally (i.e., with minimum effort) produce a desired movement outcome.

CHAPTER 4

THE MOTOR CORTEX AND STABILIZATION OF MOTOR MEMORY

4.1 INTRODUCTION

In Chapter 3, we aimed to understand the role of the cerebellum in the fast and slow processes of motor memory. Evidence from our cerebellar degeneration patient study demonstrated that the cerebellum may play a large role in learning from large errors, supporting the fast adaptive process. In Chapter 4, we explore the role of the primary motor cortex in motor learning. We attempt to tease apart the contributions of the primary motor cortex to the slow adaptive process, based on the size of error and the stability of the training environment.

Theories of motor control suggest that motor learning involves two forms of computation (Shadmehr and Krakauer, 2008): 1) learning to predict the sensory consequences of motor commands (Bhushan and Shadmehr, 1999; Wolpert et al., 1995), and 2) learning to produce motor commands that maximize the probability of reward and minimize effort (Izawa et al., 2008; Xu-Wilson et al., 2009). This framework proposes that the cerebellum plays a role in learning to predict the sensory consequences of motor commands (Blakemore et al., 2001; Miall et al., 2007) and the motor cortex plays a role in learning control policies that produce motor commands in response to predicted and observed sensory information (Scott, 2008; Shadmehr and Krakauer, 2008). While there

is experimental evidence suggesting a role for the cerebellum in learning to predict consequences of self-generated motor commands (Pasalar et al., 2006; Tseng et al., 2007), less is known regarding the specific contribution of the motor cortex to motor learning.

Neurophysiological data from the motor cortex of monkeys is available in a well-studied task in which subjects perform reaching movements while adapting to a visuomotor or force field perturbation. During adaptation, changes in motor output often lead changes in the firing patterns in the primary motor cortex (M1) (Paz et al., 2003). For example, in early adaptation trials there are rapid improvements in performance, but little or no change in M1 cell activity (before onset of the movement). Robust changes in M1 activity appear after performance has reached a plateau (Paz et al., 2003). When the perturbation is removed, the motor output returns to baseline, yet the changes in M1 firing patterns that developed during adaptation do not washout (Li et al., 2001; Paz et al., 2003). Thus, neurophysiological data suggests that the memory that forms in M1 has a slower trial-to-trial dynamics than changes in motor output.

In humans, transcranial magnetic stimulation (TMS) has been used to produce physiological data from the motor cortex during motor adaptation using. In a seminal paper, Cothros et al. (2006) confirmed earlier observations that learning to reach in a clockwise force field (field A) impaired the ability to adapt to a counterclockwise force field (field B), as the memory of A interfered with learning of B (Shadmehr and Brashers-Krug, 1997). They reasoned that if the memory of A resided in M1, then its disruption should eliminate the interference. Indeed, after completion of training in A, repetitive TMS (rTMS) of M1 improved the ability to learn B, but impaired the ability to

recall A (Cothros et al., 2006). This suggests that after adaptation to a perturbation, a memory specific to that perturbation is either stored or consolidated in M1.

Despite this evidence for a role for M1 in storage of motor memory, experiments have not found evidence that disruption of M1 affects the ability to acquire that memory. For example, rTMS before the practice session (Cothros et al., 2006; Richardson et al., 2006) and single pulse TMS during the practice session (Hadipour-Niktarash et al., 2007) both impair retention of the learned skill, but leave no discernable effect on performance during learning. This lack of an effect on performance during learning is puzzling, as it is unclear why disruption of M1 affects the retention of the motor memory, but not its acquisition.

Here we used TMS to investigate the role of M1 during learning of reaching movements. A single TMS pulse was delivered at the end of the trial, near the time when error feedback is expected to arrive in the motor cortex. Unlike previous TMS experiments, the adaptation phase included occasional 'error-clamp' trials, during which movement was constrained to a straight line to the target. Minimization of error in these trials allowed us to measure the compensatory forces produced by subjects independent of feedback mechanisms that respond to movement errors.

4.2 METHODS

Fifty seven right-handed volunteers with no known neurological disorders participated in this study. All participants were naive to the purpose of the experiment. All procedures were approved by the Institutional Review Board of the Johns Hopkins School of Medicine and all participants signed a consent form.

4.2.1 Behavioral Training

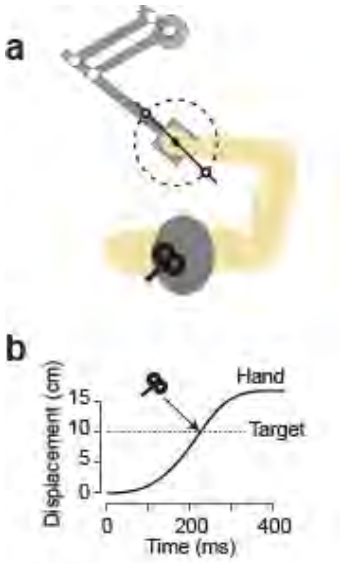

Figure 4.1 a. Experimental set-up. Subjects were seated in front the robot and were asked to hold the handle and 'shoot' through a 10 cm distant target in 230ms. b. TMS was delivered when the hand crossed the target during force-field trials.

Subjects performed a 'shooting task' while holding the handle of a robotic manipulandum (Huang and Shadmehr, 2009). The hand was covered by a horizontal screen, upon which a small white cursor (5x5 mm) was displayed at all times. A target (5x5 mm) was positioned at 10-cm from the center of the screen at either 121.5^{o} (toward the right shoulder) or 301.5^{o} (in a pseudo random sequence) (Figure 4.1, top). As the cursor crossed the invisible 10-cm radius circle, a yellow dot appeared at the crossing point to emphasize the endpoint error, i.e., the distance between the strike crossing point and the target. Beyond the invisible circle, a dampening force field acted as a 'pillow' to absorb the strike, after which subjects brought their hand back to the target. Once the cursor was placed in the target, the center mark reappeared and the robot brought the hand back to the center. The required movement time (time to cross the target) was 230ms. If the movement duration was too long (> 230ms), a blue dot appeared instead. Because the subjects were instructed to strike quickly through the target, peak velocity was usually achieved near the crossing point. Hand position, velocity and force at the handle were recorded at 100Hz.

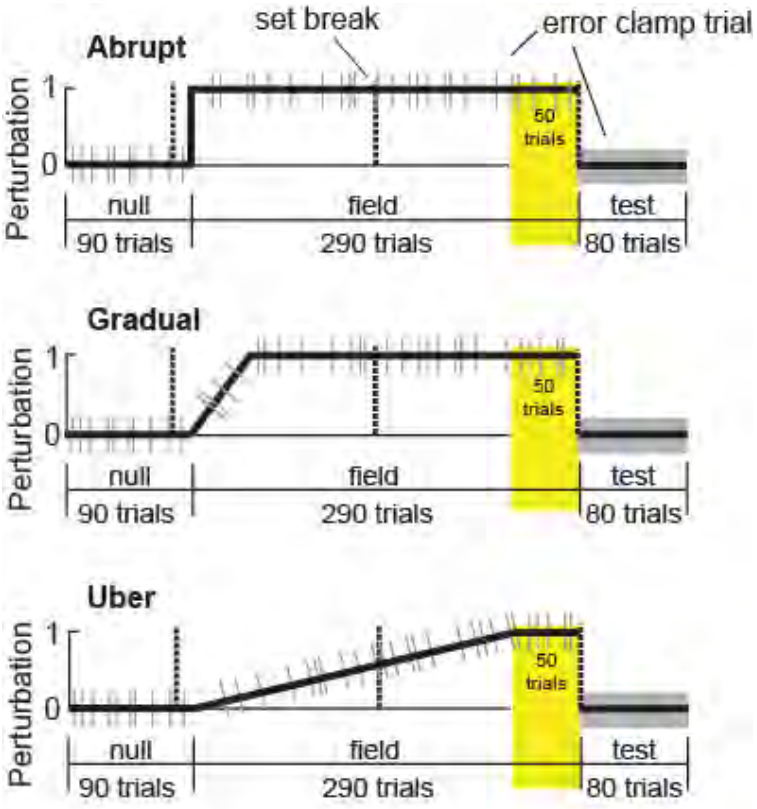

Figure 4.2 Study protocol and performance during adaptation. Subjects participated in one of three experiments: Abrupt, gradual and uber introduction of a force field. They held the handle of a light-weight robotic arm and made shooting movements to a target. In the first 90 trials the robot produced a null field (no forces). In the subsequent 290 trials, a curl force field was introduced, perturbing the hand perpendicular to its direction of motion. The gray bars schematically represent 'error-clamp' trials during which the robot produced a stiff channel that allowed us to measure the subject's motor output perpendicular to the direction of motion. Vertical dashed lines indicate brief set breaks.

TMS-abrupt experiment: The experiment consisted of four blocks (Figure 4.2, top). During the first block (80 trials), subjects made reaching movements during which no forces were applied (null). The second block began with ten null trials followed by 140 force field trials, where the force exerted by the robot was introduced at the

maximum magnitude [0 -13; 13 0] N.sec/m on the first field trial and remained at full strength for the remainder of the block (Figure 4.2, top). The magnitude of the field was maintained for the150 trials of the third block. During these three blocks, error-clamp trials were randomly interspersed with 1/5th probability. In error-clamp trials, the hand motion was constrained to a straight line to the target by an error-clamp wall that counteracted forces perpendicular to the movement direction (spring coefficient: 2500 N.m; damping coefficient: 25 N.s/m). The fourth block, consisting of 80 error-clamp trials was used to assay the rate of decay of the memory. In the TMS-abrupt group (TMS_{ABR} n=9 subjects), a single TMS pulse was applied at the end of each adaptation trial (see below). In the control-abrupt group ($CTRL_{ABR}$ n=9 subjects), no TMS pulses were given.

TMS-gradual experiment: In this experiment subjects performed 80 trials in the null condition in the first block. The second block began with ten null trials followed by 140 force field trials. During the first 45 force field trials, the force exerted by the robot gradually ramped up to the maximum magnitude (Figure 4.2, middle). The magnitude of the field was maintained for the 95 remaining trials of this block and for the 150 trials of the third block. In the TMS-gradual group (TMS_{GRAD} n=10 subjects), a single TMS pulse was delivered at the end of each adaptation trial. In the control-gradual group ($CTRL_{GRAD}$ n=11 subjects), no TMS pulses were given.

TMS-uber experiment: In this experiment subjects also performed 90 trials in the null condition, followed by 290 field trials. However, the magnitude of the perturbation was gradually increased over the first 240 trials and then remained at full strength for the last 50 trials (Figure 4.2, bottom). In the TMS-uber group (TMS_{UBER} n=9

subjects), a single TMS pulse was delivered at the end of each adaptation trial. In the control-uber group ($CTRL_{UBER}$ n=9 subjects), no TMS pulses were given.

TMS protocol: TMS was applied over the biceps and deltoid representations of the left primary motor cortex at 120% of the resting motor threshold. The coil was placed tangential to the scalp with the handle pointed backwards at a 45° angle with respect to the anterior-posterior axis. The resting motor threshold was defined as the minimum stimulator intensity that produced an EMG response in the right first dorsal interosseous muscle in 5 out of 10 stimulations. The pulse was delivered when the hand crossed an imaginary 10cm radius circle centered at the start position of the reaching movement (Figure 4.1).

4.2.2 Data Analysis

The movement duration was computed offline as the time from movement onset (time at which the velocity reaches a threshold of 10 cm/s) and movement offset (time at the cursor crosses the 10cm radius). Trials completed in less than 300ms and with an angular endpoint error smaller than 30° were included in the analysis (greater than 95% of all movements). For each error-clamp trial, the ideal force was computed as the field magnitude times the hand velocity. The baseline force that subjects produced during null trials were subtracted from the force they produced during adaptation trials. For each error-clamp trial, the dependent measure was the maximum force exerted by the subjects. For each force-field trial, we computed the endpoint angular error, i.e. the angle between a straight line to the target and endpoint position. In addition, perpendicular velocity at the end of the movement was assessed at 90% of movement duration. For some analyses of field trials, movement trajectories were divided into the early and late phase of the

movement on the basis of the parallel position (<5cm for early and >5cm for late). Average perpendicular velocity was then computed separately for each segment. For some analyses of error-clamp trials, the force profile for each trial was normalized in time (0% is the movement onset and 100% is the movement offset) and then resampled in 5% time intervals. The intermediate data points were computed from a spline curve fitted on the raw data points (spline function in Matlab, Mathworks Inc., Natick, MA).

We focused on two periods during adaptation: the first 50 trials after the perturbation reached full intensity (early training period, trials 136-185, as shown in Figure 4.1) and the last 50 trials of the perturbation (late training period, trials 331-380). In each period, we had five error-clamp trials in each direction. We compared the dependent measures from each TMS group to the corresponding CTRL group for each of these periods separately. In this respect, we submitted the dependent measures to repeated measures ANOVA and with groups as a between-subject factor. Finally, to reject the possibility that differences in speed might explain our results, we performed an analysis of covariance (ANCOVA) after having rejected the possibility that the speed-force relationship was different for the different groups (homogeneity of slopes hypothesis). For the ANCOVA, we had the maximum force recorded during the error-clamp trials as the dependent measure, the group as the between-subject factor and the peak velocity as the covariate. Parameter extraction was implemented in Matlab (Mathworks Inc, Natick, MA) and statistical analyses were performed with Statistica (Statsoft Inc, Tulsa, OK).

The post-adaptation retention period was composed entirely of a sequence of error-clamp trials. We examined the rate of decay of the force output during the error-clamp trials of the test period. This rate was estimated by fitting a single exponential of

the form $f(n) = a\exp(-bn)$ to the data set for each subject. In this equation, $f(n)$ is the peak force on trial n. This continuous-domain equation can be well approximated in the discrete domain: $f^{(n+1)} = (1-b)f^{(n)}$ in which $(1-b)$ is an estimate of sensitivity of the memory to trial. Therefore, b is fraction of the force that is lost from one trial to the next.

4.3 RESULTS

Volunteers performed reaching movements while adapting to a force perturbation. The target appeared in either the NW or the SE direction, and a single pulse was delivered to M1 as the hand crossed the target. In the abrupt, gradual and uber protocols, the subjects were divided into two groups, a control group and a TMS group ($CTRL_{ABR}$, TMS_{ABR}, $CTRL_{GRA}$, TMS_{GRA}, $CTRL_{UBER}$, TMS_{UBER}).

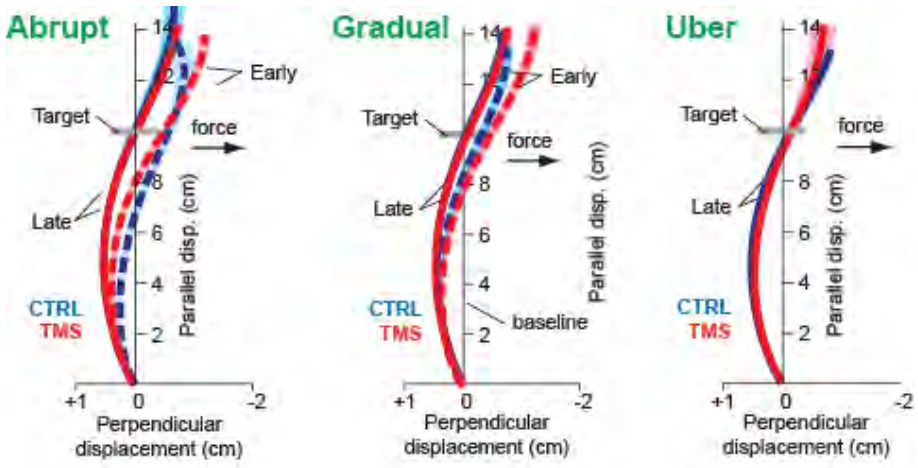

Figure 4.3 Average trajectory profiles during the early (trials 136-185) and late periods (trials 331-380). Trials were rotated such that the target is represented 10cm away in the North direction. Areas around the curves represent SEM.

4.3.1 TMS did not affect movement trajectories during adaptation

In the abrupt condition, the introduction of the perturbation produced endpoint errors (Figure 4.3, left), but with practice both the $CTRL_{ABR}$ and TMS_{ABR} groups reduced this error to near zero. To quantify adaptation, we compared the endpoint error during the early phase of adaptation (trials 136-185, as shown in Figure 4.2, top) to late phase of adaptation (trials 331-380). We performed an ANOVA with period (early and late) as a within-subject factor, and group ($CTRL_{ABR}$ and TMS_{ABR}) as a between-subject factor. The endpoint errors decreased comparably from the early to late period in the control and TMS groups (Figure 4.4, top, main effect of period: $F(1,16)=51.63$, $p<0.001$; main

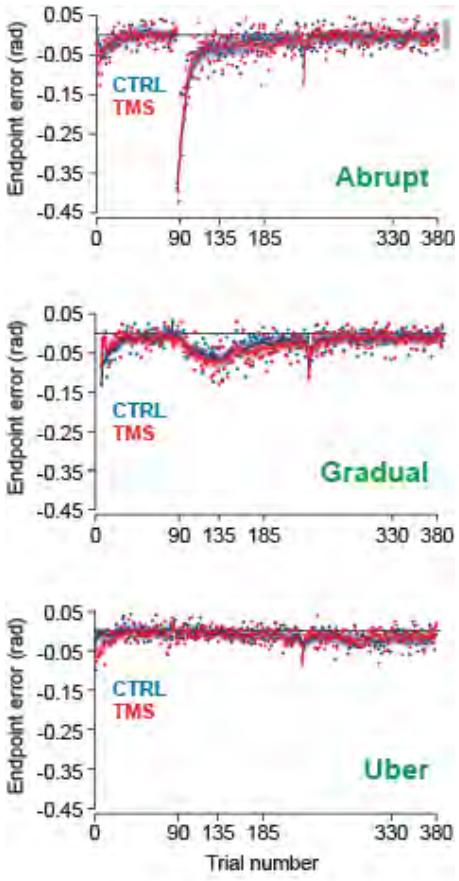

Figure 4.4 Endpoint error during the null and adaptation phases in the abrupt, gradual, and uber protocols. Error bars are SEM.

effect of group: $F(1,16)=0.018$, $p>0.40$; interaction $F(1,16)=0.73$, $p=0.4$). When the forces were gradually ramped up during the first 50 field trials, we also saw comparable performance in the $CTRL_{GRAD}$ and TMS_{GRAD} conditions from the early to the late period in the control and TMS groups (Figure 4.4, middle, main effect of period: $F(1,19)=77.7$, $p<0.001$); main effect of group ($F(1,19)=2.26$, $p=0.15$); group by period interaction ($F(1,19)=1.4$, $p=0.25$). Similarly, in the uber condition endpoint errors changed comparably for the control and TMS groups (Figure 4.4, bottom, main effect of group: $F(1,16)=0.16$, $p>0.40$; interaction $F(1,16)=0.31$, $p>0.4$). Thus, TMS had no reliable effect on endpoint errors.

We next compared the reach trajectories to the target. The optimum trajectory to compensate for the force perturbation is to over-compensate early in the movement when the field is weak, and then allow the robot to bring the hand back to the target (Izawa et al., 2008). All six groups produced reach trajectories that exhibited over-compensation (Figure 4.3). This over-compensation increased over the course of trials. However, over-compensation was comparable for control and TMS groups.

4.3.2 TMS affected force production in error-clamp trials

Hand trajectories in field trials are a reflection of both what the subject predicts about the perturbation and their ability to utilize sensory feedback to compensate for the perturbation. However, during an error-clamp trial there is no perturbation. Rather, a channel constrains the movement to a straight line to the target, eliminating the need to correct for an error. Thus, we can view the forces that the subjects produced against the channel walls as a proxy for the forces that they expected from the external perturbation.

Despite the similarity in reach trajectories in the $CTRL_{ABR}$ and TMS_{ABR} groups, the forces that subjects produced in error-clamp trials evolved differently (Figure 4.5). In the TMS_{ABR} group the peak force in error-clamp trials rose rapidly and reached a plateau that was significantly smaller than the $CTRL_{ABR}$ group (Figure 4.5, top, main

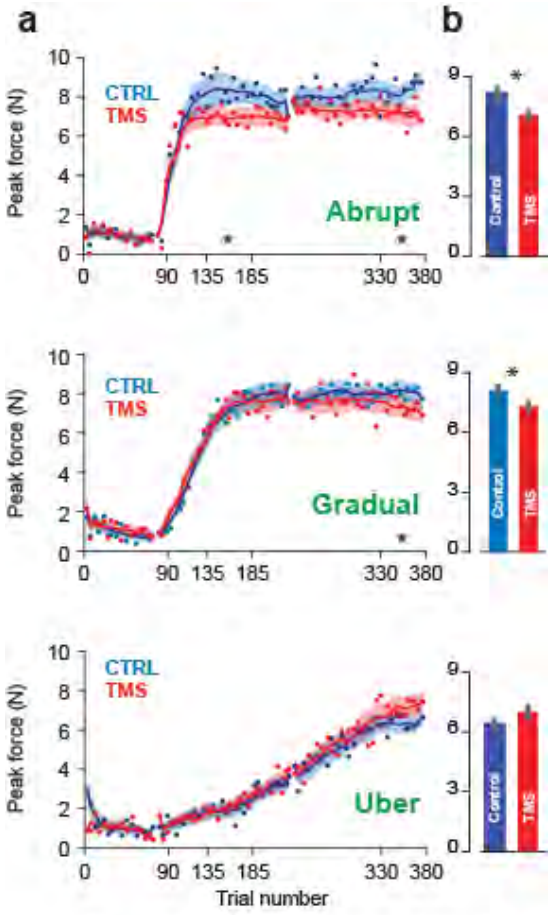

Figure 4.5 a. Peak force during the null and adaptation phases in the abrupt, gradual, and uber protocols. The solid curves represent the running average over a window of 10 trials. Error bars are SEM. b. Average peak force at the end of adaptation (trials 331-380).

effect of group: $F(1,16)=15.1$, $p=0.001$; of period $F(1,16)=0.03$, $p>0.40$; interaction: $F(1,16)=0.17$, $p>0.4$). ANCOVA analysis showed that differences in the peak force were not due to differences in speed as we found a significant group effect on the force produced during the late training period ($F(1,15)=5.76$, $p=0.03$) when taking into account the significant effect of speed ($F(1,15)=8.05$, $p=0.012$).

In the gradual condition, the perturbation was ramped up over the first 50 trials of the adaptation period. To investigate the trial by trial change in this force, we categorized the movements based on duration and compared the peak force produced by the two groups (Figure 4.2). As the perturbation was ramped up (trials 90-135), the forces that subjects produced increased rapidly (Figure 4.5a, middle). During this 'fast' period of adaptation there appeared to be no reliable difference in the forces produced by the two groups. However, by the end of the training period, the CTRL subjects were producing significantly more force than the TMS group (Figure 4.5b, middle). There was an interaction between group and period (Fig. 2B, $F(1,19)=4.95$, $p=0.038$), and by the late period there was a significant difference between the force in the two groups ($t(19)=2.12$, $p=0.047$) but no difference in the early period ($p>0.40$). From the early to the late adaptation period, the CTRL group showed a 15% increase in peak force ($t(10)=3.9$; $p=0.003$), whereas during the same period TMS_{BOTH} group showed no significant changes (2% increase, $t(9)=0.39$; $p>0.40$). Note that the difference observed at the end of the learning period could not be explained by a difference in speed as the ANCOVA demonstrated a significant effect of group ($F(1,18)=5.58$, $p=0.03$) on the force produced during the last 50 error-clamp trials while taking into account the effect of speed ($F(1,18)=13.45$, $p=0.002$).

To summarize, TMS of M1 did not affect the forces that subjects produced during the 'fast' phase of adaptation in which both the motor output and the perturbation changed quickly. Rather, TMS impaired the phase of learning during which the perturbation was constant and the performance improvements had stabilized.

The observation that TMS affected both the early and late phase in the abrupt condition and only the later phase in the gradual condition may be simply due to the number of pulses given to the brain: perhaps it takes a certain number of pulses to produce an effect on force output. In this scenario, the effect of TMS should be unrelated to the rate of change in the perturbation. Alternatively, TMS of M1 may affect a process of stabilization that occurs after the perturbation has stopped changing.

To test these interpretations, the perturbation was very gradually ramped up over 240 trials in the uber group (Figure 4.2, bottom). If the effect of TMS depends on the number of pulses, then the uber condition should produce impairments in the TMS group. On the other hand, if the effect of TMS is specific to a period after the perturbation has stopped changing, then it should not have an effect in the gradual condition.

In the TMS_{UBER} group the peak force rose gradually and was never different than the $CTRL_{UBER}$ group (Figure 4.5, bottom, main effect of group: $F(1,16)=3.53$, $p=0.08$; of period: $F(1,16)=366$, $p<0.001$; interaction: $F(1,16)=1.29$, $p=0.27$). The trend toward a higher force by the end of training for the TMS_{UBER} group disappeared when we took into account differences in peak velocity (ANCOVA, effect of group: $F(1,15)=,0.95$ $p=0.35$; Effect of speed: $F(1,15)=9.57$, $p=0.007$). In summary, disruption of M1 produced impairments in adaptation of motor output particularly when the perturbation reached

steady state, as in the abrupt (early and late) and gradual (late) conditions, but not when it was continually changing as in the uber (early and late) conditions.

4.3.3 TMS did not affect the rate of decay after adaptation

The adaptation blocks were followed by a long series of error-clamp trials in which we assayed the rate of decay of the adapted response. The TMS was discontinued at this stage of the experiment. Our proxy for the adaptive response was the peak force in error-clamp trials. The data for the abrupt and uber conditions are shown in Figure 4.6. We fit a single exponential to the individual subject data and estimated the time constant of the exponential. In all conditions, TMS had no reliable influence on the rate of

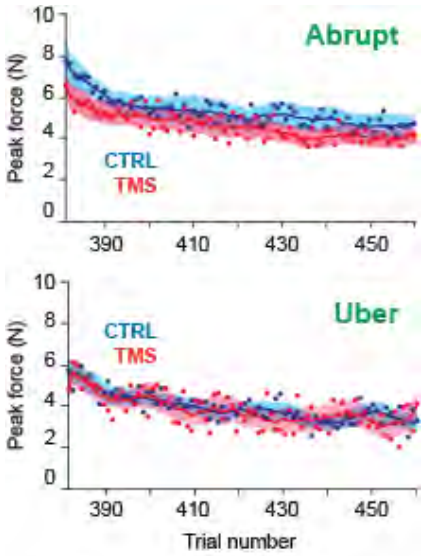

Figure 4.6 Peak force in error-clamp trials following adaptation in the abrupt and uber protocols. None of the subjects were stimulated in these trials. Error bars are SEM.

forgetting ($CTRL_{ABR}$ vs TMS_{ABR}: $t(16) = 0.03$, $p>0.40$; $CTRL_{UBER}$ vs. TMS_{UBER}: $t(16) = 0.59$, $p>0.40$). For the gradual condition, the comparison of the rates of forgetting were potentially biased by a different duration between the adaptation and test blocks in the $CTRL_{GRAD}$ vs TMS_{GRAD} groups even though they were not significantly different ($t(19) = -0.28$, $p>0.4$).

4.3.4 TMS produced a greater dependence on online control

Finally, we considered the question of why TMS affected force production during error-clamp trials, but did not influence the endpoint errors during free reaching. We found that during the late phase of adaptation, in the control groups ($CTLR_{ABR}$ and $CTLR_{GRAD}$ collapsed together) an individual's force output in error-clamp-trials was a predictor of their endpoint kinematics in free reaching. For example, the maximum force recorded in error-clamp trials was a predictor of perpendicular velocity at the end of the movement ($r=0.45$, $p=0.048$). In contrast, this correlation did not exist in the TMS groups ($r=0.13$, $p>0.40$). Furthermore, in the control groups the motor commands early in the movement were predictors of endpoint kinematics. For example, the average perpendicular velocity before the subjects crossed the midpoint of the movement was a significant predictor of endpoint error (Figure 4.7a, $r=0.47$, $p=0.03$). In contrast, this correlation was not present in the TMS groups (Figure 4.7c, $r=0.12$, $p>0.40$). That is, the within subject correlations suggested that in the control groups, endpoint kinematics in free reaches were related to motor commands that started these movements. In contrast,

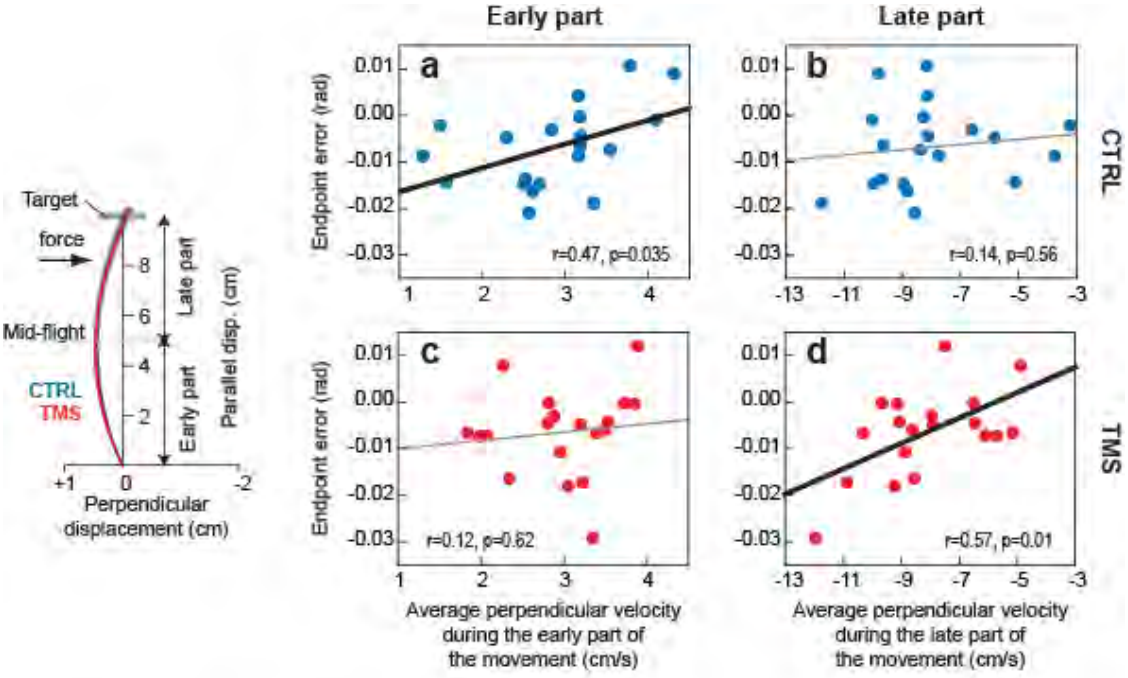

Figure 4.7 TMS dependence on online control. Left graph: schematic representation of how the trajectories were spatially divided in two phases (Early phase: parallel position < 5cm. Late phase, parallel position > 5cm). Scatterplots: inter-subject relationship between the average perpendicular velocity and endpoint error for the CTRL and TMS groups (left and right columns, respectively). The average perpendicular velocity was computed either during the early (top row) or late (bottom row) phase of the movement. For this analysis, CTRL (CTRLABR and CTLRGRAD) and TMS (TMSABR and TMSGRAD) groups across the ABR and GRAD conditions were collapsed together.

in the TMS groups endpoint kinematics were more closely related to motor commands that arrived late in the movement. For example, for the second half of the movement, the average perpendicular velocity was a predictor of endpoint error for the TMS groups (Figure 4.7d, r=0.57, p=0.01) but not for the control groups (Figure 4.7b, r=0.13, p>0.40).

To explore this idea further, we fit a multiple regression model to predict endpoint error from the measures of perpendicular velocity between the early and late phase of the movements. The multiple regression analysis provided good fits of the data (r^2=0.74 for

the control groups and r^2=0.85 for the TMS groups). Interestingly, the weight of the independent factors differed between the two groups (given here with normalized coefficient):

$$CTRL: \quad Error = 1.27 \cdot Vel_{1^{st}\ half} + 1.07 \cdot Vel_{2^{nd}\ half} \qquad R^2 = 0.74$$

$$TMS: \quad Error = 1 \cdot Vel_{1^{st}\ half} + 1.27 \cdot Vel_{2^{nd}\ half} \qquad R^2 = 0.85$$

For all groups, the independent factors were always significant (p-values<0.0002). Standard error of the normalized regression coefficients were 0.181 and 0.136 for the control and TMS groups, respectively. Results of this analysis suggests that during free reaching, the TMS groups relied more on the late phase of the movement to correct for the perturbation, whereas the control groups relied on motor commands that they produced early in the movement. The motor commands that the control groups produced in error-clamp-trials were a better predictor of their performance in free reaches than for the TMS groups.

4.4 DISCUSSION

The role of the primary motor cortex in motor learning is complex (Lalazar and Vaadia, 2008). Neurophysiological studies report that a cell's preferred direction changes during reach adaptation and the new preferred direction is maintained even during the washout period (Gandolfo et al., 2000; Li et al., 2001; Paz et al., 2003; Paz and Vaadia, 2004; Paz et al., 2005). The importance of these learning-related signals has been explored in humans using non-invasive stimulation paradigms (Muellbacher et al., 2002; Baraduc et al., 2004; Richardson et al., 2006; Hadipour-Niktarash et al., 2007; Reis et al., 2009). The consistent result has been that stimulation of the motor cortex during acquisition generally alters processes that maintain the memory.

In the present study, we found in the abrupt and gradual groups that while TMS over M1 did not affect reach trajectories during adaptation, it produced a deficit in the predictive component of reaching as measured during error-clamp trials. In an oversimplified schema of motor control, we can assume that there are two main components that determine movement kinematics and dynamics: a feed-forward (predictive) component determined before movement onset and a feedback (reactive) component that relies on internal predictions (Gritsenko et al., 2009) and sensory feedback (vision and proprioception; Prablanc et al., 1986; Pélisson et al., 1986; Prablanc and Martin, 1992; Pisella et al., 2000; Kalaska et al., 2003; Rossetti et al., 2003; Saunders and Knill, 2003, 2005; Gosselin-Kessiby et al., 2008; Gosselin-Kessiby et al., 2009). During error-clamp trials, the role of the reactive component is minimized, unmasking the predictive component. While TMS reduced the predictive component, it increased the reliance on the reactive component (Figure 4.7).

Recent evidence suggests that the feedback component has a 'fast' timescale, i.e. it both learns and forgets quickly (Xu-Wilson, Chen-Harris, Zee and Shadmehr, 2009; Chen-Harris et al., 2008). In our study, TMS did not change the rate of forgetting of the predictive component of the learning, but decreased the weight assigned to that component because TMS subjects were not able to learn about the perturbation as well as control subjects. We attributed this difference to a difference in the weight assigned to the fast-decaying reactive and slower-decaying predictive components between the TMS and control groups.

An important issue related to the use of TMS is the specificity of the observed effect. TMS stimulation produces a clicking sound and subjects usually feel a shock-like

sensation that might startle or distract them. In the uber condition, the subjects received the same number of pulses as in the abrupt condition, yet TMS impaired performance in the abrupt condition but not the uber condition. In addition, introduction of the perturbation in the abrupt and gradual conditions produced large errors, yet TMS did not affect the rapid rise in motor output.

As outlined in the previous paragraph, TMS only affected the learning process when the errors were low and the environment stabilized. This impairment was not related to an error-driven process, as it did appear neither during the initial phase of the learning when the perturbation was introduced abruptly nor during the course of learning when the perturbation was introduced gradually in the uber condition. It only appeared when the environment was stable and a strong memory could be formed. This is consistent with the hypothesis that the initial (error-driven) learning might be subserved by a fast system that relies on the cerebellum (Xu-Wilson et al., in press). The observed effect might be explained by disruption of non error-driven learning processes such as the teaching of the slow process by the fast process (Criscimagna-Hemminger and Shadmehr, 2008) or the creation of an optimal manifold to control the movements (Rokni et al., 2007).

Our results are in agreement with the involvement of the supplementary motor area (SMA) in the early stage of motor learning and M1 in the latter stage (Paz et al., 2005). In this perspective, building of the kinematic to dynamic transformation would first take place in the SMA and would be transferred to M1 once stabilized (Padoa-Schioppa et al., 2002, 2004). This theory is consistent with difference in synaptogenesis in M1 during early and late phase of skill acquisition (Kleim et al., 2004).

Cellular/molecular evidences suggest the existence of different stages in motor learning (Luft and Buitrago, 2005). The early stage involves temporary changes in M1 architecture but later stage produced formation of new synapses and specific protein synthesis (Kleim et al., 2004; Luft et al., 2004). Of particular importance is the role of the $GABA_A$ neurotransmitter. Its concentration decreases over the time of motor learning but not over the course of motor performance (Floyer-Lea et al., 2006). This decrease can eventually be measured over the course of learning by double pulse TMS (Perez et al., 2004; Rosenkranz et al., 2007). This local reduction of GABA concentration might facilitate plasticity by unmasking existing horizontal connections (Jacobs and Donoghue, 1991; Huntley, 1997), hence providing a way of setting up an new optimal manifold (Rokni et al., 2007). In contrast, TMS does evoke firing of excitatory and inhibitory neurons (Huerta and Volpe, 2009), hence presumably increasing the local concentration of GABA. Therefore, TMS pulses might counteract the decrease in GABA concentration, hence impairing the formation of the new memory.

CHAPTER 5

DISCUSSION

At the age of eight, I went figure skating for the first time. When I stepped out onto the ice I fell down immediately. I quickly stood up, hoping my friends had not noticed, and took a few steps only to fall again. Yet, by the end of the day, I was whizzing around the rink at a frantic pace, even demonstrating simple tricks like skating on one foot. My first experience on the ice is an example of how motor adaptation can be characterized by at least two timescales. First, during the early phase of learning I experienced large errors, falling down repeatedly, but I made rapid adjustments to reduce my error and minimize bruising. This early phase was followed by a late phase during which my error was smaller and number of falls minimized, but the improvement in the quality of my strokes became more gradual. This initial exposure to figure skating was followed by ten years of intense practice. Not only was error a critical aspect of perfecting my strokes, but the passage of time in between practice sessions allowed for both forgetting and consolidation. The main aim of this thesis is to uncover these time and error-dependent correlates of the multiple time scales of learning and memory and to find the neural basis of these processes in the cerebellum and motor cortex of human beings.

In Chapter 2, we demonstrated that brief training in field B (20 trials) following extended training in field A (~400 trials), did not cause unlearning of field A. Instead, it formed two competing memories, a slow memory of A and a fast memory of B. What is

necessary to form two independent competing memories? One possibility is that following initial training in field A, cues during initial performance in field B signaled the brain to 'label' field A and field B as distinct memories. In turn, field A was protected from unlearning during performance in field B. If labeling is required for protection from unlearning, what cues promote labeling? Studies have shown that subjects can adapt to two opposing force fields if different hand configurations (Gandolfo et al., 1996) or color and auditory cues were assigned to each field (Osu et al., 2003). However, in our current work the hand configuration was constant and no color or auditory cues were given to denote the direction of the force field, yet participants were able to learn both field A and field B.

We hypothesize that error is a critical cue for labeling and protection in our paradigm. In the **A**+B (bold indicates extended training for the purposes of this discussion), participants experienced large errors when first performing field A, yet the extensive training resulted in near perfect performance by the end of adaptation. When participants began performance in field B, they experienced errors that were twice as large as those experience in field A, inducing labeling and protection. However, a number of studies have demonstrated that training in field A, followed by training in field B causes interference, preventing recall at a later time (Brashers-Krug et al., 1996; Shadmehr and Brashers-Krug, 1997; Caithness et al., 2004; Mattar and Ostry, 2006). Like our study, participants experienced large errors in field B in these experiments. If error is sufficient to label and protect the memory of A, why was there no evidence of the existence of A? Krakauer and colleagues hypothesized that performance in field B did not destroy learning of field A, but rather masked the memory and prevented recall

(Krakauer et al., 2005). If error is sufficient to label and protect the memory of A, what cues recall?

Recently, our laboratory performed a simple experiment to examine the role that error plays in labeling, protection and recall. Participants performed ~400 in field B, followed by ~400 null trials, and then 20 additional trials in field B (**B**+**null**+B). When participants completed training in field B they had near perfect performance, but subsequently experienced large errors when beginning performance in the null field. If error is sufficient to induce labeling, protection and recall we can make two clear predictions: 1.) field B should be protected from unlearning during the null and be evident in savings, ie faster relearning of B in the 20 trials following the null, and 2.) the large error in relearning of field B should cause recall of the original learning, resulting in a slower decay of the memory of B in the error-clamp trials. Preliminary results show that participants demonstrate both savings (labeling and protection) and a slower rate of spontaneous recovery (recall).

To further confirm our hypothesis, we performed additional experiments. In the current study, participants perform ~400 trials in field B, followed by ~400 trials in field A, and finally 20 trials in field B (**B**+**A**+B). In Chapter 2 we showed that in the **A**+B paradigm, spontaneous recovery was driven by the decay of the fast memory of B. In the current paradigm **B**+**A**+B, if error is sufficient to label and protect A and B and recall B, we can make two clear predictions; 1.) the existence of the memory of **B** should be evident by savings, ie faster relearning of field B in the 20 trials following field A, and 2.) the pattern of spontaneous recovery should demonstrate the presence of not only a slow A and fast B (as in **A**+B), but also a slow B (recall).

Preliminary results in the **B**+**A**+B paradigm demonstrate that participants show savings during the 20 trials of B. During error-clamp trials, as the fast B decays performance spontaneously recovers to zero. This is markedly different from the pattern of spontaneous recovery in the **A**+B paradigm, where performance recovered to a positive value, indicative of the remaining slow memory of A. We know from the **A**+B paradigm, that slow A is present in the error-clamp trials following B and from the **B**+null+B paradigm that slow B is present in the error-clamp trials following B. This preliminary data reinforces the main conclusions from Chapter 2 and demonstrates that error may be a critical cue in labeling, protecting and recalling memories. Further studies where error is minimized are required to confirm our hypothesis.

Our results can also be viewed in a probabilistic framework (Chen and Sabes, 2007; Kording, 2007). When experiencing a disturbance, the brain faces a credit assignment problem and must integrate information from prior and current experience to assign a timescale to the disturbance. The knowledge of a Bayesian learner is represented as a probability distribution. A step perturbation induces large errors, resulting in increased uncertainty and fast learning. Given that the disturbance appears to be transient, there is a high probability that it has a fast timescale and should be easily forgotten. However, as the number of trials increases, the learner begins to now associate the perturbation with a slow timescale. In the **A**+B paradigm, after ~400 trials in field A the learner would perceive the memory as having a slow timescale and following the 20 trials in field B the learner would view the memory as having a fast timescale.

Imagine an experiment where participants performed 20 trials in field A, followed by 20 trials in field B (A+B). The learner would most likely associate field A and field B

with a fast timescale, quickly improving performance in each field and then rapidly forgetting. Would the large errors in this scenario be sufficient to label and protect the memory of A from learning in B? Krakauer and colleagues observed that increased training in the A+B paradigm in a visuomotor rotation task prevented learning of B from interfering with learning of A (Krakauer et al., 2005). This increased number of trials allowed the learner to further associate the rotation with a slow timescale. One requirement for labeling and protection, in the absence of changes in hand conformation or color and auditory cues, could potentially be that the learner must have associated at least one of the disturbances with a slow timescale. If this were the only requirement, then in the proposed experiment above (**A**+B, where A is gradually ramped up and error is minimized), would result in the same pattern of spontaneous recovery when A is presented as a step (Chapter 2).

Importantly, Huang and Shadmehr demonstrated that the statistics of change in the environment alter the rate of forgetting (Huang and Shadmehr, 2009). More specifically, they found that if a perturbation is presented to a learner gradually and then subsequently abruptly, the rate of forgetting following the abrupt presentation is slow. However, if they adapt to an abrupt perturbation first, then gradual, there is a fast rate of forgetting. These results highlight that both the current and previous statistics of the environment are important. In the potential experiment proposed above (**A**+B, where A is gradually ramped up), the history of minimal errors in field A may alter the rate of forgetting in field B, resulting in a slower rate of spontaneous recovery than when A is presented as a step.

In Chapter 2, we also observed that the fast process decays quickly over trials, but with the passage of time the fast memory transforms into a slow memory. Again, we can examine this result from the point of view of a Bayesian learner. After performing **A**+B and passage of either 2 min, 10 min, 1 hr, 6 hr or 24 hr, participants performed 30 error-clamp trials. The learner combines prior knowledge with the current state. When performing in field B, participants rapidly reduce their errors. On the very first error clamp trial following the break, the learner experiences minimal error. From the point of view of the learner, it appears that the environment has not changed during the break, small errors before the break, small errors now. Thus, given the apparent stability of the environment, they assign field B a higher probability of being a slow timescale. This results in less forgetting of the memory of B. With greater passage of time, the environment appears to have remained stable for longer, possibly resulting in assignment of an even slower timescale. Therefore, it is possible to interpret our results in two ways: 1.) passage of time transforms the fast into slow or 2.) passage of time, followed by trials in which error is minimized results in assigning a slower timescale to the initially fast disturbance. One would expect these two possibilities to be neurally distinct.

While the two-state model is an elegant framework for understanding the multiple timescales of motor memory, it is unable to account for the much of our results. The model predicts that in **A**+B, B causes unlearning of A, yet we observed the formation of a competitive process. In a **B**+**A**+B, the model does not predict savings. Yet, our preliminary results show faster relearning of B.

Huang and Shadmehr's results suggest that one can preferentially engage the fast and slow processes by altering the training environment. In Chapter 3, we employed a

gradual training paradigm that forms a more stable memory (Huang and Shadmehr, 2009). We hypothesized that the fast process, but not the slow process is dependent on the cerebellum. This framework makes two predictions: 1.) Cerebellar ataxia patients should be able to learn a force field adaptation task that preferentially engages the slow process. 2.) The rate of forgetting for the patients should be slower than controls, as their learning is more heavily based on the slow process. Indeed, we observed improved performance in the gradual, as compared to the abrupt condition, as well as a slower rate of forgetting.

Recall that the two-state model posits that motor learning engages two distinct processes with different sensitivities to error. Previous work has shown that sensory prediction error drives motor learning and the formation of an internal model (Wallman and Fuchs, 1998; Noto and Robinson, 2001; Tseng et al., 2007). Additionally, the cerebellum has been implicated as a potential site for formation of an internal model (Shidara et al., 1993). In Chapter 3, we conclude that neural bases of learning from large and small predictions errors are likely distinct, as cerebellar patients we able to learn from small, but not large errors. However, if we closely compare the abrupt and gradual paradigms there are three clear distinctions, 1.) the size of the prediction error, 2.) the amount of reward, and 3.) awareness of the perturbation.

What was the driving for cerebellar patient learning in the gradual condition? Patients experienced both small errors and large reward in the gradual condition. An alternate hypothesis to that presented in Chapter 3 is that the increase in reward was the driving force in learning in cerebellar ataxia patients. If so, then although the patients altered their motor output to account for the perturbation, they may have had deficits in

state estimation as reward-based learning may not prompt formation of an internal model. Our study does not have the power to conclusively determine whether or not the learning was error or reward based. It may have been a combination of both forms of learning.

Is error-based learning and formation of an internal model cerebellar dependent? In 2006, Mazzoni and Krakauer explored the relationship between the implicit and explicit strategies employed in adaptation to a visuomotor rotation task (Mazzoni and Krakauer, 2006). Prior to exposure to a 45-degree rotation, participants were informed that the cursor would be rotated in the counterclockwise direction and were instructed that in order to make accurate movements they must aim in the clockwise direction. While explicit knowledge of the rotation was sufficient to prevent initial reaching errors, participants began to overcompensate for the rotation, making large errors. Thus, the explicit strategy was overcome by implicit adaptation, resulting in formation of an internal model. Can cerebellar patients utilize explicit information to prevent initial reaching errors? If so, would they show the same overcompensation as controls?

We recently replicated the Mazzoni and Krakauer results in healthy adults. Preliminary results with cerebellar ataxia patients indicate that they are able to utilize explicit knowledge of the perturbation to minimize initial performance errors. The declarative system may have supported these rapid changes in motor commands in response to the visual rotation (Keisler and Shadmehr, 2009). However, initial findings show that cerebellar patients do not demonstrate overcompensation, suggesting that the implicit strategy did not overcome the explicit strategy because patients were unable to form an internal model. Additional data is required to confirm these preliminary findings

and future studies are needed to understand if reward, in the absence of error, can promote adaptation in cerebellar degeneration patients.

In Chapter 4, we investigated the role of the human primary motor cortex in formation of motor memories during a force field adaptation paradigm in which movements were brief (~230ms) and a single transcranial magnetic stimulation (TMS) pulse was delivered at the end of each trial. We used abrupt, gradual and uber paradigms to vary the size of the prediction error and the number of trials for which the motor output had reached a plateau. We observed an impairment from TMS of M1 during the abrupt (early and late) and gradual (late) conditions. No impairment was seen in the uber condition. We conclude that the primary motor cortex contributes to motor learning when the training environment and motor output have reached steady state for an extended number of trials.

We hypothesized that the primary motor cortex may play a role in the formation of memories that are less susceptible to error. We modified the statistics of the environment to either maximize (abrupt) or minimize (uber) the size of the sensory prediction error. We observed that in the uber condition, errors were always minimal, yet M1 did not appear to play a role in adaptation. It is important to point out again that there are distinct differences in the abrupt, gradual and uber paradigms; 1.) the size of the prediction error, 2.) the amount of reward, 3.) the number of trials that the environment was at steady state, and 4.) awareness of the perturbation. In Chapter 3, we observed improved adaptation in the gradual condition. This learning may have been due to a decrease in error and/or an increase in reward. It is possible that a reward-based strategy is used during adaptation to a gradual perturbation, not just as an alternative to error-

based learning in cerebellar degeneration patients. In the uber condition, control participants were continually increasing their motor output, while errors were small and reward was high. If a reward-based strategy was employed, the basal ganglia may have contributed, explaining why we do not see an impairment in adaptation when TMS was applied to the primary motor cortex.

Despite the impairments seen in error clamp trials, TMS subjects were able to perform the task as well as control subjects in field trials by relying more heavily on feedback. Importantly, previous TMS studies show no impairment during the later stages of learning, only during retention (Hadipour-Nikitarash et al., 2007). Maybe learning was impaired, but the impairment was compensated for in some other manner? Our hypothesis is that M1 is engaged in the predictive component when perturbation and motor output have reached steady state, relying on feedback to compensate for the impairment in the primary motor cortex. The posterior parietal cortex has been implicated in using feedback to correct for motor errors (Goodale 1986, Prablanc and Martin 1992). Removing the cursor during the movements would prevent participants from using feedback to compensate for the impairment caused by TMS of the primary motor cortex. We predict that future experiments without visual feedback would also show an impairment in the field trials, as participants would be unable to rely feedback as a compensatory mechanism.

While this thesis contributes to uncovering the time and error dependent correlates of the multiple timescales of motor memory and understanding the role of the cerebellum and primary motor cortex in error dependent learning, many wonderful questions remain unanswered. It is clear that the brain can simultaneously learn two

force fields, but further studies are required to understand what cues are required for labeling, protection and recall. In cerebellar degeneration patients we observed an increased ability to adapt in the gradual condition, however the neural basis of the compensatory learning mechanisms is not well understood. We also found that disruption of the primary motor cortex impairs feed-forward control. Does the primary motor cortex, in concert with the cerebellum play a role in the formation of an internal model? Most importantly, we currently lack a theoretical framework that combines both error and reward based learning mechanisms that could potentially allow this work to be seen through a new lens. My sincere hope is that someone will find these questions as intriguing as I have and that the process of discovery will bring them the same joy that this experience has brought me.

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EDUCATION

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The Johns Hopkins University, 1998-2002

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PUBLICATIONS

- Orban de Xivry JJ, Criscimagna-Hemminger SE, Shadmehr R (2010) Disruption of the motor cortex impairs the transition from a rapidly changing to a gradually changing motor memory. (in preparation).
- Criscimagna-Hemminger SE, Bastian AJ, Shadmehr R (2010) Size of Prediction Error Alters Cerebellar Contributions to Motor Learning. Journal of Neurophysiology (in revisions).
- Criscimagna-Hemminger SE and Shadmehr R (2008) Consolidation patterns of human motor memory. Journal of Neuroscience 28:9610:9618.
- Diedrichsen J, Criscimagna-Hemminger SE, and Shadmehr R (2007) Dissociating timing and coordination as functions of the cerebellum. *Journal of Neuroscience,* 27:6291-6301.
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HONORS

- Siebel Scholar 2009
- Open Society Institute Fellow 2009
- Echoing Green Fellow 2009
- International Society of Motor Control Travel Scholarship to Progress in Motor Control VII 2009
- Neural Control of Movement Travel Award 2009

- A. Lolordo. “True grit, plenty of gumption.” *The Baltimore Sun* 7 Feb 2009.
- Ruth L. Kirschstein National Research Service Award (NRSA) 2008
- K. Jackson. Interview with Sarah Hemminger (IMP Founder) and Judeith James (IMP Student). WJZ Channel 13 News. 20 Jan 2008
- Whitney M. Young Award 2007
- Neuroengineering Training Initiative Trainee: 2004-2007
- Human Brain Mapping Travel Award Recipient 2006
- Martin Luther King Jr. Award 2005
- Johns Hopkins University SOURCE Volunteer Award 2004
- Baltimore Albert Schweitzer Fellow 2003-2004
- The Dean’s Undergraduate Research Award 2002
- Dean’s List: Spring 2001, Fall 2001, Spring 2002
- The Provost Undergraduate Research Award 2001
- Business and Professional Woman’s Club Scholarship 1999
- Vice Admiral E.P. Traver’s Scholarship 2001
- American Council on Italian Matters: 1999-2000 & 2000-2001

CONFERENCE PROCEEDINGS

- Crisicmagna-Hemminger SE, Orban de Xivry JJ, Shadmehr R Role of the primary motor cortex in the fast and slow adaptive processes. Johns Hopkins University. *Progress in Motor Control 7th Annual Meeting.* Marseille, France, July 2009.
- Criscimagna-Hemminger SE, Bastian AJ, Shadmehr R. Linking the Cerebellum to Multiple Timescales of Motor Memory. Johns Hopkins University. *Neural Control of Movement 19th Annual Meeting*. Kona, HI, May 2009.
- Criscimagna-Hemminger SE and Shadmehr R. Consolidation patterns of human motor memory. Johns Hopkins University. *Society for Neuroscience Meeting.* Washington D.C., November 2008.
- Criscimagna-Hemminger SE and Shadmehr R. The multiple timescales of acquisition and forgetting of motor memories. Johns Hopkins University. *Society for Neuroscience Meeting.* San Diego, CA, November 2007.
- Hemminger SE, Diedrichsen J. and Shadmehr R. Learning and Generalization to Visual Rotations with and Without Online Corrections. Johns Hopkins University. *Neural Control of Movement 16th Annual Meeting*. Key Biscayne, FL, May 2006.
- Hemminger SE, Diedrichsen J. and Shadmehr R. Dissociating timing and coordination of movements. Johns Hopkins University. *Human Brain Mapping*. Florence, Italy, June 2006.
- Hemminger SE, Donchin O, Ariff GD, Young ED, Shadmehr R. Intermanual Generalization of Arm Dynamics in Extrinsic Coordinates. Johns Hopkins University. *Society for Neuroscience.* San Diego, CA, October 2001.

PROFESSIONAL EXPERIENCE

- Teaching Assistant, Johns Hopkins University, Department of Biomedical Engineering, Systems Bioengineering (2006 and 2007).
- Founder and Executive Directors, Incentive Mentoring Program (IMP), Paul L. Dunbar High School (2004-present)
    - IMP empowers struggling teenagers to break the cycle of poverty, drugs and lack of education by surrounding them with "families" of 5-10 mentors who fill critical gaps in academic and social support.
    - Obtained 501C3 status and over $350,000 in funding.
    - Recruited and managed over 350 Johns Hopkins University graduate and medical student volunteers.
    - Created a four facet mentoring model strategically founded in academic assistance, community service, teamwork and customized solutions.
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- Biomedical Engineering Intern, Medtronic XOMED, Department of Research and Development (2001 and 2002).