The Role of Basal Ganglia and Redundancy in Supervised Motor Learning

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IN THE FACULTY OF ENGINEERING

by

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DEDICATED TO

My beloved parents...

CERTIFICATE

This is to certify that the thesis entitled, **"The Role of Basal Ganglia and Redundancy in Supervised Motor Learning"** is the outcome of the work carried out by Puneet Singh, for the degree of Doctor of Philosophy in the Faculty of Engineering, at the Indian Institute of Science, Bangalore, India.

The work presented here is original and has not been submitted previously for the award of any degree or diploma of the Indian Institute of Science or any other university. This work is completely based on the guidelines given by the Indian Institute of Science and is a record of the candidates own efforts.

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DECLARATION

I hereby declare that I am the sole author of this thesis. I authorize Indian Institute of Science, Bengaluru, to lend this thesis to other institutions or individuals for the purpose of scholarly research.

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Abstract

Human sensorimotor control can achieve highly reliable movements under circumstances of noise, redundancy, uncertainty, and sensory delays. Our ability to achieve reliable and accurate movements is in the fact we have a nervous system that learns these limitations and continuously compensates for them. The purpose of the thesis is to understand brain mechanisms and computations underlying supervised motor learning, its interaction with reinforcement learning and study its relation to motor variability. To address these issues, we have investigated factors influencing supervised motor learning such as neurological disease condition, the role of the reinforcement signal, motor variability and motor redundancy.

Traditionally, supervised or error-based learning and reinforcement or reward based learning are thought to be occurring at anatomically different places and have functionally separate mechanisms. By leveraging the performance of human patients with Parkinson disease and cerebellar ataxia disease, we demonstrate how the presence and absence of dopamine medication and subthalamic deep brain stimulation (STN-DBS) influenced supervised learning. Furthermore, we also show that the presence and absence of reinforcement at the end of the trial profoundly affected learning such that the difference in learning as a consequence of medication reduced significantly. These results suggest that the basal ganglia modulate the gain of supervised learning in the cerebellum based on the reinforcement received at the end of the trial.

Furthermore, we explored motor variability (thought to be an unwanted characteristic of the motor system) and investigated its significance and effect on supervised motor learning. We propose that some part of motor variability arises out of the redundancy in the joints in the human arm. We showed that greater uses of redundancy in the arm lead to faster learning across healthy subjects. We observed these both in dynamic perturbation learning and kinematic perturbation learning. Interestingly, we also found differences in the use of redundancy between the dominant hand and non-dominant hand, suggesting that the nervous system actively controls the redundancy. Furthermore, we also observed some directions in reaching are difficult to learn in comparison to others directions. To understand such behavior, we separated direction wise errors and constructed errors ellipses and found out that eccentricity of ellipse change with learning, which suggests brain while reducing errors in learning, is also trying to homogenize the distribution of errors caused by the perturbation. We also found interesting differences between redundancy and motor learning that was selectively impaired in PD patients but not cerebellar patients, possibly pointing to a role of the basal ganglia in processing of the use of redundancy in motor learning.

In summary, the results in the thesis provide experimental support for the hypothesis that the basal ganglia modulate the gain of supervised learning and exploration of redundancy aids in learning and that the redundancy component of the motor variability is not noise. In future, we hope that this relationship between basal ganglia, reinforcement, and redundancy in supervised motor learning can be leveraged to enhance motor rehabilitation and motor skills in patients with motor deficits.

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Chapter 1

Introduction

Human sensorimotor control can achieve highly reliable movements under circumstances of noise, redundancy, uncertainty, and sensory delays. Our ability to produce precise and reliable movements despite the presence of variable and highly non-linear actuators (muscles), unprecise sensors (proprioception), and slow transmission lines is due to a nervous system that adapts or learns these limitations and continuously compensates for them. In addition to motor control, the motor system also needs to possess mechanisms to deal with changes in the external and internal environment. For example, learning new skills entail the learning of new sensory-motor mappings or new control policy. Likewise, changes in the organization of the skeletal muscular system also occur with age, fatigue and disease and they also demand a reconfiguration of existing motor commands. Motor learning involves the ability to construct or improve sensorimotor mappings or strategies, and reliably achieve desired goals.

Typically, natural motor learning, for example, learning to drive bicycle, learning to serve in badminton, or learning a bipedal walk are difficult to study and comprehend in a laboratory environment because such learning process involves large time scales and are experimentally hard to control. In a laboratory envi-

ronment, motor learning is typically studied in the context two major paradigms: supervised learning, and reinforcement learning [1]. In supervised learning tasks, subjects have to learn new sensorimotor mapping whereas, in reinforcement learning tasks, subjects have to learn a new control policy for controlling movements. In these lab paradigms, healthy human subjects show a monotonic improvement in performance by a systematic reduction in errors. This trial to a trial decrease in errors is referred to as motor learning and can be easily quantified.

Motor learning in the context of supervised and reinforcement learning is typically thought to be derived from two primary and independent sources of information, namely errors signals and reinforcement signals (see Figure 1.1). Error information based learning is called supervised learning and reward information based learning is called reinforcement learning. In other words, in supervised learning, the learning occurs due to minimization of the differences between predicted and actual sensory feedback termed the error signal. On the other hand, the learning that occurs by selecting the motor commands that maximize the reward or minimize the punishment is defined as reinforcement learning.

1.1 Supervised motor learning

To execute movements reliably and faster under sensory delays, uncertainty, and noise (motor control), the brain appears to predict two kinds of information. First, given the desired change in sensory state, it predicts the motor commands that are likely to produce the desired movement by using the sensory information about the goal. These sensory to motor predictions are thought to reflect the computations made by an inverse model [2, 3, 4]. Similarly, given the desired motor command, the brain is believed to predict the sensory consequences of those

[1] Other forms of learning such operant conditioning, Pavlovian conditioning learning, and unsupervised learning while being important in their own right, are beyond the scope of the current thesis.

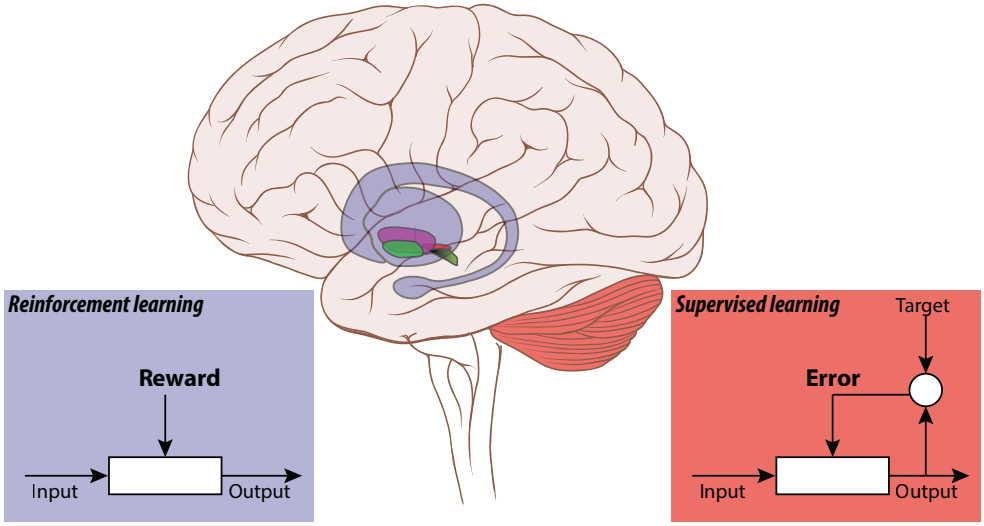

Figure 1.1: Illustration of two major types of learning. The cerebellum (in red color), specialized for supervised learning (model-based learning), predicts the error signal. The basal ganglia (in blue), specialized in reinforcement learning (model-free learning), predicts the error in anticipated and actual reward (figure adapted from Doya et al. 2000 [1]).

motor commands. A forward model is believed to generate these desired motor command to sensory consequences of action and reflects a prediction. These predicted sensory consequences can be compared with the actual sensory feedback to generate a composite error signal that can be used to control the motor command as the movement is executed.

The inverse model and forward model are collectively termed as internal models of actions [5]. If these models are accurate, they are capable fo generating valid motor commands even in the absence of sensory feedback, which is often delayed by more than 100 ms. However, motor commands are notoriously noisy as are the muscle actuators and sensory feedback is desirable to minimize or mitigate the presence of such noise. Thus it is envisioned that in addition to a feedforward motor command, sensory feedback also provides an additional control signal to update the ongoing motor command. While this computational

architecture provides a mechanism for motor control, independent feedforward and feedback control in and of itself does not change the internal model per se. However, their integration (see Figure 1.2) provides an error signal which is the difference between the sensory and actual feedback which can be used to update the internal models and forms the basis of supervised motor learning. Thus when subjects are exposed to a new paradigm to learn or adapt, due to the inaccurate internal model of new tasks errors are repeatedly experienced. Then brain tries to construct or update the internal model, and error signal serves as teaching signal to govern the learning. Such mechanisms of learning constitute supervised motor learning [6, 7, 8, 9].

1.1.1 Types of supervised motor learning

Typically two kinds of learning paradigms are used to study supervised learning in a laboratory setting. The first type of learning involves a kinematic perturbation, where the relationship between sensory input and motor output is perturbed, for example, a visuomotor rotation, visuomotor reversal, or visuomotor gain amplification [11, 12, 13]. In visuomotor learning tasks, a subjects hand position is coupled with a cursor on the screen. On a given trial, one of the targets will appear on the screen and subject has to move the hand so that the cursor reaches the target. In the baseline period, the mapping between cursor and hand is congruent such that wherever the hand goes the cursor will move accordingly. However, in perturbation trials, the standard mapping between cursor and hand is rotated by 45 degrees. Such a perturbation will typically result in a movement error since the final position of the cursor will be 45 degrees apart from the target location as illustrated in Figure 1.3A. However, as a consequence of learning, the brain will learn to compensate for this perturbation in approximately 50 to 100 trials such that the cursor will eventually start moving directly towards the target. Such learning is thought to occur in an extrinsic coordinate system because errors are

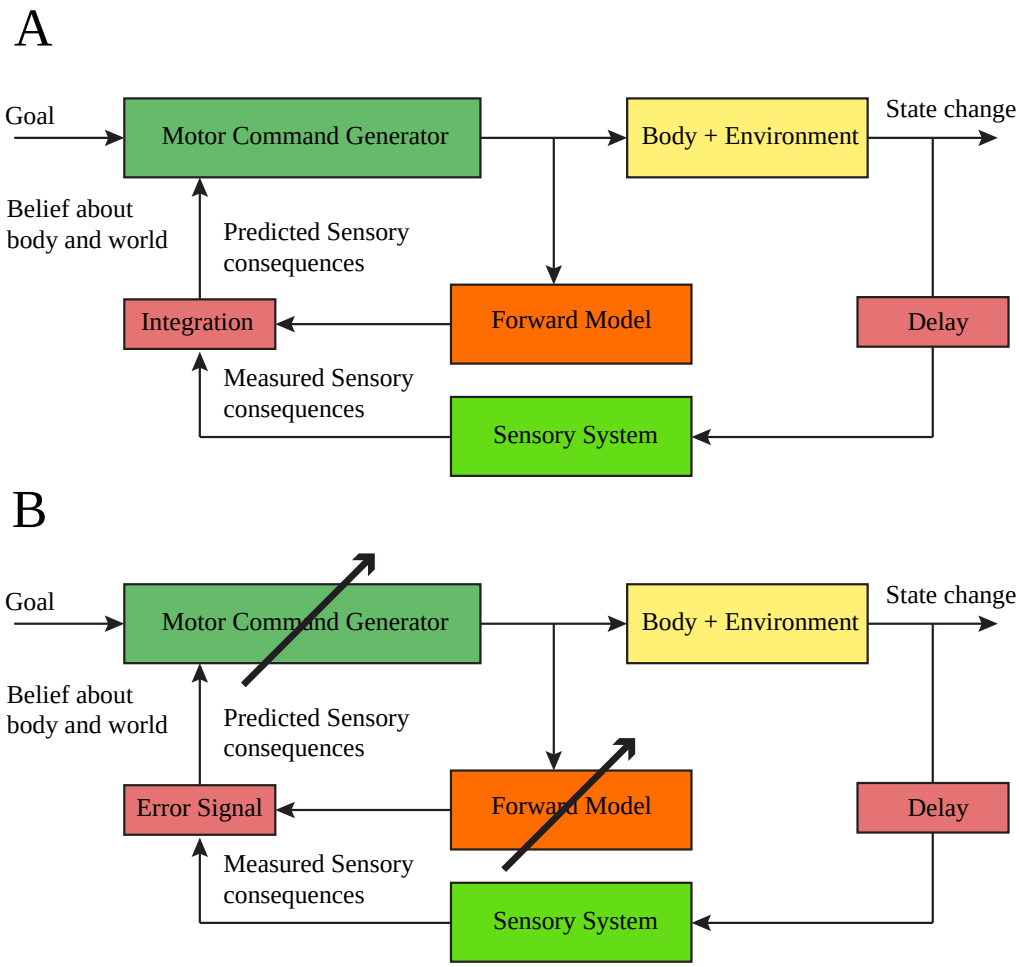

Figure 1.2: Internal models for motor control and motor learning. (A) The learning composed of two compensatory processes. Predict the motor commands that likely to make desired movement. Given desired motor command, predicts the sensory consequences of that motor commands. (B) Internal models for motor learning capability of updating the forward model and feed-forward motor commands. (figure adapted from Shadmehr et al. 2010 [10]).

caused in the extent and direction of movement as seen on the screen, and hence visuomotor rotation tasks are also called kinematic learning tasks.

The second type of motor learning studied in the laboratory involves a dynamic perturbation, where an external applied force changes the physical characteristics or dynamics of the motor system. Such perturbations often involve the use of force-fields and the addition of external loads [14, 15, 16]. Such dynamic errors are thought to be learned in an intrinsic coordinate system because the sensory prediction error is thought to be proprioceptive in nature. In force-field learning tasks, subjects have to move a robotic arm with their hand. On a given trial, one of the targets will appear on the screen and subject has to move the robotic arm to the target. In the baseline period, the robotic arm does not apply any external force. However, in perturbation trials, the robotic arm applies forces on the subjects arm, which moves the hand in a distorted trajectory that leads to an error as illustrated in Figure 1.3B. As a consequence of motor learning the brain will gradually learn to compensate for this perturbation in approximately 50 to 100 trials eventually producing movements directed towards the target with minimal error. In such tasks, subjects have to learn a new sensory to motor transformation based on the structure of the task.

Evidence in the literature, suggests that kinematic and dynamic learning are independent mechanisms resulting from updating different internal models [17]. In contrast, some studies indicate the presence of interference between kinematic and dynamic learning and raise the possibility of a single internal model for kinematic and dynamic learning [18, 19]. Thus whether kinematic and dynamic learning occurs via a single internal model or separate internal models, remain an open question in the field of motor learning.

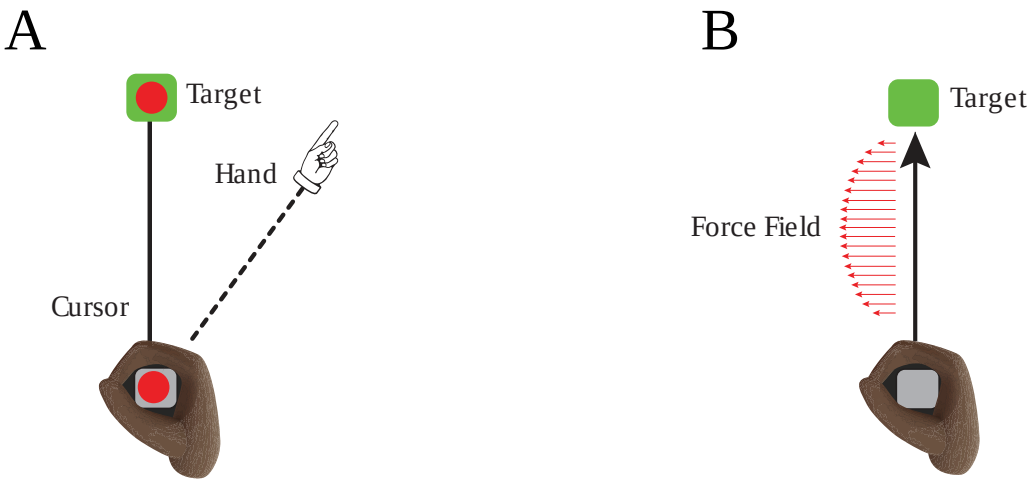

Figure 1.3: Kinematic and Dynamic supervised learning. Both paradigms require subjects to make reaching movements to targets (green color). (A) Kinematic learning paradigm involves learning a new relationship between actual hand position and the visually shifted cursor (red color). This perturbation causes a perception error between actual hand positions and perceived hand position. (B) Dynamic learning paradigm involves the learning of a new relationship between the motor commands and an arm movement. This perturbation causes a discrepancy between the predicted and actual motor commands required to counter the perturbation.

1.1.2 Neural basis for supervised motor learning

The cerebellum has been widely implicated to be critical in motor learning. The earliest critical evidence for the involvement of the cerebellum in supervised learning came from human patients with cerebellar disease. When cerebellar disease patients where asked to throw darts at a target while wearing wedge prism spectacles they were unable to adapt to the induced visuomotor perturbation compared to healthy controls [20]. In this experiment, the wedge prism caused a perturbation in the form of visual shift and patients have to learn the new relationship between actual hand position and target location as illustrated in Figure 1.4. Furthermore, patients with lesions of the mossy fibers, the cerebellar peduncles, and

the inferior olive showed similar impairments in supervised learning [20]. These studies indicated that the whole cerebellum contributes to or is responsible for supervised learning. Furthermore, studies in patients with cerebellar lesions or cerebellar ataxia also have shown deficits in both kinematic learnings [21, 22] and dynamic learning [23, 24]. Additionally, the cerebellum is also thought to be a potential candidate for representing internal models [2, 7, 25]. The deficit in supervised learning is thought to be due to the inability of the system to update the forward model and not due to failure in computing the inverse model [26]. Interestingly, patients with basal ganglia diseases, for example, Parkinsons and Huntington diseases patients show no deficit in supervised motor learning. However, savings or consolidation is absent in c disease patients [27, 28, 29], which indicate that other processes may also be involved in supervised learning for the consolidation of motor memories.

The circuit of the cerebellum is mostly feed-forward in nature as illustrated in Figure 1.5. In the cerebellum, the mossy fibers carry input, which includes both sensory and cerebral afferent signals and the granule cells combine different mossy fibers and work as expansion encoders. The parallel fiber takes input from granule cells and converges to Purkinje cells and climbing fibers. Purkinje cells receive approximately two million connections through parallel fibers and only one climbing fiber. This circuitry of parallel fiber inputs and climbing fiber inputs are distinguished as two different forms of spikes. The simple spikes from Purkinje cells encode movement related signals, and complex spikes generated from the input of the climbing fiber encode for the error signal. Hence, the cerebellum is proposed to be specialized for supervised learning based on the capability of the climbing fibers to encode an error signal. Furthermore, evidence from the vestibular-ocular reflex (VOR), which is a reflex to stabilize images on the retinas during head movement by producing eye movements in the direction opposite to

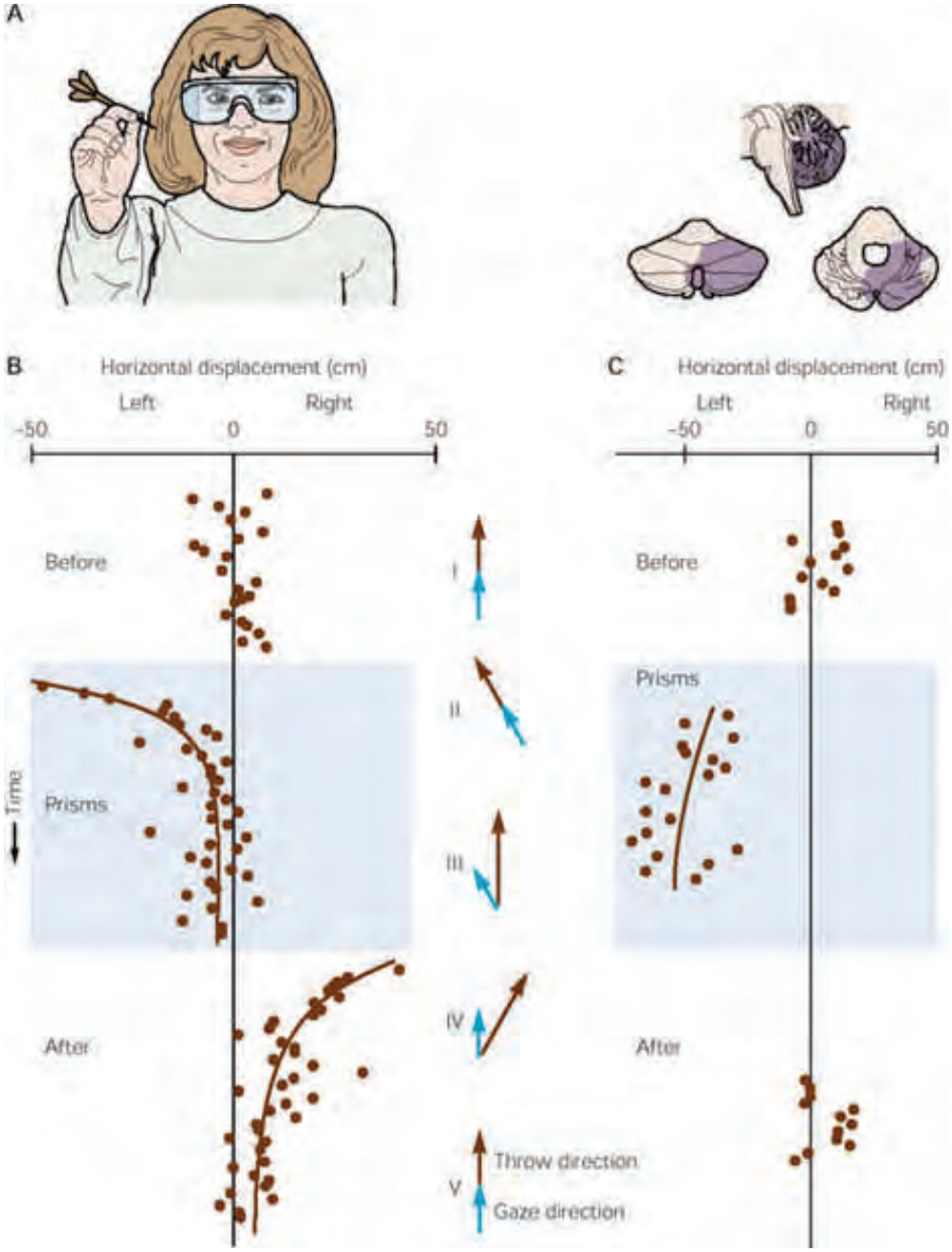

Figure 1.4: Supervised motor learning with prism glasses. (A) Wedge prisms bend the optical path to the subject's right causing a visual shift. (B) Error in throwing the dart before learning, during learning, and after learning is shown for a representative healthy subject it demonstrates the progression of learning across trials. (C) Error in throwing the dart before learning, during learning, and after learning for a cerebellar disease subject. The errors indicate that no learning occurs in these subjects. (figure adapted from Kandel et al. 1998)

head movement also implicates the cerebellum. During the learning of the VOR which involves a change in the gain of the oculomotor response, Purkinje cell synapses elicit the long-term depression (LTD) following climber fiber simulation, suggesting that the climbing fiber input is the neural substrate of such error-based learning [30]. Neurophysiological recordings from cerebellum also demonstrated cerebellum is not directly related to motor commands per se. Instead, Purkinje cells in the cerebellum reflect the kinematic properties of the movement and not the actual motor commands [31]. Furthermore and interestingly, Purkinje cell activity precedes the kinematic state of the system, which suggests that the cerebellum could encode the internal model and predict the sensory consequences of motor commands. Interestingly, cerebellar Purkinje cells may also have motor properties and are thought to encode the gain in the VOR, thus potentially encoding an internal inverse model/ adaptive motor controller as well.

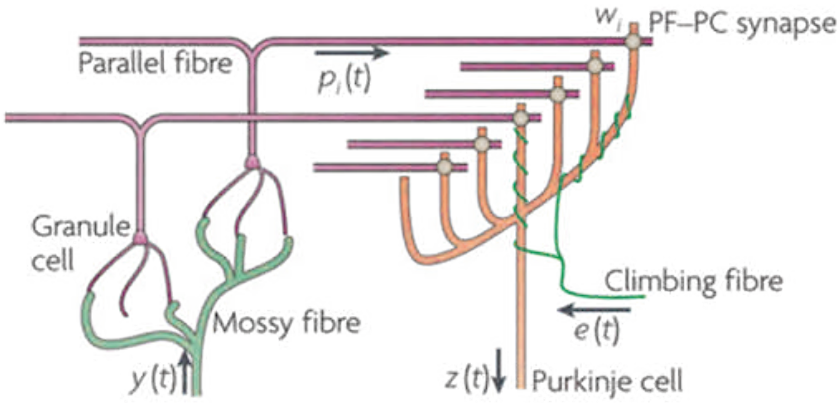

Figure 1.5: The circuit of the cerebellum. Mossy fibers input carry both sensory and cerebral afferent signals. Granule cells combine different mossy fibers. The parallel fiber takes input and converges to Purkinje cells and climbing fibers. (figure adapted from Doya et al. 1999 [32]).

1.2 Reinforcement motor learning

In contrast to supervised motor learning, learning through trial and error to explore the space of potential actions and track which action leads to a beneficial outcome is called reinforcement learning [33, 34, 35]. In reinforcement learning tasks, subjects have to move the hand toward the target and learn the trajectory or movement which maximizes reward in the absence of any cursor feedback. After successful trials subjects receive a graded or binary reward based on the prescribed value function. In the baseline period, the mapping between virtual cursor and hand is congruent just as in the case of the similar to supervised motor learning task. However, in perturbation trials the mapping between the virtual cursor and hand is rotated by some prescribed value and feedback about success and failure in a trial is given by reward or punishment. As a consequence of learning the brain gradually compensates for the induced perturbation and in approx 50 to 100 trials makes the desired movement that maximizes reward.

1.2.1 Neural basis for reinforcement motor learning

Reinforcement learning, particularly in the context of learning new actions has been traditionally thought to be instantiated by the basal ganglia [34, 36, 37]. The first clear evidence for the role of dopamine in reinforcement learning was derived from a Pavlovian conditioning task in which monkeys learned stimulus-reward continencies. In their pioneering studies, Shultz and coworkers [38, 39] showed that, monkeys did not associate the stimulus with reward with dopamine neurons in the substantia nigra pars compacta within the basal ganglia. the neurons responded to after the reward. However, after monkey learns the task, dopamine neurons start to respond only to the conditioned stimulus instead of responding to actual reward. Unexpected withdrawal of reward after learning, however, produced a decrease in the firing rate of dopamine neurons. Thus the

activity of dopamine neurons not only encode immediate reward but also a prediction of future reward [40]. More interestingly, the capability of encoding the prediction of future reward and comparing it with actual reward received allows the dopamine cells to encode a reward prediction error signal that in principle can drive reinforcement learning. Further, the change in control policy (namely, sensorymotor mapping) that tries to maximize the expected sum of future reward it is commonly thought to brought about by changes in the synaptic strength of the cortico striatal synapses enabled by dopaminergic input into the striatum [41].

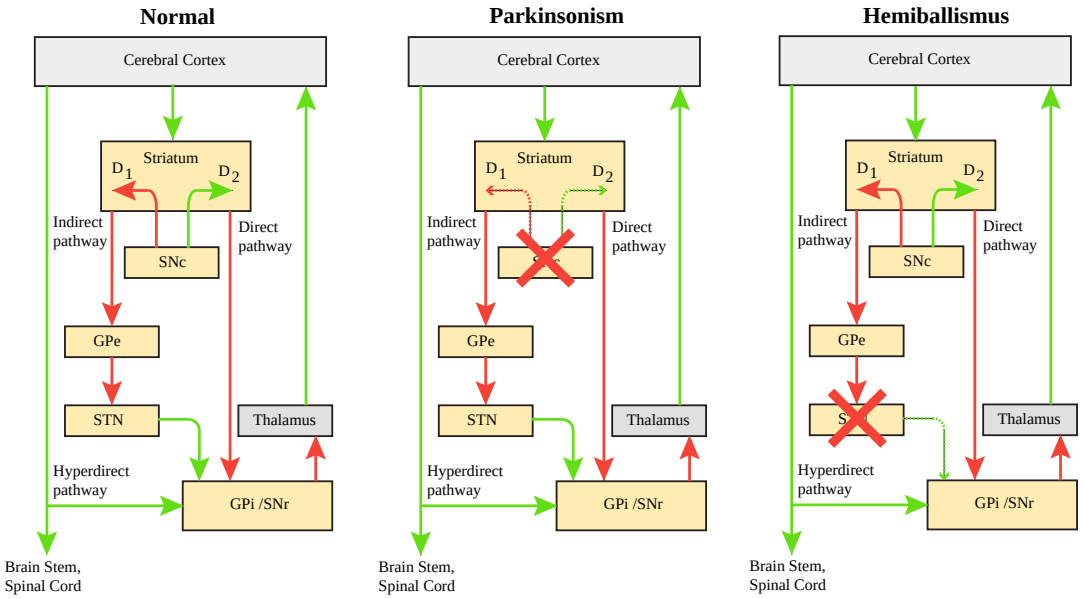

Figure 1.6: Neural circuit of the basal ganglia. STN represent subthalamic nucleus; SNc represents substantia nigra pars compacta; SNr represents substantia nigra pars reticulate; GPi represents an internal segment of globus pallidus; GPe represents an external segment of globus pallidus; Red color represents inhibitory connection; Green color represents the excitatory connection..

In addition to motor learning, the basal ganglia are a collection of smaller and higher interconnected nuclei that are intimately associated with motor control. The subthalamic nucleus (STN) is an integral part of the indirect pathway

involved in response inhibition and cognitive control. The striatum receives the main input from the cerebral cortex and project to direct and indirect pathways, both pathways work complimentary to each other. The outputs of substantia nigra pars reticulata and an internal segment of globus pallidus are directed through the thalamus to specific areas in the cerebral cortex as illustrated in Figure 1.6. In addition to modulating synaptic strength, dopamine released from the substantia nigra pars compacta differentially influences the balance of activity between the direct and indirect pathways by inhibiting the indirect pathway via D2 dopamine receptors and facilitating transmission in the direct pathway via D1 dopamine receptors. High activity of the indirect pathway relative to the direct pathway leads to hypokinetic state such as Parkinsonism (Figure 1.6). Similarly, lesions of the subthalamic nucleus (STN) and an increase in activity of the direct pathway relative to the indirect pathway causes hyperkinetic syndromes such as hemiballismus and chorea as illustrated in Figure 1.6.

Interestingly long term change in the dopamine content due to loss of dopaminergic neurons in the substantia nigra causes a Parkinson disease (PD) and restructures the circuitry [42, 43]. Parkinson disease patients show deficits in reinforcement learning tasks, indicating that basal ganglia are responsible for reinforcement learning. Consistent with the idea that the loss of dopamine as a consequence of Parkinsons disease potentiates the indirect pathway [44], lesions and high-frequency stimulation of the subthalamic nucleus both attenuate the symptoms of Parkinsons disease such as resting tremors. Nevertheless, whether deep brain stimulation of the subthalamic nucleus modulates reinforcement learning is not known.

1.3 Independence and interdependence of supervised and reinforcement motor learning

As explained earlier, reward prediction errors are at the heart of reinforcement learning, while a sensory prediction error signal is necessary for supervised learning. In contrast, supervised learning that relies on an error in predicted sensory feedback and reinforcement learning is thought to based on an error in predicted reward function. The goal of reinforcement learning is to determine the optimal value function to guide learning. Learning in reinforcement learning is typically very slow, even for basic tasks, because the exploration of the environment is necessary to achieve optimal policy. On the other hand, reinforcement learning requires relatively simple computations because reward functions experience directly lead to changes in the control policy. In contrast, supervised learning needs to update the forward model and then cause a change in the control policy. Thus, in contrast to supervised learning, no washout effect is observed because of the absence of any update in the internal model since only the control policy is expected to adapt. Similarly, reinforcement learning also does not show any form of generalization in learning, but the generalization is an important feature of supervised motor learning [45]. Generalization allows motor learning in a specific environment to extrapolate to an unfamiliar environment without any further training. For example, a subject who learns to compensate for perturbation in one direction will be able to generalize the perturbation in all other directions [46, 47]. Reinforcement learning does not show generalization while supervised learning does, which again suggest both are independent mechanism for motor learning.

On the other hand, a recently discovered bidirectional anatomical pathway between the cerebellum and basal ganglia [48, 49] suggests that these structures

may not necessarily be independent information processing units as have been typically assumed. In particular, it was shown [49] that the cerebellum sends a strong di-synaptic projection to the striatum through the thalamus, while STN sends a di-synaptic projection to the cerebellar cortex by way of the pontine nuclei.Indeed, a functional prediction of such crosstalk is the presence of common symptoms exhibited by diseases of the basal ganglia and cerebellum [50].

However, contrary to the conventional view that supervised learning is independent of reinforcement signal growing evidence suggests that supervised learning involved a combination of reinforcement and supervised learning [51, 52]. A recent study Galea et al. 2015 [53] has shown how graded reinforcement and punishment can differentially modulate learning in a supervised learning task (visuomotor rotation). In this study, graded reward feedback did not speed the learning, but it increased the retention of learning and graded punishment accelerated learning but with poor retention of learning as illustrated in Figure 1.7. In contrast, another recent study found binary reward did not affect supervised learning [54]. These findings raise the possibility that multiple independent learning mechanisms may play a role in supervised learning and raise new questions about the interaction between reinforcement and supervised learning. The first aim of this thesis attempts to address these issues.

1.4 Motor learning and motor control

As explained earlier, internal models were proposed to understand how the motor system can function reasonably well despite noise and inherent delays in sensory feedback. Such internal models generate an error signal based on the difference between predicted and actual sensory feedback and thus minimize error for optimal motor control. An additional feature of such internal models is the ability of the error signal to modify the internal models or control policies allowing the

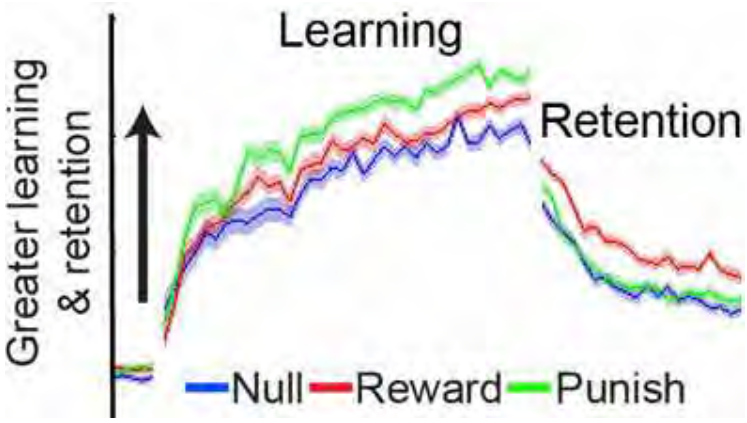

Figure 1.7: Effect of reinforcement signal on supervised learning. The errors in the pre-learning (baseline), visuomotor learning, and post-learning across three groups. Red indicates reward group, which received a reward after the correct trial, green indicates punishment group, which received punishment after the wrong trial and blue indicates random group, which received reward and punishment randomly across trials. (figure adapted from Galea et al. 2015 [53])

same representations to help in the motor control and motor learning. An intimate relation between motor learning and motor control is also supported by neuropsychological, neuroimaging and neurophysiological studies showing shared neural representations. Thus the cerebellum and the basal ganglia are implicated in both motor learning and motor control. Likewise, deficits in these neural structures also cause a shortfall in motor control function. For example, cerebellum patients (ataxia diseases) have dis-coordinated movements and basal ganglia patients with Parkinson disease have tremors or high stiffness.

1.4.1 Motor variability and motor learning

A particular unwanted attribute of motor control is a trial to trial variability. In beginning of motor task motor variability is high, but as motor learning progress

the motor variability reduced as the motor system learned the task as illustrated in Figure 1.8. Note that as motor system learned the tasks and motor variability reduced but it never goes to zero. The source of variability is thought to be the inherently stochastic nature of the nervous system and the noise in the sensory, motor or sensory-motor systems. It is widely believed that motor control tries to minimize this variability to achieve movements accurately [55, 56]. On the other hand, motor variability has also been shown to help in both types of motor learning (reinforcement and supervised learning) [57, 58, 59]. As motor variability increases in subjects, the amount of motor learning ability also increases. This is shown in figure 1.9. There is a positive correlation between motor variability and motor learning across subjects. For example, when the subject is trying to find the toy with eyes closed; they begin by exploring the space of all possible locations with a significant amount of variability in their movements. Once they hit the toy, the subject changes his/her strategy to exploitation, in which the same movements are repeated (Figure 1.10). In such context, motor variability is believed to be a source of exploring in motor space as illustrated in the example.

Along the same lines, in songbirds, motor variability and motor learning ability are reduced by inactivating lateral magnocellular nucleus (LMAN) [60, 61]. Such experiments seem to suggest that motor variability is not just noise in the system. These studies indicated variability might be a deliberate output of the motor control, which is an essential feature for exploration of the task space to find the optimal response. In contrast, other recent studies did not find any clear relationship between motor variability and motor learning [62]. Thus the relationship between motor variability help in motor learning remains unclear. Exploring this relationship is a second aim of this work.

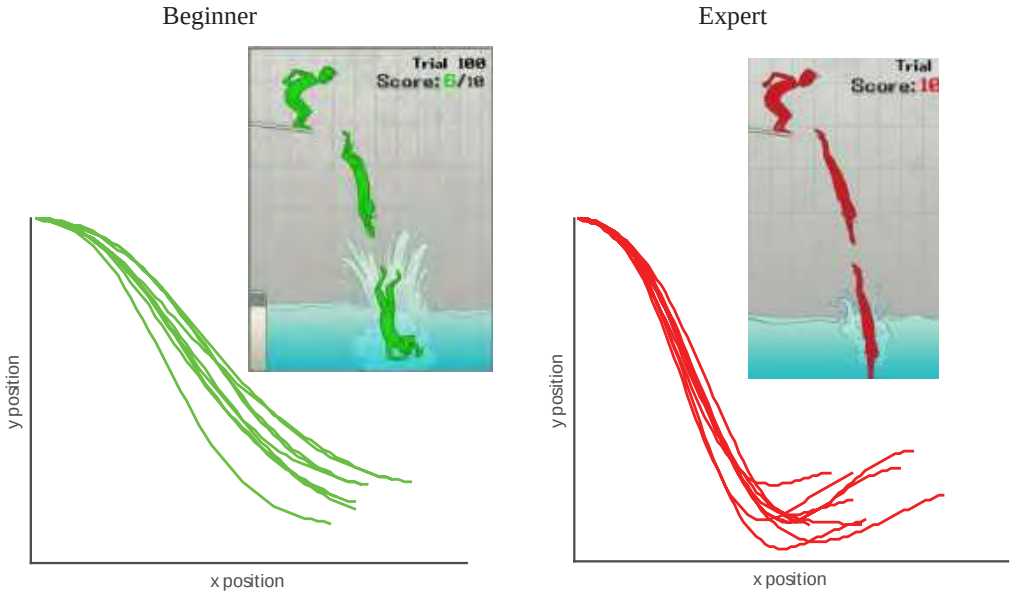

Figure 1.8: The beginner vs. expert motor variability in motor learning. In begging motor variability is high as illustrated in the green color scheme, but as motor learning progress the motor variability reduced as the motor system learned the task as shown in the red color scheme. Note that as motor system learned the tasks, motor variability reduced but it never goes to zero.

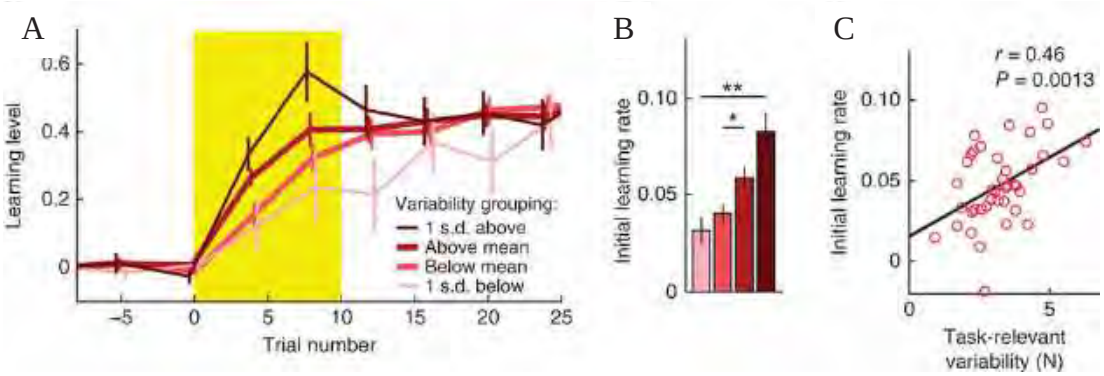

Figure 1.9: Motor variability helps in motor learning. (A) The errors in the pre-learning (baseline) and force-field learning across groups (groups divided based learning level). (B) Group by group comparison of motor learning. (C) Subject by subject variability correlation with learning. (figure adapted from Wu et al. 2014 [59])

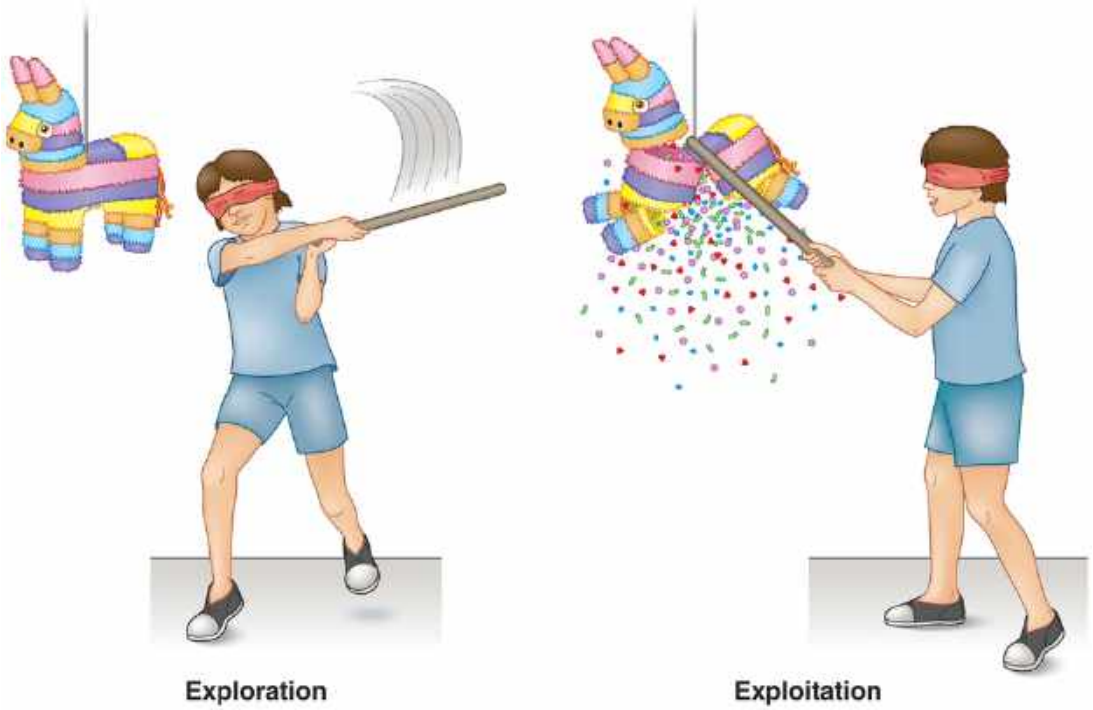

Figure 1.10: Exploration vs exploitation in motor learning. Motor variability in motor learning, the subject is trying to find the toy with eyes closed; the subject begins by exploring the space of all possible locations, with higher motor variabilities. Once they hit the toy, the subjects change their strategy to exploitation, in which the same movement repeated. (figure adapted from David et al. 2014 [63])

1.5 Thesis objectives

The principal purpose of the thesis is to understand brain mechanisms and computations underlying the mechanisms in supervised motor learning, its interaction with reinforcement learning and study its relation to motor control/variability. To address these issues, we have investigated factors influencing supervised motor learning such as neurological disease condition, the role of the reinforcement signal, motor variability and motor redundancy.

1.5.1 Role of basal ganglia in supervised learning

A common understanding is that cerebellum controls supervised learning and basal ganglia control reinforcement learning. Contrary to this understanding, we show a role of the basal ganglia in supervised learning (error-based motor learning) by leveraging the performance of patients with Parkinsons disease and cerebellar ataxia disease. We also demonstrate that reward, traditionally believed to be a part of reinforcement learning, is also an essential component of supervised learning. Furthermore, we have also tested patients with Parkinsons disease (PD) who had undergone deep brain stimulation (DBS) of bilateral STN (sub-part of basal ganglia) in a supervised learning task to understand the role of basal ganglia in supervised learning.

1.5.2 Role of variability in supervised learning

Motor variability is the ubiquitous and unwanted property of the motor control, which needs to be suppressed by practice. On the other hand, recent theories of motor learning claim that motor variability facilities motor learning. In this thesis, we demonstrate that motor variability does not facilitate supervised motor learning. In an attempt to reconcile these apparently contradictory positions, we have proposed that motor variability has two components: one caused by redundancy (due to multiple degrees of freedom provided by the joints) and another component that is random noise. In this work, we explored motor redundancy component and investigated its significance and effect on supervised learning. We demonstrate that a greater use of redundancy was correlated to faster learning across subjects. We tested this hypothesis in dynamic perturbation learning and kinematic perturbation learning. Furthermore, to identify the neural substrate for exploration of redundancy in supervised learning, we have tested patients with Parkinsons disease and cerebellar ataxia disease.

1.6 Contributions of the thesis

The main contribution of the thesis are the following findings:

- Supervised motor learning is modulated by the presence/absence of dopamine and deep brain stimulation in Parkinsons disease patients.
- Reinforcement given at the end of the trial is an essential component that may modulate the gain of supervised motor learning.
- The motor variability component resulting from joint redundancy may assist both dynamic and kinematic learning ability across healthy subjects without affecting task-space variability.
- The differences in learning of novel dynamics by the dominant and non-dominant hand in healthy subjects suggest that the nervous system actively controls the redundancy.
- Differences between the correlation of redundancy and motor learning that was selectively impaired in Parkinsons disease patients but not in cerebellar impaired patients possibly points to a role of the basal ganglia in processing the use of redundancy and exploration in motor learning.

1.7 Preview

The thesis contains 4 chapters: In chapter 1, the motivation and relevant literature on motor learning is presented and discussed in detail. Chapter 2 presents the role of basal ganglia in supervised motor learning. In chapter 3, the role of motor variability in supervised motor learning is presented. Finally, Chapter 4 presents the conclusions and presents the scope for future work.

Chapter 2

Role of basal ganglia in supervised learning

2.1 Introduction

Traditionally, supervised learning (error based) and reinforcement learning (reward based) are thought to be anatomically and functionally separate mechanisms [1, 32, 45, 64]. While the mechanisms underlying supervised learning is thought to involve minimizing the differences between the predicted and actual sensory feedback [5, 14, 17]; reinforcement learning is believed to occur by selecting the motor commands that maximize reward or minimize punishment [59, 65, 66]. The supporting evidence for this hypothesis derives from a motor learning experimental study with visuomotor rotations. These experiments resulted in a recalibration of proprioception for supervised learning but not for reinforcement learning [51, 67]. Additionally, the retention of the learned motor skill appears to be selectively stronger for reinforcement learning than supervised learning.

Supervised and reinforcement learning is also thought to have distinct anatomical representations involving the cerebellum and the basal ganglia, respectively

[1]. In support of this notion, patients with focal cerebellar damage show selective impairments in supervised learning [21, 22, 25]. However, they show little impairment during reinforcement learning of the same task [66, 68]. Meanwhile, Parkinsons disease (PD) patients having impairments in their basal ganglia (on dopaminergic medication) show no impairment in supervised learning [27, 28].

The conventional view is that supervised learning is independent of reinforcement learning. However, the existence of bidirectional anatomical pathways between the cerebellum and basal ganglia [48, 49] suggests that these structures are not necessarily independent information processing units. In particular, it has been shown [49] that the cerebellum sends a strong di-synaptic projection to the striatum through the thalamus, while the subthalamic nucleus sends a di-synaptic projection to the cerebellar cortex by way of the pontine nuclei. These anatomical connections suggest that both are not independent of each other.

Consistent with this view it has been shown that PD patients without dopaminergic medication also show impairment in supervised learning [69, 70, 71]. This is in contrast to the finding that PD patients on dopaminergic medication show no impairment in supervised learning [27, 28]. One possible hypothesis that could explain this discrepancy is that reinforcement by dopamine differentially influences motor learning [53]. This leads to the hypothesis that the basal ganglia might modulate the cerebellums sensitivity to errors, thus priming the cerebellum to weight its predictions or to update its forward models based on predicted reward.

To test this idea and better understand the role of basal ganglia in the modulation of supervised motor learning, we manipulated the extent of dopamine, subthalamic nucleus, and reinforcement to study its effect on supervised learning. We tested PD patients with and without medication, with and without reward, and with and without deep brain stimulation of the subthalamic nucleus.

2.2 Materials and methods

In this section, the experimental procedure and experimental setup is discussed.

2.2.1 Subjects

A total of 116 (64 patients and 52 healthy) individuals participated in this study. Patients were recruited from the neurology outpatient clinics and movement disorders services of the National Institute of Mental Health & Neurosciences, Bangalore, India. For Experiment 1, we recruited 20 patients with autosomal dominant cerebellar ataxia and 20 age-matched healthy controls. Assessment of the severity of ataxia was done by the International Cooperative Ataxia Rating Scale (ICARS) [72]. Further details about the ataxia patients characteristics and scores are shown in Table (2.1). For Experiment 2 and Experiment 4, we recruited 32 patients with idiopathic Parkinsons disease (PD) and 32 age and gender matched healthy controls. For Experiment 3, we recruited 12 idiopathic Parkinsons disease patients with bilateral STN deep brain stimulation (DBS). The diagnosis of PD was made as per the UK brain bank criteria [73]. Motor symptoms of PD were assessed by the section-III of the Unified Parkinsons Disease Rating Scale (UPDRS-III) both during OFF-medication and ON-medication states. Further details about the DBS patients characteristics and parameters of stimulation are shown in Table (2.3) and details about the Parkinsons disease patients are listed in Table (2.2) and Table (2.4). Mini-mental state examination (MMSE) [74] was used to screen participants for cognitive impairment and patients with MMSE $>$ 26 was set as an exclusion criterion. All participants had normal or corrected to normal vision and no cognitive deficits. The handedness of subjects was tested by the modified Edinburgh Handedness Index [75]. The study was approved by the Indian Institute of Science ethics review board, and all of the participants gave informed consent in accordance with the guidelines of the ethics committee.

2.2.2 Experimental setup

Participants sat on a chair with their right hand placed on the front table as shown in Figure 2.1A. They looked straight ahead onto a monitor (refresh rate 60 Hz) that displayed targets and the instantaneous hand cursor position while they moved the cursor in a horizontal plane. The experiment was performed using the Psychophysics Toolbox in MATLAB [76] that displayed visual stimuli, sampled and stored the data and other behavioral parameters. Hand positions and joint angles were recorded with a spatial resolution of 7.62 mm by using an electromagnetic position and orientation tracking device manufactured by Polhemus, US (Model-LIBERTY).

2.2.3 Experimental paradigm

For all experiments, trials were divided into three phases, namely baseline or pre-adaptation, adaptation, and post-adaptation. Each trial started with the presentation of a square fixation box (1.5 cm $\times$ 1.5 cm) at the center of the screen where the subject had to fixate the hand cursor. After successful fixation, a square target (1.5 cm $\times$ 1.5 cm) was displayed randomly in any one of 2 locations 20 cm away from the central fixation box. The subject moved their hand to the target after the fixation box disappeared. All subjects performed $\sim$10 practice trials before the experimental session. Then subjects performed the experimental paradigm with 100 trials per session, with a typical session lasting for 15-20 minutes. Trials were aborted if a premature movement was made. During the visuomotor perturbation, the cursor movement was rotated according to Equation (2.1),

$$\begin{bmatrix} P_x \\ P_y \end{bmatrix} = \begin{bmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{bmatrix} \begin{bmatrix} p_x \\ p_y \end{bmatrix} \tag{2.1}$$

where P_x, P_y correspond to the position of the cursor, p_x, p_y correspond to the actual position of the hand and θ denotes the perturbation angle about the centre of work space with theta equal to 45°. This perturbation led to a trajectory error that was gradually compensated over the course of many trials till the hand trajectory straightened again.

2.2.4 Quantifying learning

The error was calculated as the maximum perpendicular distance of the hand trajectory from the straight line joining the central fixation box to the target location. The error, denoted by $f(n)$, is related to the trial number by the following equation,

$$f(n) = a \exp(-\beta\ n) \tag{2.2}$$

The above equation represents a first-order learning process with a being a constant (which depends on the subject), n representing the trial number and β represents the natural learning rate of a subject [17, 77, 78]. To compute the population level learning in perturbation trials, errors were fitted with an exponential fit using a robust least squares method.

2.2.5 Reaction time analysis

The psychophysics toolbox (MATLAB) and the position tracking system (Polhemus) were interfaced in real time by triggering a pulse on the tracking system after target onset. Reaction time (RT) was calculated as the difference between movement onset and target onset (triggered pulse). An in-house developed code detected movement onset in MATLAB. To remove outliers, we considered Reaction time within 25th percentile - 1.5 times the inter-quartile range and 75th percentile + 1.5 times the inter-quartile range.

2.2.6 Statistical analysis

The data was assessed for normality using Lilliefors test. For pairwise comparisons between the groups, a two-tailed t-test was performed if the data was normally distributed, otherwise Wilcoxon signed-rank test was used. Comparisons of two independent groups were made using a two-sample t-test. All the correlational analyses were performed using the Pearsons correlation method.

Table 2.1: Demographics of cerebellar ataxia patients.

S. No	Age (years)	Age of onset	Sex	Diagnosis	ICARS scores
AT1	19	18	M	SCA	27
AT2	15	14	M	SCA 2	40
AT3	42	38	M	SCA	40
AT4	37	34	F	SCA 1	25
AT5	23	20	M	SCA 3	26
AT6	24	20	M	SCA 2	47
AT7	43	42	M	SCA 1	54
AT8	39	37	F	SCA	32
AT9	72	68	M	SCA 12	21
AT10	40	35	F	SCA 1	39
AT11	44	40	F	SCA 12	34
AT12	29	24	M	SCA	58
AT13	26	20	F	SCA	37
AT14	57	51	M	SCA	30
AT15	24	19	M	SCA	59
AT16	43	42	M	SCA 1	48
AT17	39	32	F	SCA	47
AT18	35	24	F	SCA 2	40
AT19	21	18	M	SCA	57
AT20	32	27	M	SCA 1	41

AT = ataxia patients group; SCA = spinocerebellar ataxia types; ICARS = International Cooperative Ataxia Rating Scale.

Table 2.2: Demographics of Parkinsons disease patients

S. No	Age	Age of onset	Sex	H &Y Index	UPDRS scores	
					Drug-OFF	Drug-ON
PD1	64	53	M	1.5	12	03
PD2	22	21	M	1.5	20	07
PD3	40	37	M	02	35	04
PD4	58	55	M	02	30	16
PD5	60	52	F	02	25	11
PD6	55	54.5	F	01	14	04
PD7	68	60	M	02	19	13
PD8	45	40	F	02	35	15
PD9	40	36	F	01	30	11
PD10	38	35.5	M	1.5	11	04
PD11	56	50	M	2.5	44	31
PD12	48	40	F	02	15	05
PD13	58	49	M	02	19	11
PD14	66	60	F	03	69	25
PD15	49	33	F	2.5	30	18
PD16	38	34	M	1.5	13	03
PD17	66	56	M	1.5	22	05
PD18	54	42	M	03	48	07
PD19	70	61.5	M	1.5	24	14
PD20	48	45	M	1.5	41	10

PD = Parkinson disease patient group; H & Y Index = Hoehn and Yahr scale; UPDRS = Unified Parkinsons Disease Rating Scale. The drug-off state was induced by withholding dopaminergic medication for at least 12 hours before the test. The drug-ON state was the best possible improvement after taking a supramaximal dose of Levodopa (usually 60-90 minutes after taking levodopa)

2.3 Results

In this section, we present role of basal ganglia in supervised learning by leveraging the performance of human patients with Parkinsons disease and cerebellar ataxia disease.

Table 2.3: Demographics of Parkinsons disease patients with deep brain stimulation.

S. No	Age	AO	Sex	Voltage		PW	Freq.	H &Y	UPDRS	
				R	L				DBS-OFF	DBS-ON
DB1	46	40	M	1.8	1.8	60	130	1.5	23	13
DB2	62	55	F	2.6	2.8	60	130	1.5	32	03
DB3	51	48	M	02	02	60	130	02	21	04
DB4	62	50	M	2	1.8	60	130	02	22	03
DB5	42	32	M	3.4	3.2	60	130	02	16	03
DB6	57	48	M	2.9	3.3	60	130	01	16	04
DB7	63	46	M	1.9	1.8	60	130	02	46	28
DB8	38	30	M	3.1	3.2	60	180	02	19	06
DB9	44	38	M	1.8	1.5	60	130	01	27	05
DB10	62	52	M	03	2.5	60	180	1.5	55	20
DB11	47	45	M	3.7	3.7	60	100	2.5	24	12
DB12	55	40	M	1.8	02	60	130	02	35	15

DB = deep brain stimulation patient group; AO = Age of onset; H & Y Index = Hoehn and Yahr scale; UPDRS = Unified Parkinsons Disease Rating Scale. To test the impact of STN stimulation only, all patients remained OFF medication for a minimum period of 12 hours before the test.

2.3.1 Cerebellum disease patients in visuomotor adaptation

To confirm the well-known role of the cerebellum in the supervised learning, we assessed the differences in learning of autosomal dominant cerebellar ataxia patients (n=20), and age-matched healthy control subjects group (n=20) in a standard visuomotor rotation task (Figure 2.1A & 2.1B). Both groups performed point-to-point reaching movements in visuomotor adaptation, along two directions presented in random order. In visuomotor adaptation experiment, the cursor was rotated by 45 degrees from the original hand trajectory. The person could not see his hand and only feedback was from the cursor location on screen. Overall, the pattern of trajectories in the baseline condition (without the visuomotor pertur-

Table 2.4: Demographics of Parkinsons disease patients without reinforcement

S. No	Age	Age of onset	Sex	H &Y Index	UPDRS scores	
					Drug-OFF	Drug-ON
NR1	60	56	M	1.5	23	13
NR2	53	48	M	1.5	32	03
NR3	56	49	M	02	21	04
NR4	52	44	M	02	22	03
NR5	57	54	M	02	16	03
NR6	57	54	M	01	16	04
NR7	56	50	M	02	46	28
NR8	47	42	M	02	19	06
NR9	56	52	M	01	27	05
NR10	77	60	M	1.5	55	20
NR11	65	57	F	2.5	24	12
NR12	43	37	F	02	35	15

NR = Parkinson disease patients without reinforcement signal group; H & Y Index = Hoehn and Yahr scale; UPDRS = Unified Parkinsons Disease Rating Scale. The drug-off state was induced by withholding dopaminergic medication for at least 12 hours before the test. The drug-ON state was the best possible improvement after taking a supramaximal dose of Levodopa (usually 60-90 minutes after taking levodopa)

bation) showed nearly straight trajectory across both groups but showed strongly curved trajectories in the presence of a visuomotor perturbation (Figure 2.1C & 2.1D). The curved trajectories gradually became straight with practice over the course of about sixty trials in the case of the healthy control group but not in the case of cerebellar ataxia group consistent with previous work (Figure 2.2A). In addition, as a consequence of the absence of motor learning, cerebellar ataxia patients group showed no washout effect in post-adaptation – washout effect is the observed change of direction of errors in the opposite direction when the visuo-motor perturbation is turned off. However, errors in the healthy control group showed the characteristic washout effect. This washout error converged to baseline levels typically within twenty trials. The reduction in maximum error as

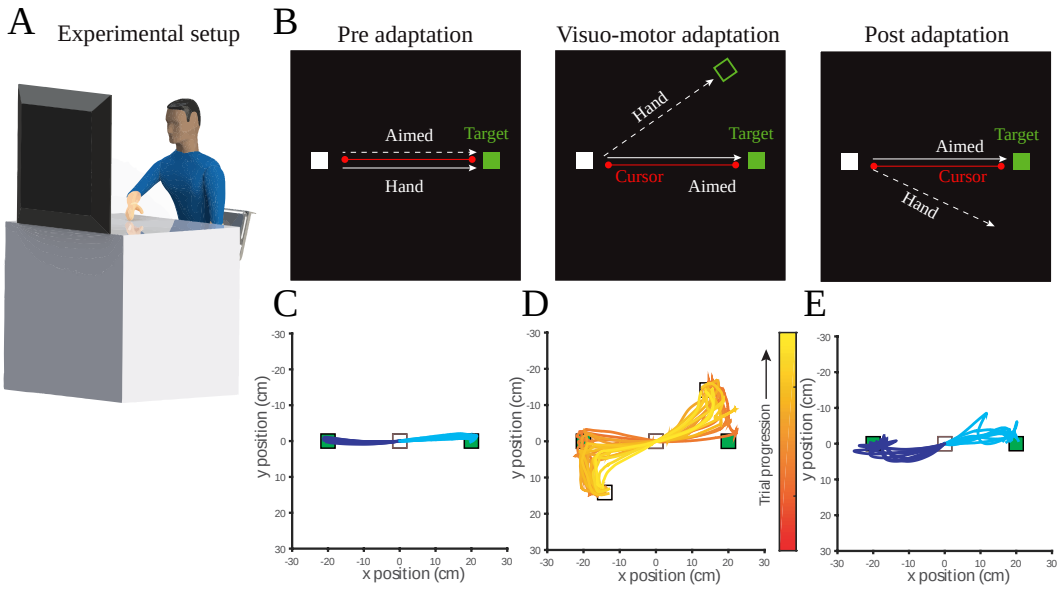

Figure 2.1: Experiment setup and design visuomotor adaptation: (A) Subjects made point-to-point reaching movements to visual targets in 2 directions, 20 cm away from the central start point, in each trial. (B) Experiments were divided into a pre-adaptation (baseline), adaptation (visuomotor rotation) and post-adaptation (washout) epochs. (C) First five pre-adaptation trials from an example subject, showing the baseline motor variability. (D) First ten visuomotor adaptation trials from the same subject, showing the disturbed hand trajectory. (E) First five post-adaptation trials from the same subject, indicating the washout effect of adaptation.

given in equation 2.2 was used as a metric to quantify the learning rate for each subject. We observed that the mean learning rate for the ataxia group (mean = 0.0071 $\pm$ 0.010) was significantly less than the mean learning rate for the control group (mean = 0.023 $\pm$ 0.015) (Figure 2.2B; p = 3.3e-4, t (38) = 3.94). This is consistent with the literature [21, 22, 25]. The difference in learning rate between the cerebellar ataxia group and healthy control group indicates the vital role of the cerebellum in supervised learning.

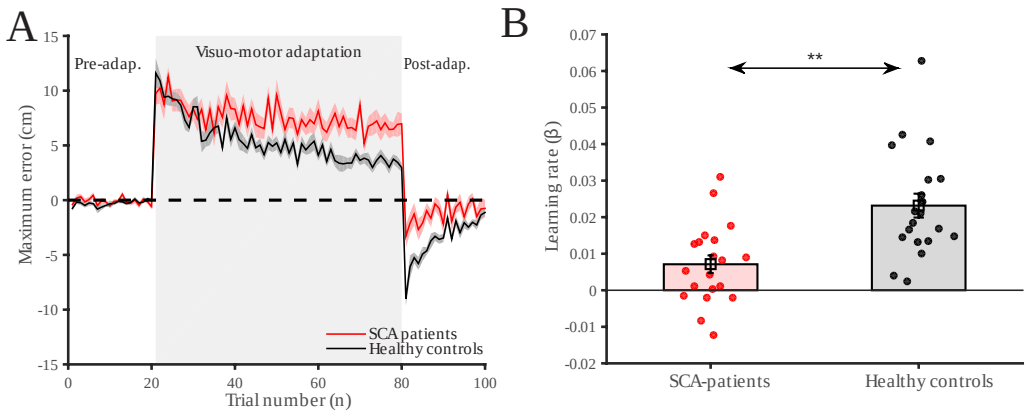

Figure 2.2: Ataxia patients in visuomotor adaptation. (A) Maximum error in pre-adaptation, visuomotor adaptation, and post-adaptation across Ataxia patients (n=20). Red indicates Ataxia patients and black indicates healthy controls. (B) Learning differences in Ataxia patients (red) and healthy controls (black) (n=20) reveal faster learning in healthy controls. Solid lines indicates mean and error bars or shaded areas are SEM ($*P < 0.05; **P < 0.005; ***P < 0.0005$).

2.3.2 Parkinsons disease patients in visuomotor adaptation

Parkinsons disease (PD) is classically considered as a primary basal ganglia disease occurring due to death of dopaminergic neurons, and we used the performance of PD patients relative to controls as a proxy of basal ganglia contribution to supervised motor learning. We trained Parkinsons disease patients (n=20) and age-matched healthy control subjects (n=20) on the same two directions visuomotor rotation task as the cerebellar ataxia patients. To test the impact of dopaminergic medication, all PD patients were tested in two sessions: OFF medication and ON medication. PD-OFF medication was defined as being off medication for 12 hours before the test, and PD-ON medication was defined as being tested within 1 hour after medication. To avoid confounds due to the transfer of learning between sessions, the order of testing between ON and OFF medication were counterbalanced.

Overall, the pattern of hand trajectories in the baseline condition showed nearly straight trajectory across groups, and they show strongly curved trajectories in the presence of a visuomotor perturbation (Figure 2.3A). The curved trajectories gradually became straighter with practice, over the course of about sixty trials, in the control group and PD-ON medication group but not in the case of PD-OFF medication group. In addition to this, as a consequence of no motor learning, the PD-OFF medication group showed no washout effect. In contrast, the control and PD-ON medication groups showed a washout effect when the learned visuomotor perturbation was turned off.

As before, the reduction in maximum error equation 2.2 was used as a metric to quantify the learning rate for each subject. We observed that the mean learning rate for the PD-OFF medication group (mean = 0.004 $\pm$ 0.010) was significantly lesser than the mean learning rate for the PD-ON medication group (mean = 0.019 $\pm$ 0.007) (Figure 2.3B; p = 1.54e-07, t (19) = 8.04). We also observed no difference in the mean learning rate between the PD-ON medication group and the healthy control group (Figure 2.3B; p = 0.54, t (38) = 0.613).

2.3.3 Parkinsons disease patients in visuomotor adaptation without reward

Although, the level of dopamine appeared to modulate the rate of learning in what is traditionally thought to be an error based task, we examined whether this modulation was a consequence of motivation provided by the auditory feedback given to subjects at the end of each trial following successful completion of the trial (i.e., the cursor reaching the target location). To test this hypothesis, we trained a new set of PD patients (n=12) in the OFF and ON medication conditions to do the same visuomotor rotation task but in the absence of auditory feedback.

Similar to the previous experiment, the pattern of trajectories in baseline

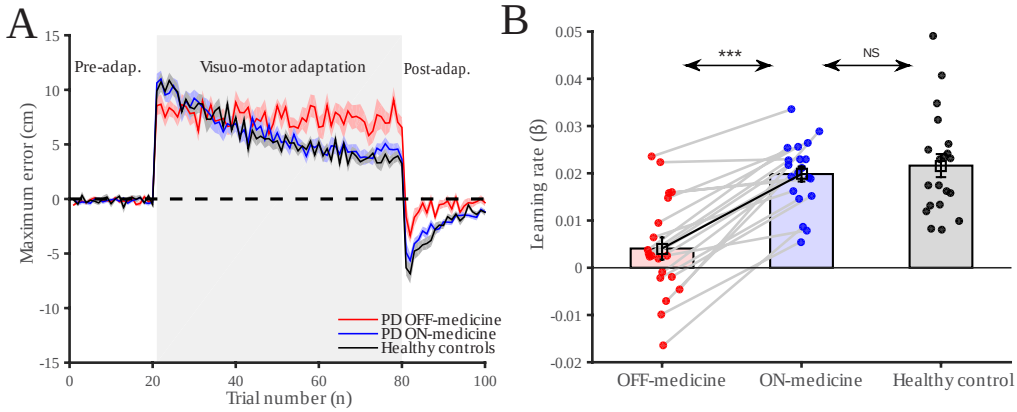

Figure 2.3: Parkinsons disease patients in visuomotor adaptation (A) Maximum error in pre-adaptation, visuomotor adaptation, and post-adaptation in Parkinsons disease patients with across medication differences (n=20). Red indicates medication OFF; blue indicates medication ON, and black indicates healthy controls. (B) Learning differences in the medication OFF (red) and medication ON (blue) (n=20), reveal faster learning in the medication ON and also show no differences between the medication ON and healthy controls.

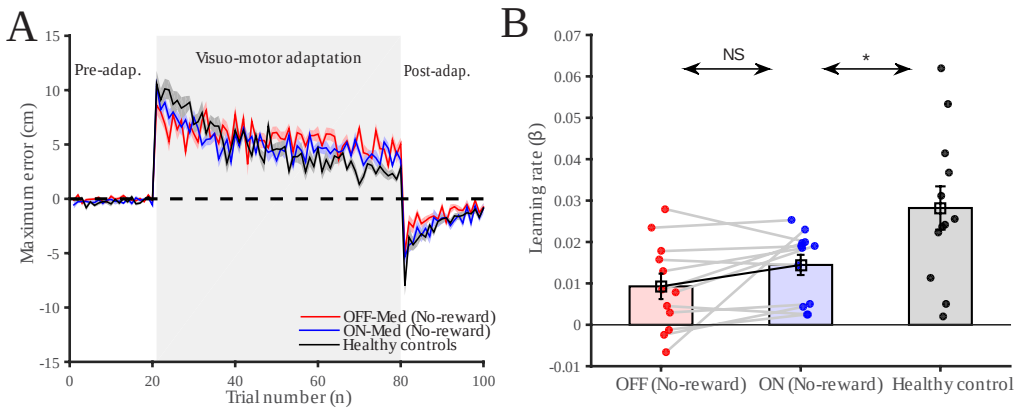

Figure 2.4: Parkinsons disease patients without reward in visuomotor adaptation (A) Maximum error in pre-adaptation, visuomotor adaptation, and post-adaptation in Parkinsons disease patients across medicine differences absence of auditory reward (n=12). Red indicates OFF-medication with no reward, blue indicates ON-medication with no reward and black indicates healthy controls with no reward. (B) Learning differences in the OFF-medication with no reward (red) and ON-medication with no reward (blue) reveal no differences in medication-ON and OFF-medication conditions and also reveal faster learning in the healthy controls.

condition showed nearly straight trajectories across groups but showed strongly curved trajectories in the presence of a visuomotor perturbation (Figure 2.4A). We observed that the mean learning rate for the PD-OFF medication without reward group (mean = 0.009 ± 0.010) was similar to the mean learning rate of the PD-ON medication without reward group (mean = 0.015 ± 0.008). Surprisingly, we observed no difference in the mean learning rate between the PD-OFF medication without reward group and PD-ON medication without reward group (Figure 2.4B; p = 0.08, t (11) = -1.89), suggesting that reward is a critical component which regulates supervised learning through basal ganglia.

To further test the role of the motivational influence of dopamine we also measured the reaction times (RTs) of subjects while they performed the visuomotor adaptation task. As previous studies have suggested, there is a direct benefit of reward on reaction times in non-human primates [8, 79, 80]. Consistent with this notion we observed that during the learning phase, controls exhibited the smallest RT (mean RT = 493.00 ± 100.72), followed by PD patients in medication- ON condition (mean RT = 647.28 ± 219.18) and PD patients in medication- OFF condition showed the longest RT (mean RT = 717.43 ± 249.0). Nevertheless, the effect of RT was not directly related to learning per se since we did not detect any consistent trend in learning among the patients with PD or in the control subjects (Figure 2.5A & 2.5B). Interestingly, the same differential effect between controls, PD with medication and without medication was observed in the absence of reward (mean RT = 532.22 ± 248.60 (controls), mean RT = 580.90 ± 219.15 (ON-medication) and mean RT = 663.78 ± 194.40 (OFF-medication)). These results indicate that the differences in motor learning observed between the groups with or without reward were not strictly due to reaction time.

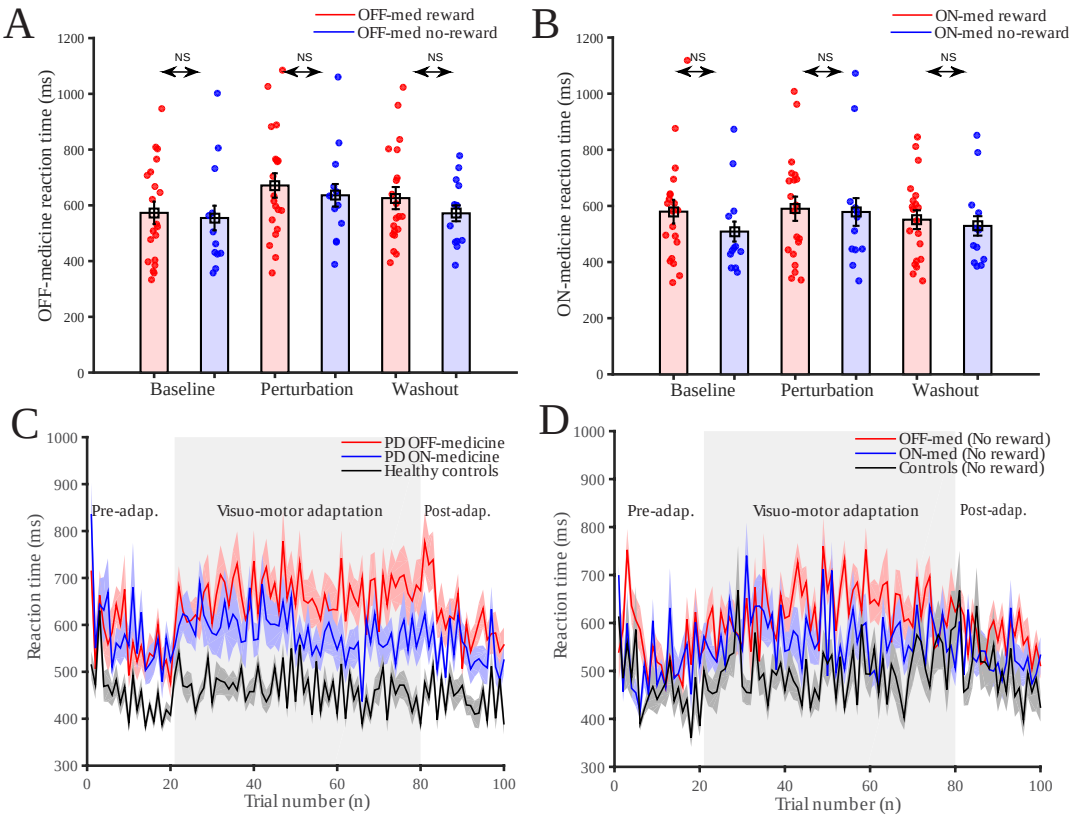

Figure 2.5: Parkinsons disease patients reaction time (RT) during visuomotor adaptation (A) RT in pre-adaptation, visuomotor adaptation, and post-adaptation in OFF-medication. Red indicates reward group and blue indicates no reward group. (B) RT in pre-adaptation, visuomotor adaptation, and post-adaptation in ON-medication. Red indicates reward group and blue indicates no reward group. (C) RT in pre-adaptation, visuomotor adaptation, and post-adaptation across Parkinsons disease patients under medication (n=20). Red indicates OFF-medication; blue indicates ON-medication and black indicates healthy controls. (D) RT in pre-adaptation, visuomotor adaptation, and post-adaptation across Parkinsons disease patients ON and OFF medication conditions in the absence of reward (n=12). Red indicates OFF-medication condition with no reward; blue indicates ON-medication condition with no reward and black indicates healthy controls with no reward.

2.3.4 Parkinsons disease patients with deep brain stimulation in visuomotor adaptation

Although the previous result indicates a role of dopamine in supervised learning, dopamine per se is thought to manifest its effects indirectly by modulating the activity of other nodes of the basal ganglia. To directly test the role of these structures, we used deep brain stimulation (DBS) of the subthalamic nucleus (STN) to manipulate the basal ganglia directly. We tested Parkinsons disease patients with DBS electrodes placed bilaterally in the STN (n=12) on visuomotor rotation. To verify the effect of subthalamic nucleus stimulation only, all DBS patients remained OFF medication for 12 hours before the test. All patients with DBS implanted were tested in two sessions, namely OFF-DBS and ON-DBS. The orders of the two sessions were counterbalanced across subjects.

Once again to quantify the error, we used the maximum error along the trajectory (Figure 2.6A). The reduction in maximum error equation 2.2 was used as a metric to quantify the learning rate for each subject. We observed that the mean learning rate for the OFF-DBS group (mean = -0.003 $\pm$ 0.009) was significantly lesser than the mean learning rate for the ON-DBS group (mean = 0.017 $\pm$ 0.011) (Figure 2.6B; p = 5.97e-06, t (11) = -8.07). In addition, the OFF-DBS group showed no washout effect, indicating no learning. In contrast, the ON-DBS group under L-DOPA medication showed a sound washout effect. Furthermore, we found no differences between the reaction times of baseline and perturbed conditions trails. Interestingly, we also found a strong positive correlation between baseline stimulation voltage and learning rate (r = 0.74, p = 0.001). The difference in the learning rate between the ON-DBS group and OFF-DBS group indicates that there could be a pathway between the cerebellum and basal ganglia presumably involving the STN that is essential for supervised learning.

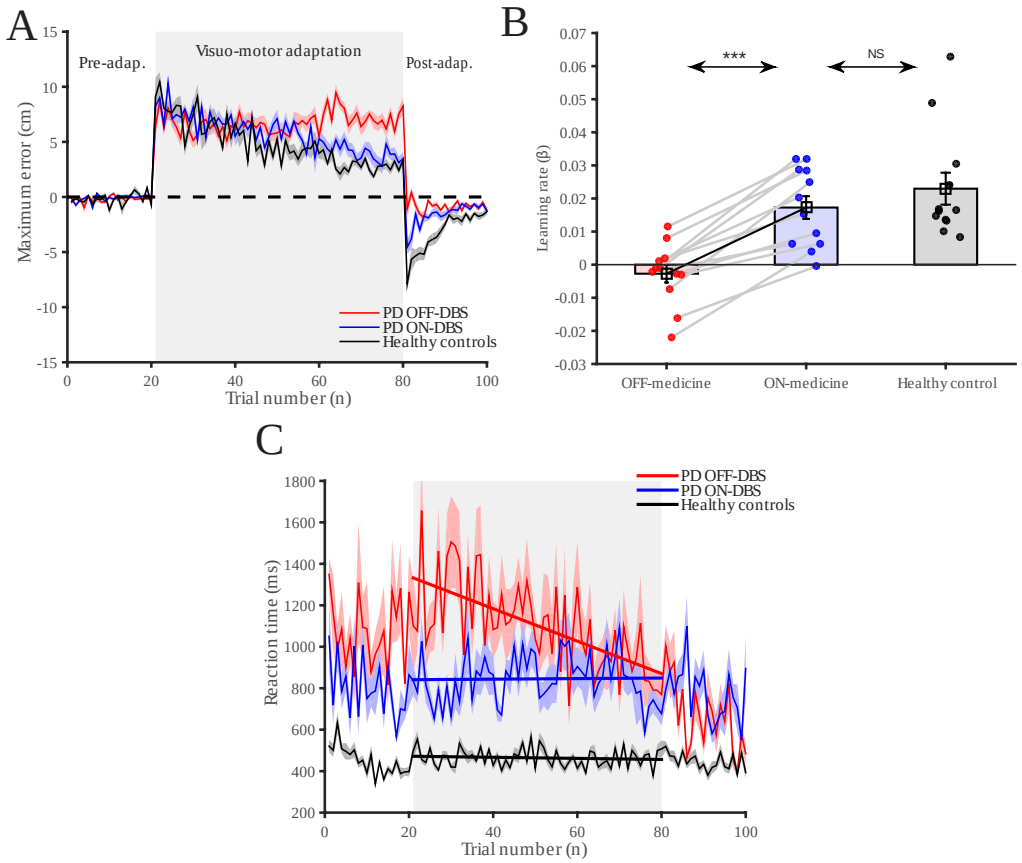

Figure 2.6: Parkinsons disease patients with subthalamic deep brain stimulation (A) Maximum error during pre-adaptation (baseline), visuomotor adaptation, and post-adaptation as a function of the trial number in PD patients, with and without DBS relative to healthy controls. Red indicates OFF-DBS, blue indicates ON-DBS and black indicates healthy controls. The learning curves are an average across the population (n=12). The shaded area indicates the corresponding SEM shown.(B) Learning rates in the OFF-DBS (red) and ON-DBS (blue) conditions relative to healthy controls (black; n=12 for each group). (C) Mean population RT in pre-adaptation, visuomotor adaptation, and post-adaptation epochs as a function of the trial number in PD patients with and without DBS relative to healthy controls. Red indicates DBS-OFF, blue indicates DBS-ON and black indicates healthy controls. The shaded area indicates the corresponding SEM.

Furthermore, subthalamic nucleus (STN), a component of basal ganglia is thought to play a critical role in inhibiting pre-potent or ongoing actions [81, 82, 83]. It might be the case that improved learning by DBS could be due to a consequence of better inhibitory control that allows the patients in DBS-ON state to inhibit the pre-potent actions and learn new optimal actions better than the patients in the OFF-DBS state. A proxy of such improved inhibitory control and conflict is expected to result in an increase reaction time (RT) [84, 85]. Interestingly, in the OFF-DBS state, we did find any evidence of such inhibitory/conflict signals being reflected in the pattern of RT across learning. The mean RT in the baseline period was relatively shorter compared to when the perturbation was introduced and when conflict and inhibitory controls were expected to be greatest (RT in the first ten perturbation trials, $p = 0.005$, $t(11) = -3.46$). Subsequently, with time RT gradually decreased (linear regression for OFF-DBS, $r = 0.64$, $p = 3.27e\text{-}08$). Contrary to the conflict hypothesis this decrease in RT was not related to learning, which was minimal in the OFF-DBS condition. Furthermore, we observed that RT was faster in the DBS-ON condition relative to the OFF-DBS condition and was fastest in the healthy control group that showed the highest learning rate. Moreover, we found no systematic trend of decreasing RT with trial number as learning proceeded for the DBS-ON and control groups (linear regression for DBS-ON $r = 0.02$, $p = 0.87$, and for control $r = 0.10$, $p = 0.42$). Also, there was no significant difference in RTs between the baseline epoch and the learning epoch for ON-DBS and control conditions (Fig. 6C), indicating that greater conflict was not necessarily imposed as a consequence of the visuomotor adaptation.

2.3.5 Clinical correlates of motor learning

Although the cerebellum and basal ganglia are known to be involved in motor learning, these same areas are also involved in motor control. To test whether

differences in motor learning are a consequence of deficits in motor control, we correlated the clinical scores, a proxy of deficits in motor control, in cerebellar and PD disease patients with motor learning rate. It was observed that the score of the International Cooperative Ataxia Rating Scale (ICARS), directly related to ataxia disease state, was not correlated with motor learning (Figure 2.8A; r = 0.02, p = 0.987). The score of the Unified Parkinson Disease Rating Scale (UPDRS), related to Parkinson disease state, was also found to have no correlation with learning (Figure 2.8B; r = 0.32, p = 0.165 (OFF medication) and r = 0.08, p = 0.742 (ON medication)). Similarly with Parkinson disease patients without reward (Figure 2.8C; r = 0.48, p = 0.110 (OFF medication No reward) and r = 0.18, p = 0.576 (ON medication No reward)) no significant correlation was observed. Interestingly, the score of the Unified Parkinson Disease Rating Scale (UPDRS), was correlated with learning in the ON-DBS group (Figure 2.8D; r = 0.58, p = 0.049 (ON-DBS)) and not with the OFF-DBS group (Figure 2.8D; r = 0.32, p = 0.315 (OFF-DBS)). We also observed that, the differences in learning rate for the PD no reward group (mean = 0.005 $\pm$ 0.009) was significantly less than the differences in learning rate for the PD under medication with reward group (mean = 0.016 $\pm$ 0.009) (Figure 2.7A; p = 0.003, t (30) = -3.21). We also observed no difference in the mean learning rate between the PD under medication group and PD DBS group. (Figure 2.7A; p = 0.19, t (30) = -1.33). Similarly, we also correlated the differences between clinical scores with differences in learning rate. We observed no correlation between differences in clinical scores with differences in learning rate in any of the groups (Figure 2.7B).

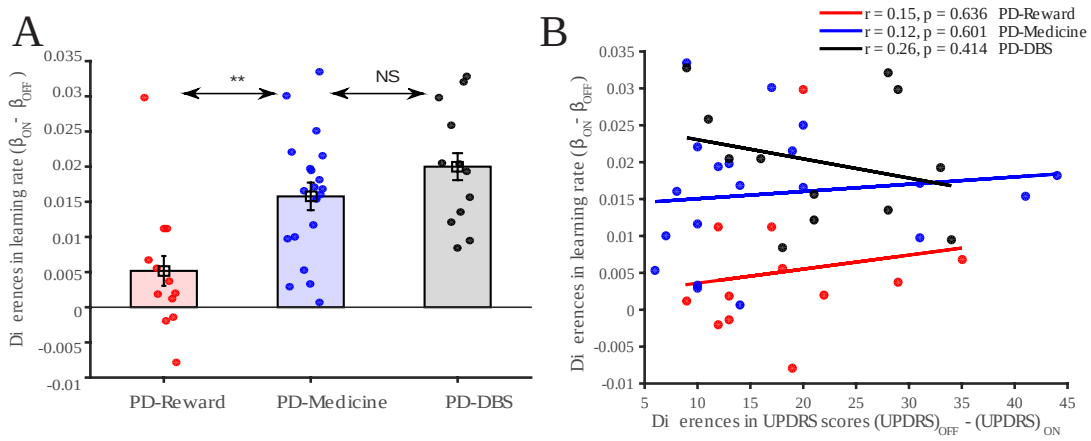

Figure 2.7: Learning differences in the Parkinsons disease patients (A) Learning differences without reward (red), with and without medication-patients (blue) and with and without DBS-patients (black). (B) Correlation between the differences in UPDRS scores with the differences in learning rate between the Parkinsons disease patients shows no correlation.

2.4 Discussion

In this chapter, we have presented two significant observations. First, we demonstrated how the presence and absence of dopamine influenced supervised learning thereby implicating the role of basal ganglia in supervised learning. Secondly, we also show that reinforcement at the end of the trial profoundly affected drug-induced learning (dopaminergic) learning in PD patients. Taken together we suggest that these results indicate a link between dopamine, reward in the modulation of supervised learning which is independent of reaction time, conflict and disease severity.

2.4.1 Role of basal ganglia in supervised learning

We examined supervised learning using a well-studied visuomotor perturbation (error-based task) with a few small modifications. Firstly, subjects had to learn to compensate for a rotation of 45 degrees whereas in most previous work the

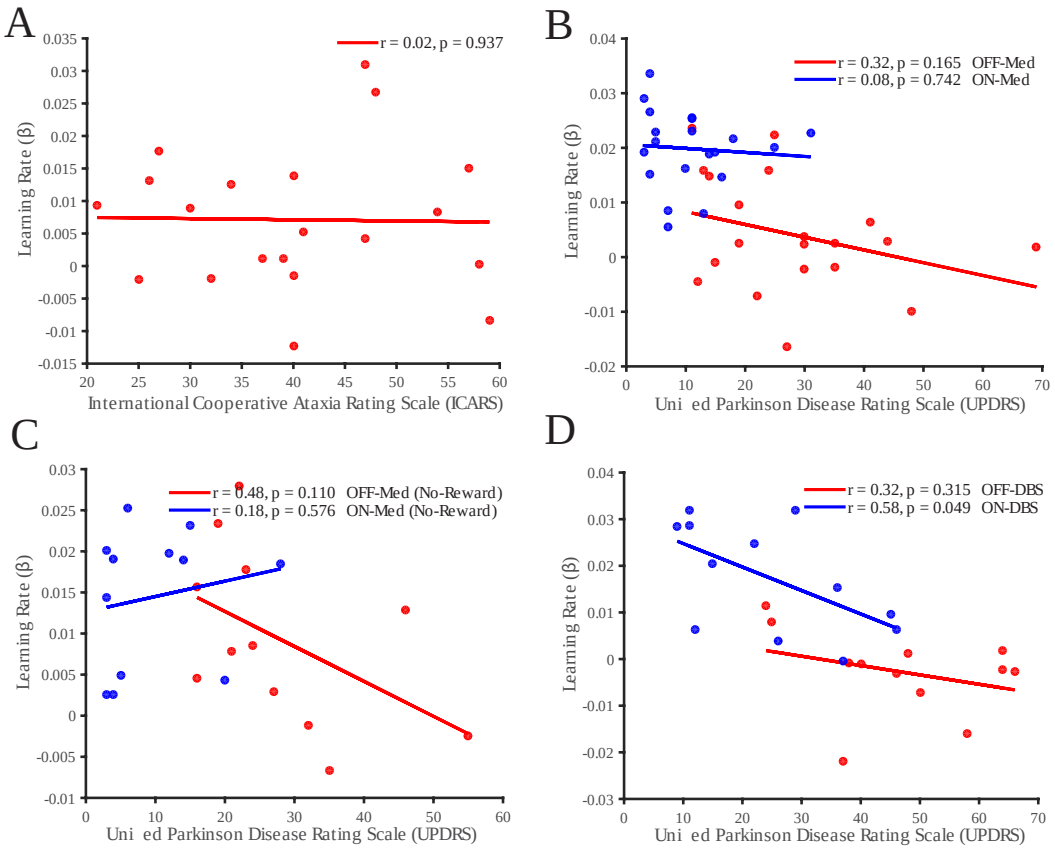

Figure 2.8: Disease state and supervised learning (A) The comparison of International Cooperative Ataxia Rating Scale (ICARS) with learning rate shows no significant relationship between ICARS score and learning rate in ataxia patients. (B) The comparison of Unified Parkinson Disease Rating Scale (UPDRS) with learning rate shows no significant relationship between UPDRS score and learning rate in Parkinsons disease patients and red indicates OFF-medication, blue indicates ON-medication. (C) The comparison of Unified Parkinson Disease Rating Scale (UPDRS) with learning rate shows no significant relationship between UPDRS score and learning rate – red indicates OFF medicine without reward, blue indicates ON medicine without reward. (D) The comparison of Unified Parkinson Disease Rating Scale (UPDRS) with learning rate shows a significant relationship between UPDRS score and learning rate of Parkinsons disease patients with ON-DBS but not in OFF-DBS.

rotations are typically 30 degrees rotations. Secondly, the subjects made the movements on a table top but observed the effects on the screen. Thus one could argue that a larger error and the more complex motor to vision mapping may have involved basal ganglia selectively [86]. This appears not to be the case as, patients with cerebellar degenerative diseases also exhibited similar deficits indicating that our task paradigm tapped into the implicit supervised learning [22, 23, 87]. Secondly, the pattern of learning deficits was not restricted to the initial component of learning when the errors were larger but rather reflect a global decrease in learning rate captured by the exponential fit. Previous works on patients with Parkinsons disease, to identify the role of basal ganglia in modulating supervised learning, have reported mixed results. While some studies showed no deficits in supervised learning [27, 28, 70, 29], other studies showed impairment in learning [69, 71]. The critical factor contributing to these differences, as revealed in our results, was that the effect of ON-medication and OFF-medication conditions. Performances were not compared using the same subjects in ON-medication and OFF-medication conditions in these studies [70]. Taken together, our findings indicate that the difference in learning rate between the OFF-medication group and ON-medication group suggest that basal ganglia is a necessary neural structure which participates in supervised learning.

2.4.2 Role of reinforcement in supervised learning

We propose that the ability to learn from errors is also dependent on the basal ganglia, which is driven by reinforcement of successful actions. In all the studies on supervised learning, reward reinforcement is inextricably embedded in the task design [5, 8, 7]. The reward is typically an auditory tone (our task) or a visual display that occurs when subjects successively reach the target, and it takes the form of a secondary reinforcement. Thus it is not entirely surprising that one should see the influence of basal ganglia in supervised learning. Recently, studies using a

reinforcement signal during a visuomotor rotation task have shown that a graded reinforcement signal altered supervised learning [53] while a binary reinforcement signal did not influence supervised learning [54]. Consistent with this result, healthy controls did not show differences in learning with and without binary reinforcement signal. However, we observed differences in the OFF-medication and ON-medication groups in the presence of the reinforcement signal, indicating that reinforcement and reward are essential components regulating learning.

The mechanism by which reward influences supervised learning is not clear. One recent hypothesis advocates that rewards affect learning through dopaminergic enhancement [53, 54], which results in better learning as well as better retention or consolidation. In this study, we explicitly tested this hypothesis by manipulating the levels of dopamine (ON versus OFF) and reinforcement. It was observed in this study that an interaction between these two variables such that the difference between OFF-medication and ON-medication in the presence of reinforcement disappeared in the absence of reinforcement. These differences in learning as a consequence of reinforcement did not appear to be a result of decreased vigor since we obtained the same pattern of reaction times [88] and disease severity (UPDRS) with and without reinforcement. Thus, these results can be explained by gain hypothesis in which reward mediated at the end of the completion of a successful trial causes dopamine release in the proportion that changes the extent of learning occurring in the cerebellum.

2.4.3 Role of subthalamic nucleus in supervised learning

Dopamine induced changes in learning may manifest by modulating downstream areas within the basal ganglia such as the subthalamic nucleus. One attractive hypothesis by which the STN and the basal ganglia can play a direct role in motor learning is by conflict resoltion and inhibitory control. STN is known to be a critical nucleus in the basal ganglia which allows conflict resolution between

multiple actions via inhibitory control of habitual responses, enabling the expression of novel behaviours [81, 82, 83, 89, 36]. This view provides an attractive framework to understand the role of STN in the learning of new behaviours. In support of this view, a recent study by Brown and colleagues [90] reported that low-frequency beta power from the STN is correlated with performance error in a visuomotor learning task. However, since this study did not assess motor learning in the presence and absence of stimulation, the causal contribution of STN could not be verified. Moreover, analogous to structures such as the medial prefrontal cortex, which are implicated in executive control [91, 92, 93], it remains unclear whether learning by STN can be driven by error and/or conflict signals. By recording the same subjects in ON-DBS versus OFF-DBS conditions we show a causal contribution of STN in supervised learning. While the RT during ON-DBS was faster than OFF-DBS and is consistent with DBS having an inhibitory effect on STN function causing greater impulsivity [94, 95, 96], the improved learning was independent of changes in RT and contrary to predictions of STN acting via conflict/inhibitory control.

The conjoint effects of increased learning without systematic changes in RT with DBS suggest that STN plays a more direct role in supervised learning independent of its role in conflcit and inhibition. Traditionally, error-based learning is thought to be governed by cerebellum [22, 23, 97, 98]. On the other hand, a recently discovered bidirectional anatomical pathway between the cerebellum and basal ganglia [48, 49] suggests that these structures may not necessarily be independent information processing units as have been typically assumed. In particular, it was shown [49] that the cerebellum sends a strong di-synaptic projection to the striatum through the thalamus, while STN sends a di-synaptic projection to the cerebellar cortex by way of the pontine nuclei. Indeed, a functional prediction of such crosstalk is the presence of common symptoms exhibited

by diseases of the basal ganglia and cerebellum [99]. The observation in our study shows that the motor control deficits, as assessed by the UPDRS score, have a significant negative correlation with learning during ON-DBS condition but not in OFF-DBS condition. This supports a distinct role of STN in supervised learning learning independent of its role in conflcit and inhibition.

Taken together, the findings of this chapter, are in line with the hypothesis of bidirectional anatomical pathways between the cerebellum and basal ganglia [48, 49], suggesting that these structures not be mutually exclusive information processing units. In particular, it has been shown that the cerebellum sends a strong disynaptic projection to the striatum through the thalamus, while the subthalamic nucleus sends projection to the cerebellar cortex by way of the pontine nuclei. Taken together, these results suggest that the basal ganglia modulate supervised learning in the cerebellum.

2.5 Summary

It is commonly thought that supervised learning is mediated by the cerebellum while reinforcement learning is mediated by the basal ganglia. In contrast to this strict dichotomy, we demonstrate a role of the basal ganglia in supervised learning (error-based motor learning) in patients with Parkinsons disease (PD) by comparing the degree of motor learning during medicine-OFF state and medicine-ON state. We further show similar modulation of learning rates in the presence and absence of subthalamic deep brain stimulation. We also report that reinforcement is also an essential component of supervised learning by demonstrating the absence of motor learning in patients with PD during the medicine-ON state relative to the medicine-OFF state in the absence of a reinforcement signal. Taken together, these results suggest that the basal ganglia modulate the gain of supervised learning in the cerebellum based on the reinforcement received at the end

of the trial.

Chapter 3

Role of variability in supervised learning

3.1 Introduction

As alluded to in the general introduction, the neural structures responsible for motor learning are also responsible for motor control. Thus, the deficit in these neural structures, as a consequence of disease also compromises motor performance. For example, cerebellar patients produce dysmetric movements and fail to coordinate multi-jointed movements (for example, ataxia); while subjects with compromised basal ganglia circuitry (for example, Parkinsons disease) also exhibit dysmetric movements with bradykinesia. Typically, most of these motor control disorders result in high motor variability [100, 101, 102]. As such, motor variability is a fundamental feature of motor control and thought to be a consequence of a stochastic nervous and muscular system and theories of motor control propose that motor variability is noise that needs to be suppressed.

In recent years, accumulating evidence suggests that motor variability is not a noise of system but purposefully generated to promote motor learning [57, 59, 63,

103]. The basis of such findings is thought to hinge on the idea of reinforcement learning [33, 104] that depends on the presence of variability that increases exploration; hence facilitating learning. Interestingly, such variability has also been shown to help to learn during supervised error-based learning tasks, suggesting a more general role of variability in motor learning as well as reiterating the tight coupling between reinforcement and supervised learning which was the described in the previous chapter. Nevertheless, at face value, such a relationship between motor variability and motor learning is at odds with theories of motor control that envision variability as noise that needs to be suppressed. A corollary of this some hypothesis also raises the possibility that motor disorders which are characterized by higher variability should show enhanced motor learning. Along those lines, Therrien et al. 2016 [66] tested this hypothesis in patients with cerebellar ataxia and suggested that motor variability has a tradeoff between variability and learning. For a certain level motor variability helps in learning supporting its role in exploration up to a limit, after which motor variability is just a noise and does not promote learning. In contrast, a recent meta-analysis studied indicated that motor variability does not facilities the motor learning [62]. In an attempt to reconcile these apparently contradictory positions regarding the role of motor variability in learning, we hypothesise that motor variability has two components one caused by redundancy that perhaps could help in motor learning while the other component, being random noise, would not contribute to motor learning.

This hypothesis that redundancy could aid in motor learning was based on the observation that redundancy is a ubiquitous property that renders biological systems robust to disruptions (and perturbations). Goal-directed movements also display redundancy since a given movement, such as touching one's nose, can be made in many different ways with a different combination of joint angles in the arm. Although redundancy generates flexibility, it also poses a fundamental prob-

lem for the motor system since recruiting more joints and muscles than necessary will increase variability, particularly if noisy muscles are recruited independently. However, if redundancy is controlled in an intelligent manner, it is possible to maintain acceptable levels of variability while maintaining a reasonable degree of redundancy that allows flexibility in behavior. Consistent with this view, it has been observed in a wide range of tasks [105, 106, 107, 108, 109, 110] that variability is not eliminated, but optimized [111, 112, 113] to accumulate in a task-relevant dimensions using minimum intervention principle [113]. Such variability that is a consequence of redundancy can be quantified as an uncontrolled manifold [114, 115, 116] in which task independent variability is constrained to a redundant subspace (or uncontrolled manifold).

While minimizing variability using redundancy is expected to improve task-related performance, recent evidence suggests that motor variability paradoxically helps in motor learning [57, 59, 63, 66, 103]. In this study, we tested whether motor variability arising from joint redundancy plays a role in motor learning and suggest a possible neural substrate. Furthermore, we explored a possible mechanism for redundancy to contribute to motor learning.

3.2 Materials and methods

In this section, the experimental procedure and experimental setup is discussed.

3.2.1 Subjects

All of the subjects were paid for participation and gave informed consent in accordance with the guidelines of the Indian Institute Science, ethics committee. Seventy normal subject participated in study (aged 22-70 years, 42 male and 18 female). In experiment 1, 40 subjects (all right handed) performed visuo-motor task and in experiment 2, 10 subjects (all right handed) performed generalized visuo-motor task. In experiment 3, 10 subjects (6-right handed, 4-left handed subjects) performed the force-field experiment first with their dominant and after gap of 5 days with non-dominant hands. The handedness of the subjects was tested by modified Edinburgh Handedness Index [75]. We also analyzed the performance of subjects from previous chapter, 20 patients with autosomal dominant cerebellar ataxia and 20 idiopathic Parkinsons disease (PD) in this chapter.

3.2.2 Experimental setup

In experiments 1, subjects sat on a chair while the hand is placed on front table as shown in Figure 3.1A. They looked straight on a monitor (refresh rate 60 Hz) in which they saw the targets while they moved their hand; experiments were conducted in a dark room. This experiment was performed using Psychophysics Toolbox of MATLAB that displayed visual stimuli, sampled and stored the data and other behavioral parameters. Hand positions and joint angles was recorded (spatial resolution of 7.62 mm) using an electromagnetic position and orientation tracking device (Polhemus, LIBERTY, USA).

All experiments were conducted in a dark room. Subjects sat on a chair while their chins were supported by a chin rest and their heads were locked with head

bars on both sides of their temple as shown in (Figure 3.1A). They looked down on a semi-transparent mirror on which they saw the targets while they moved a robotic arm handle (BKIN, Canada) in a horizontal plane below the plane of the mirror. Targets were presented by an inverted monitor (refresh rate 60 Hz) above the mirror setup which gave the impression that the targets appeared in a virtual plane below the mirror aligned to the plane in which the robotic arm handle moved. All experiments were performed using TEMPO/VIDEOSYNC software (Reflective Computing, USA) that displayed visual stimuli, sampled and stored the data and other behavioral parameters in real time at a resolution of 1.04 ms. Hand positions and joint angles was recorded (spatial resolution of 7.62 mm) using an electromagnetic position and orientation tracking device (Polhemus, LIBERTY, USA) interfacing with TEMPO in real time at 240 Hz.

3.2.3 Experimental paradigm

In experiments 1, trials were divided into three phases baseline or pre-adaptation, adaptation and post-adaptation. All subjects performed $\sim$ 10 practice trials. Subjects performed about 100 trials per session, with a typical session lasting between 15 minutes. Each trial started with the presentation of a square fixation box (1 cm) at the center of the screen where the subject had to fixate both his hand. After successful fixation, a square target with a length of 1 cm was displayed randomly in any one of 2 locations that uniformly spanned a circle of 20 cm radius around the central fixation box. The subject moved the hand to the target only after the fixation box disappeared. Trials were aborted if a premature movement was made. Auditory feedback was given when the subject performed the particular trial correctly.

In all other experiments, trials were divided into three phases baseline or pre-adaptation, adaptation and post-adaptation. All subjects performed $\sim$ 30 practice trials. Subjects performed about 400 trials per session, with a typical

session lasting between 1.5 to 2 hours. Each trial started with the presentation of a square fixation box (0.4 cm) at the center of the screen where the subject had to fixate both his eye and the robotic end-effector. After successful fixation, a square target with a length of 0.7 cm was displayed randomly in any one of 8 locations that uniformly spanned a circle of 15 cm radius around the central fixation box. The subject moved the robotic end-effector to the target only after the fixation box disappeared. Similar to experiment 1, trials were aborted if a premature movement was made. Auditory feedback was given when the subject performed the particular trial correctly.

Visuo-motor perturbation

During visuo-motor perturbation,as mentioned in Chapter 2, the movement is rotated according to (3.1),

$$\begin{bmatrix} P_x \\ P_y \end{bmatrix} = \begin{bmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{bmatrix} \begin{bmatrix} p_x \\ p_y \end{bmatrix} \tag{3.1}$$

where P_x, P_y correspond to the position of the cursor, p_x, p_y correspond to the actual position of the hand and θ denotes the perturbation angle about the centre of work space with θ equal to 45°. This perturbation also led to a trajectory error and to compensate the subjects altered their hand trajectory. With practice the hand trajectory tended to become straight again.

Force-field perturbation

During force-field perturbation, the robot applied a viscous curl forces depending on the instantaneous hand velocity as in (3.2),

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & -K \\ K & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} \tag{3.2}$$

where F_x, F_y correspond to the forces exerted on the robotic arm, $\dot{x}$, $\dot{y}$ correspond to the velocity components of hand and K denotes the force perturbation coefficient along the orthogonal directions with K equal to 20 Ns/m. This force-field perturbation disturbed the hand trajectory.

3.2.4 Quantification of learning

The error was calculated as the perpendicular distance of the hand trajectory at peak velocity from the straight line joining the central fixation box to the target location. To compute the learning in perturbation trials, as mentioned in Chapter 2, were fitted with an exponential fit using the robust least squares method,

$$f(n) = a \exp(-\beta\ n) \tag{3.3}$$

The use of an exponent fit is motivated by the standard learning rule which is a first order process that depends on the current error. The goodness of fit for the population learning curve for visuomotor learning ($r^2 = 0.95$), for generalized visuomotor learning ($r^2 = 0.90$) and in force-field learning ($r^2 = 0.93$). The learning rate β was used a metric to quantify the learning rate for each subject.

Occasionally investigators have used the difference in error between first and last trials [17] for quantification of learning. However, this approach is somewhat flawed because it does not make use of the all the data points and would be expected to be more influenced by noise. Some investigators have also used the initial direction of the trajectory as an error measure. However, since in a viscous force-field the initial velocity and therefore the force is zero, so this method is not appropriate in our case.

In another approach to quantify learning rate, the mean trajectory in each of the eight directions was computed and the deviation from the mean, at each point, was obtained. The root mean square of the deviation was obtained for each trial.

For the eight directions, least square linear fits were done and the finally, the mean of the eight slopes is assumed to be the learning rate. The learning could also be quantified as the area under the curve formed by the trajectory with the straight line from the fixation point to the target as the base. However, a potential flaw in these approaches is that error is calculated over the entire duration of the trial, which comprises of both feed-forward and feedback components. From literature on learning mechanisms, it is known that feed-forward and feed-back mechanism are different [117, 118] and it is not clear how to combine both these mechanisms. In light of the above discussion, we decided to use the error at peak velocity along the trajectory. It may be mentioned that the error at the peak velocity is used extensively in literature [13, 78, 119, 120].

3.2.5 Quantification of redundancy

To specify any point in 3D space, one need to specify the three position coordinates and to additionally specify the orientation of the object three further quantities are required. At the kinematic level, the human arm (excluding the fingers) has nine degrees of freedom at the joints - two above shoulder (neck to shoulder), three at the shoulder, two at the elbow and two at the wrist. This makes the system redundant as there can be only a maximum of six equations (from the specified position and orientation of the hand) in the nine joint variables and the redundant system of equations will have infinitely many solutions for a given position and orientation of the hand. Similar redundancy occurs at different levels in the neuromotor system – for example the elbow joint has six different muscles for actuation and there can infinitely many ways to actuate the muscles to achieve a desired elbow joint rotation.

While previous work has emphasized how such redundancy and the associated flexibility may play an important role in path planning, control of noise and optimization of motion, whether and how redundancy might promote mo-

tor learning has not been investigated. In this work, we hypothesis that motor variability has two components: one caused by redundancy (due to multiple degrees of freedom provided by the joints) and another orthogonal component that is random noise. In order to calculate the redundancy component (joint-space variability) in different directions, we created a 2D forward kinematics model for the human arm. The main justification of a 2D model is that the robot arm and the wrist of the human gasping the robot arm moves only in the two dimensional X–Y plane. From standard textbooks on robotics [**ghosal2006robotics**], the 2D forward kinematics model can be derived as,

$$\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} l_1 \cos(\theta_1) + l_2 \cos(\theta_2) + l_3 \cos(\theta_3) + l_4 \cos(\theta_4) \\ l_1 \sin(\theta_1) + l_2 \sin(\theta_2) + l_3 \sin(\theta_3) + l_4 \sin(\theta_4) \end{bmatrix} \tag{3.4}$$

where the joints rotations clavicle protraction-retraction (θ_1), shoulder horizontal abduction-adduction (θ_2), elbow flexion-extension (θ_3) and wrist medial-lateral (θ_4) (Figure 3.1C). In experiment 1, we also incorporated a fifth joint - index figure abduction-adduction, and accordingly extended (3.4) to include an additional joint rotation θ_5 and an addition length l_5. For each subject the lengths $l_i, i = 1, ..., 5$ were measured from the data obtained from the motion tracker. To identify the accuracy of model, the measured end-point $(\bar{x}, \bar{y})$ was compared with those obtained from the model (x, y) and the difference was found to be negligible.

The distribution of redundancy component (joint-space variability) was computed for baseline trials for each of the different directions at the maximum reach velocity. Since the arm is redundant, we do not have a unique nominal θ vector (for going from point A to B) from which we can subtract measured θ values to get difference. We assume that the average is the nominal or the resolved unique θ values. The mean joint configuration across trials, along each of the directions, was computed at the maximum velocity v and is denoted by $\bar{\theta}^v$. The deviation

of the joint configuration for a trial k, $\Delta\theta_k$, is obtained by subtracting the joint configuration at the maximum velocity, θ_k^v, from the mean as below,

$$\Delta\theta_k = \bar{\theta}^v - \theta_k^v \tag{3.5}$$

Based on the $2D$ forward kinematics model, the Jacobian matrix at peak velocity was computed as

$$J(\bar{\theta}^v) = \begin{bmatrix} \frac{\partial x}{\partial \theta_1} & \frac{\partial x}{\partial \theta_2} & \frac{\partial x}{\partial \theta_3} & \frac{\partial x}{\partial \theta_4} \\ \frac{\partial y}{\partial \theta_1} & \frac{\partial y}{\partial \theta_2} & \frac{\partial y}{\partial \theta_3} & \frac{\partial y}{\partial \theta_4} \end{bmatrix} \tag{3.6}$$

where the elements of the Jacobian matrix are the partial derivatives of the coordinates of the position of arm with respect to the joint angles in the mean joint configuration. The null space of the Jacobian matrix represented the changes of joint configurations that keep the position of arm on the mean position. The joint configuration vector ξ_i lying in the null-space of the Jacobian matrix was computed from,

$$J(\bar{\theta}^v)\ \xi_i = 0 \tag{3.7}$$

For each trial, the sum of the component of $\Delta\theta_k$ along the null-space directions is given by

$$\theta_R = \sum_{i=1}^{m} \langle \Delta\theta_k, \xi_i \rangle\ \xi_i,\ m = 2 \text{ or } 3 \tag{3.8}$$

We quantify redundancy as the sum of the squares of θ_R across all the trials divided by the number of trials n. Mathematically, this is written as

$$N(J) = \sum_{i=1}^{n} \frac{(\theta_R)^2}{n} \tag{3.9}$$

In this work, the scalar $N(J)$ is used as a measure of redundancy space.

3.2.6 Task-space variability

We quantified the task-space variability from the hand trajectory when it reached its peak velocity. The standard deviation of the perpendicular distance of this point from the straight line joining the start and end of the trajectory was used as the metric of task-space variability.

3.2.7 Statistical analysis

All the correlation analysis uses Pearsons correlation. For pairwise comparisons between groups we first checked for normality in the data using Lilliefors test and when it satisfied normality we did a pairwise two-tailed t-test.

3.3 Results

We used two experimental setups shown in (Figure 3.1A). The subject moves the end-effector of a robot manipulator or hand alone from an initial point to a task-space target point. As shown in (Figure 3.1B), the experiment had three phases a pre-adaptation baseline period, followed by a phase with either one of two kinds of a perturbation: a visuo-motor (kinematic perturbation) or an applied viscous curl force (dynamic perturbation); and finally a post-adaptation phase when the perturbation was removed. We simultaneously measured the end point and joint angles while subjects reached to the target during the baseline period as shown in (Figure 3.1C). The map between the joint angles and the end point (x, y) point is many-to-one, i.e., there is redundancy. The joint variability in the baseline period was quantified into two components – the joint variability due to the redundancy space termed as the null-space variability that did not affect end point and the joint variability that caused changes in end point termed as task-space variability (Figure 3.1D) respectively. In this work, we studied the effect of these two types of variability on the learning of kinematic and dynamic perturbation. Additionally, we studied the simple visuomotor adaptation and generalized visuomotor adaptation. Furthermore, we studied force-field adaptation when the subject is using the dominant and non-dominant hand. Our main hypothesis is that joint redundancy helps in motor learning. To test this hypothesis we performed four experiments involving the learning of kinematics, generalized kinematics, dynamics and testing the differences between the dominant and non-dominant hand.

3.3.1 Motor variability in kinematic learning

We trained 40 subjects to learn point-to-point reaching movements using their dominant hand, along 2 directions, in a visuo-motor perturbation which was set using the Equation (3.1). In this experiment the cursor was rotated by 45° from

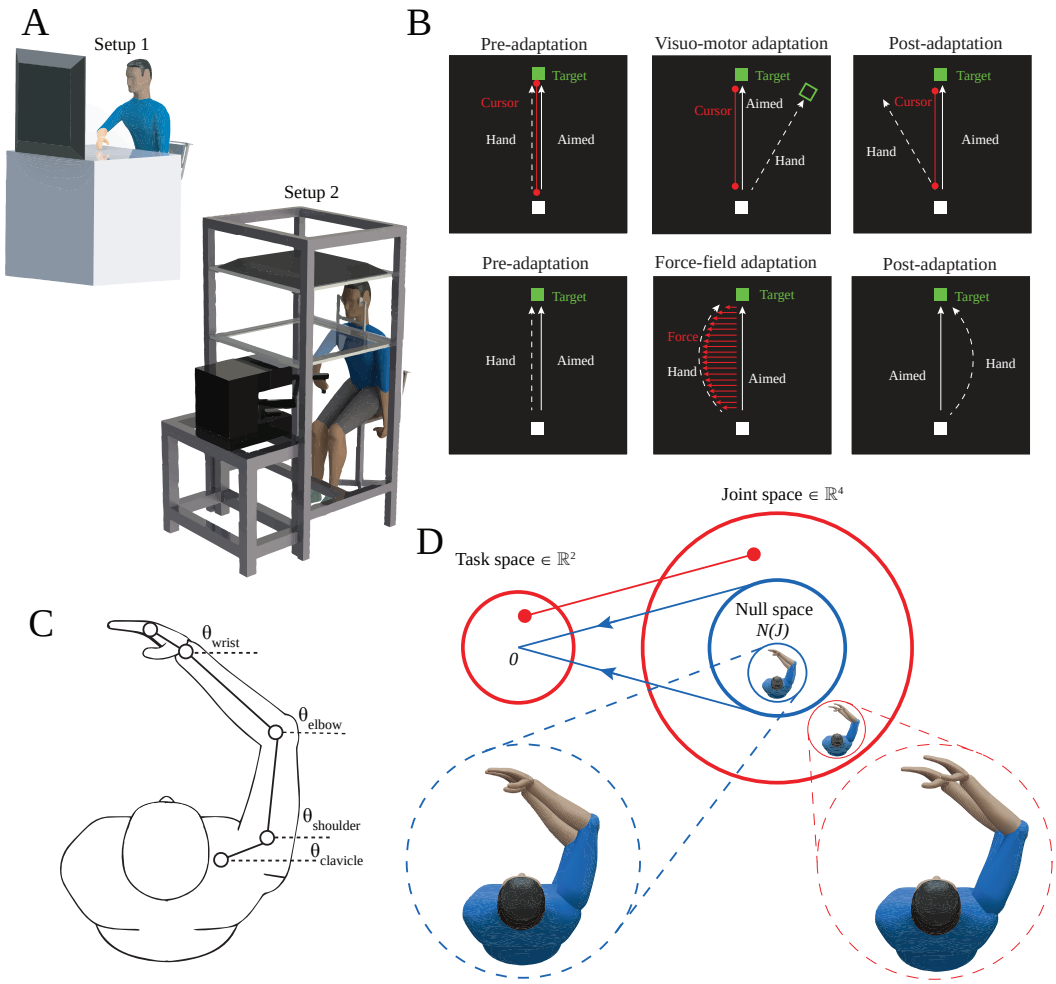

Figure 3.1: Experiment setup and design for adaptation: (A) Subjects made point-to-point reaching movements to visual targets in 1 out of 8 directions 15 cm away from the central start point in each trial. (B) Experiments were divided into a pre-adaptation (baseline), adaptation and post-adaptation (washout) epochs. Subjects adapted to a novel force-field (top panel) or a visuomotor rotation (bottom panel) in separate experiments. (C) Trackers were used to measuring joint rotation angles. (D) Illustration of null-space variability blue circle that doesn't affect task-space/end point variability, red circle affects task-space/endpoint variability.

the hand trajectory (Figure 3.2A). The trajectory of the hand for a typical subject in the pre-adaptation (baseline) (Figure 3.2B), visuo-motor adaptation (Figure 3.2C) and post adaptation (Figure 3.2D) are shown. Overall, the pattern of trajectories are consistent with previous work showing that while typical movements follow a nearly straight trajectory in the baseline condition, they show strong curved trajectories in the presence of a visuo-motor perturbation. The curved trajectories gradually become straighter with practice over the course of about sixty trials (Figure 3.2E). In addition, as a consequence of motor learning, subjects showed a washout effect (post adaptation) where errors in trajectory inverts in direction when the learnt visuo-motor perturbation is turned off. This washout error converges to baseline levels typically with in twenty trials.

To quantify the error, we have used the error at peak velocity along the trajectory. The reduction in peak velocity error (equation (3.3)) was used as a metric to quantify the learning rate for each subject. To test whether the learning rate of a subject could be predicted on the basis of motor redundancy exhibited during the pre-adaptation (baseline period), we computed $N(J)$ (equation (3.9)), the chosen measure of variability due to redundancy space called null-space variability. We found a strong positive correlation between baseline null-space variability and learning rate in the visuo-motor (Figure 3.3C; $r = 0.54, p = 0.0003$). To increases the robustness, we divide 40 subjects into two groups based on their learning rate (above mean and below mean learning group) and a three-trial running mean $\pm$ SE (shading in SE) across group subjects are shown-red indicate above mean group and blue indicate below mean group. In figure 3.3A it is very apparent that above mean group decrease errors faster than the below mean group and reveal differences in learning across groups. This is supported by the fitted exponential β values and In support of the hypothesis the null-space variability is also accordingly significantly different across the two groups as shown in (Figure 3.3A-B).

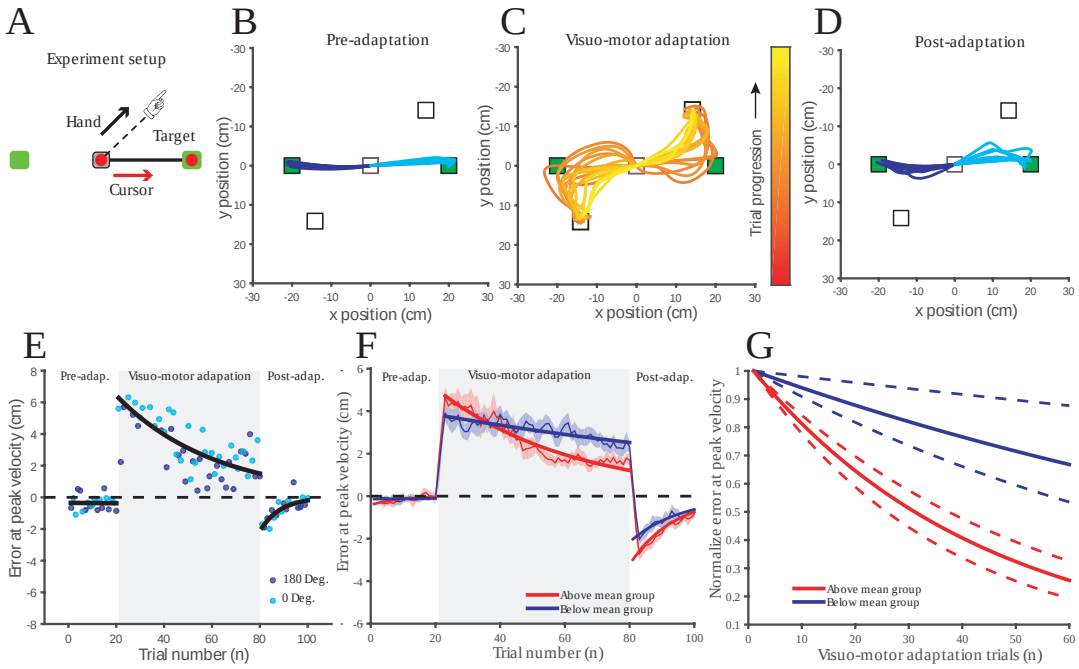

Figure 3.2: Visuo-motor adaptation task: (A) Experimental apparatus and illustration of the visuo-motor rotation task. (B) First five pre-adaptation trials from a subject showing baseline motor variability. (C) First ten visuo-motor adaptation trials (color coded) from the same subject showing the disturbed hand trajectory. (D) First five post-adaptation trials from the same subject showing the effect of adaptation. (E) Error at peak velocity in pre adaptation, visuo-motor adaptation and post-adaptation from the same subject showing the progression of adaptation. Errors in each of the two directions are color coded. Fitted exponential curves significantly account for most of the progression of errors across trials in the adaptation ($r^2 = 0.71$). (F) Three-trial running mean SE across subjects (shading is SE). Fitted exponential curves across subjects significantly account for most of the progression of errors in the adaptation (-red indicates above average learning group ($n = 20, r^2 = 0.90$), blue indicates below average learning group ($n = 20, r^2 = 0.67$)). (G) Normalized fitted exponential curves across groups mean (solid), maximum and minimum (dashed) indicating learning rate variability and differences.

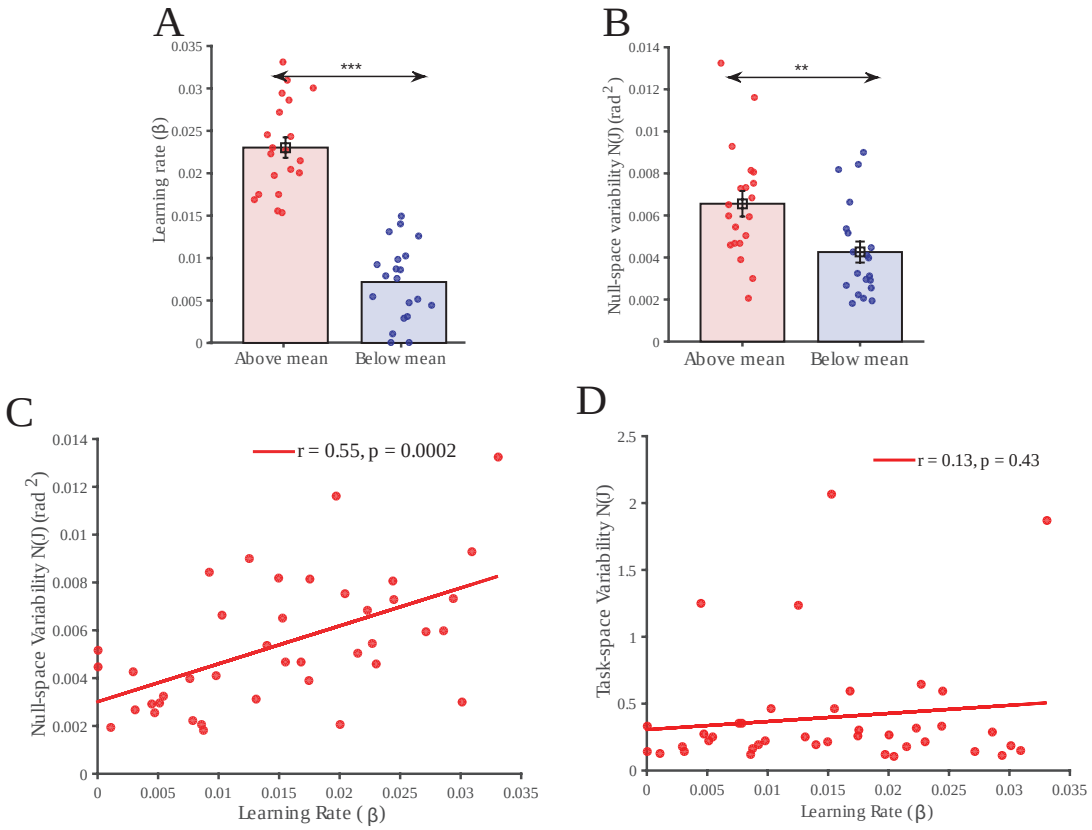

Figure 3.3: Joint redundancy predicts learning rate in a visuo-motor adaptation task: (A-B) Comparison of baseline null-space variability with learning rate between above average learning group (red) and below average learning group (blue), reveal corresponding differences in null-space variability between groups. For 2 subjects whose learning rates were negative have been clamped to 0. (C) Subject-by-subject comparison (n=40) of baseline null-space variability with learning rate shows significant positive relationship. Asterisks indicate statistically significant differences. (D) Subject-by-subject comparison (n=40) of baseline task-space variability with learning rate no significant relationship between variability and motor learning. Asterisks indicate statistically significant differences. ($*P < 0.05, **P < 0.005, ***P < 0.0005$).

3.3.2 Motor variability in generalized kinematic learning

In order to test whether redundancy could aid in learning generalized task (difficult), we next examined 10 subjects while they learnt point-to-point reaching movements with the visuo-motor perturbation (equation (3.1)) along 8 directions where in each case, the cursor was rotated by 45° from the hand trajectory (Figure 3.4A). The trajectory of the hand for a typical subject in the pre-adaptation (baseline) (Figure 3.4B), visuo-motor adaptation (Figure 3.4C) and post adaptation (Figure 3.4D) are shown. The average behavior pooled across the 10 subjects shows a similar learning pattern (Goodness of fit is $r^2 = 0.90$, Figure 3.4F). Again the learning rate in the visuo-motor perturbation and the null-space and task-space variability in the pre-adaptation baseline period were computed. A significant correlation between the null-space variability with learning rate was observed (Figure 3.4H; $r = 0.71, p = 0.021$). Interestingly, we found no correlation of the baseline task-space variability with the learning rate (Figure 3.4I); $r = 0.42, p = 0.22$).

3.3.3 Motor variability in generalized dynamic learning

In order to test whether redundancy could aid in learning in other types of perturbation, we trained 10 subjects to learn point-to-point reaching movements using their dominant hand, along 8 directions, in a force-field which was set using the force-field perturbation (equation (3.2)). In this experiment the perturbation was proportional to the velocity of the hand but perpendicular to the hand movement direction (Figure 3.5A). The trajectory of the hand for a typical subject in the pre-adaptation (baseline)(Figure 3.5B), force-field adaptation (Figure 3.5C) and post adaptation (Figure 3.5D) are shown. Similar to the visuo-motor perturbation, consistent with literature, typical hand movements follow a straight trajectory in the baseline condition and they show strong curved trajectories in the

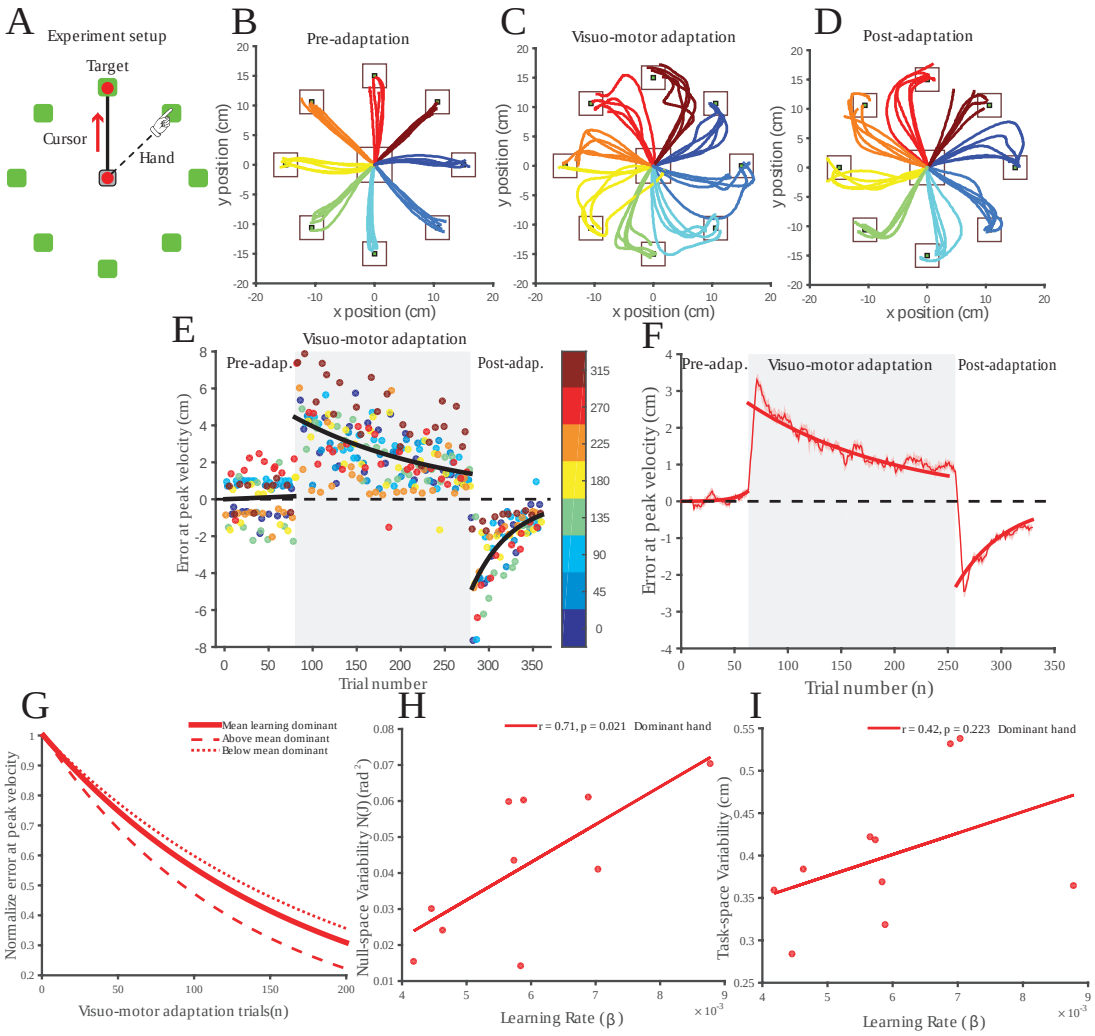

Figure 3.4: Joint redundancy predicts the learning rate in a generalized visuo-motor adaptation task: (A) Experimental apparatus and illustration of the visuo-motor rotation task. (B) First five of pre-adaptation (baseline) trials from a subject showing motor variability in pre-adaptation. (C) First five of force field adaptation trials from the same subject showing the disturbed hand trajectory. (D) First five of post-adaptation trials from the same subject showing the effect of adaptation. (E) Error at peak velocity in pre-adaptation, adaptation and post-adaptation from the same subject showing the progression of adaptation ($r^2 = 0.40$). (F) Eight-trial running mean SE across subjects (shading is SE). Fitted exponential curves across subjects, significantly account for most of the progression of errors in the adaptation ($r^2 = 0.90$). (G) Normalized fitted exponential curves, mean (solid), maximum and minimum (dashed) indicating learning rate variability across 10 subjects. (H) The comparison of baseline null-space variability at maximum velocity with learning rate shows a significant positive relationship between joint redundancy and motor learning. (I) The comparison of baseline task-space variability at maximum velocity with learning rate shows no significant relationship between variability and motor learning.

presence of a viscous curl force field. The curved trajectories gradually become straighter with practice over the course of about two hundred trials (Figure 3.5E). In addition, as a consequence of motor learning, subjects showed a washout effect (post adaptation) where errors in trajectory inverts in direction when the learnt force field is turned off in the post adaptation period. This washout error converges to baseline levels typically within a hundred trials. The average behavior pooled across the 10 subjects shows a similar learning pattern (Goodness of fit is $r^2 = 0.93$, Figure 3.5F).

As mentioned, the reduction in peak velocity error (equation (3.3)) was used as a metric to quantify the learning rate for each subject. The mean learning rate was found to be 0.006 ± 0.002 for the dominant hand and 0.004 ± 0.001 for non-dominant hand in the force-field adaptation period. To test whether the learning rate of a subject, under a viscous perturbing force, could be predicted on the basis of motor redundancy exhibited during the pre-adaptation (baseline period), we again computed $N(J)$ (equation (3.9)) as the measure of variability due to redundancy space. We found a strong positive correlation between baseline null-space variability and learning rate in the force-field (Figure 3.5G; $r = 0.72, p = 0.018$ (dominant hand), $r = 0.67, p = 0.033$ (non-dominant hand)). However, we found poor correlation between the learning rate and the task-space variability in the baseline period (Figure 3.5H; $r = 0.14, p = 0.70$ (dominant hand), $r = 0.03, p = 0.92$ (non-dominant hand)).

3.3.4 Actively linked joint redundancy and motor learning

Differences in the redundancy across subjects may reflect a difference in the intrinsic biomechanics which may assist is learning. In contrast, differences in the redundancy may also reflect the effect of neural control that assists in

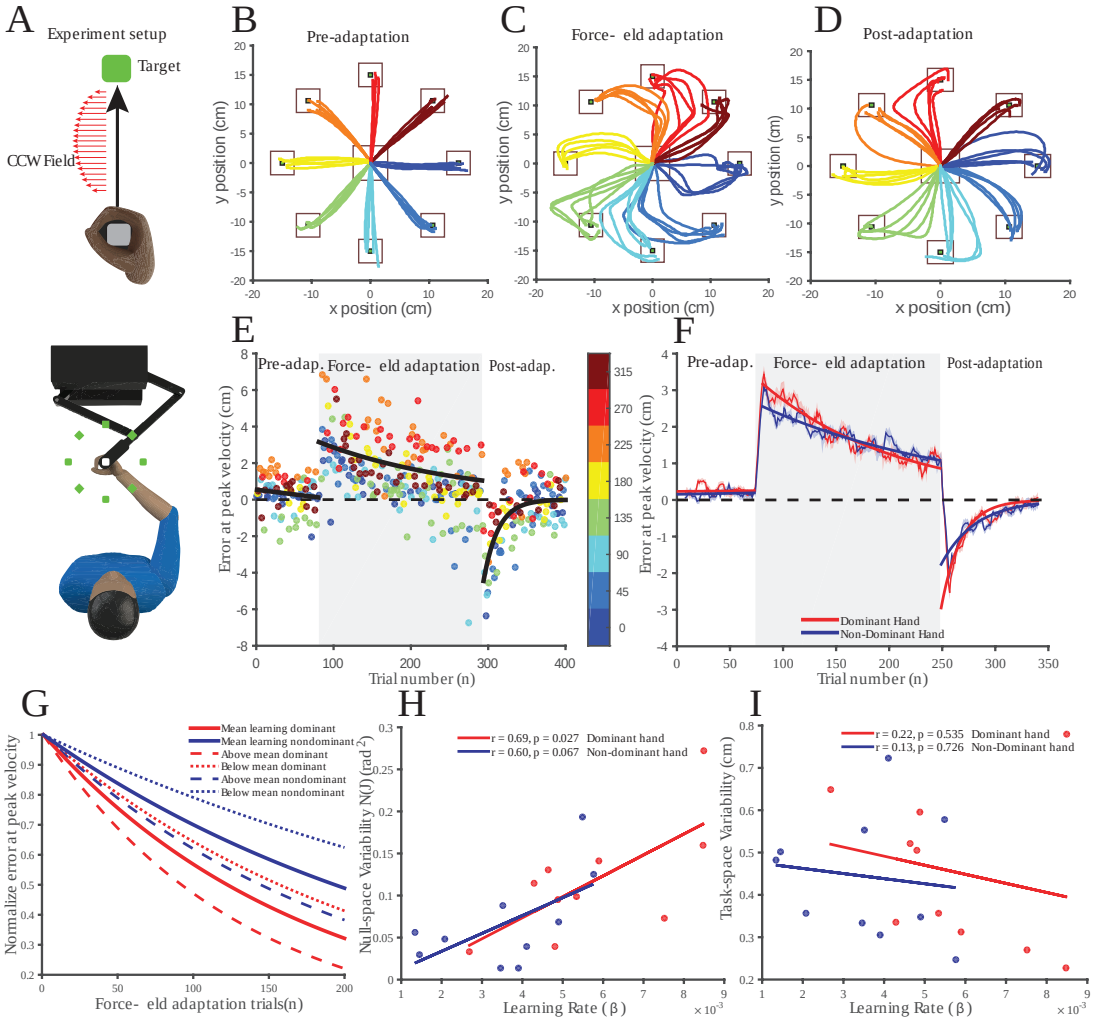

Figure 3.5: Joint redundancy predicts rate of learning in a force-field adaptation task: (A) Experimental apparatus and illustration of the viscous curl force-field. (B) First five of pre-adaptation (baseline) trials from a subject showing motor variability in pre-adaptation. (C) First five of force field adaptation trials from the same subject showing the disturbed hand trajectory. (D) First five of post-adaptation trials from the same subject showing the effect of adaptation. (E) Error at peak velocity in pre-adaptation, adaptation and post-adaptation from the same subject showing the progression of adaptation ($r^2 = 0.38$). (F) Eight-trial running mean SE across subjects (shading is SE). Fitted exponential curves across subjects significantly account for most of the progression of errors in the adaptation (red indicates dominant hand ($n = 10, r^2 = 0.91$), blue indicates non-dominant hand ($n = 10, r^2 = 0.88$). (G) Normalized fitted exponential curves across hands mean (solid), maximum and minimum (dashed) indicating learning rate variability and differences across hands learning. (H) Comparison of baseline null-space variability at maximum velocity with learning rate shows positive relationship. (I) Comparison of baseline task-space variability at maximum velocity with learning rate shows no significant relationship between variability and motor learning.

motor learning. To assess this we tested and compared the learning rate and null space variability between the dominant and non-dominant hand in 10 subjects, thereby normalizing any differences in redundancy due to the biomechanics. We observed that the mean learning rate for the non-dominant hand (mean = 0.004 ± 0.001) was significantly less than the mean learning rate for the dominant hand (mean = 0.006 ± 0.002) (Figure 3.6A; $p = 0.008, t(8) = 3.54$). Interestingly, the null-space variability was also lesser in the non-dominant hand (mean = 0.054 ± 0.036) compared to dominant hand (mean = 0.12 ± 0.066) (Figure 3.6B; $p = 0.035, t(8) = 2.54$). However, there was no difference in the mean task-space/end-point variability between the dominant and non-dominant hands, suggesting that the task-space/end-point variability did not influence learning rate. Further, we found a good correlation (Figure 3.6D; $r = 0.84, p = 0.003$) between the difference between the learning rate and difference in null-space variability of the dominant and non-dominant hand, suggesting that extent of difference in the null-space variability could partly explain the difference in learning rate between the two hands.

Furthermore, we also observed an outlier subject whose learning rate was higher in the non-dominant hand compared to the dominant hand (marked as a dotted line in Figure 3.6A-C and marked in blue in Figure 3.6D). Nevertheless, even for this subject the null-space variability was greater in the non-dominant hand compared to the dominant hand, in support of the hypothesis. Taken together these findings indicates that the difference in learning rate between the dominant and non-dominant hand maybe a consequence of the greater redundancy in the dominant hand acquired as a consequence of greater usage.

To provide further insights into how redundancy might help in motor learning, we separated direction-wise errors with mean of five trails and fitted into ellipse as illustrated in (Figure 3.7A). Furthermore, we computed the orientation of el-

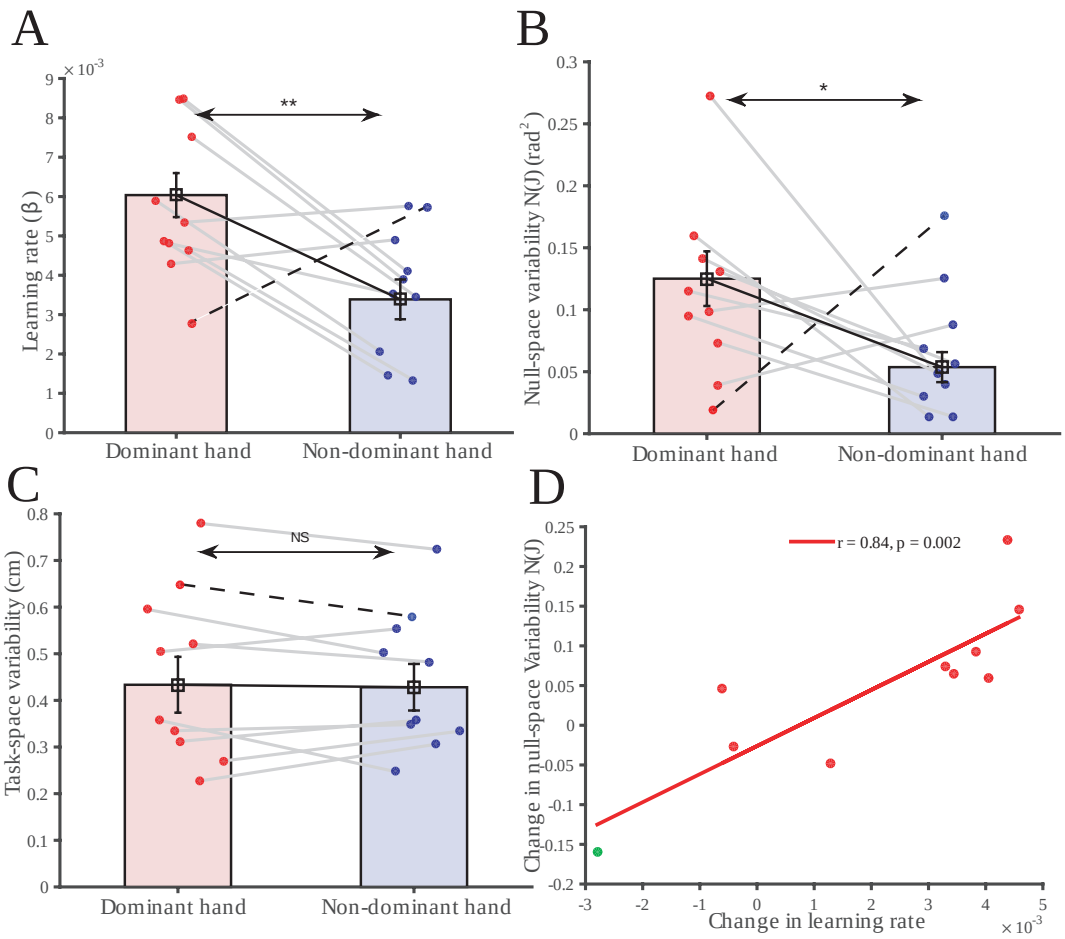

Figure 3.6: Learning differences between the dominant hand and non-dominant hand: (A) Learning differences in the dominant hand (red) and non-dominant hand (blue) (n=10), reveal faster learning in the dominant hand. (B) Baseline null-space variability in the dominant and non-dominant hand reveal differences in null-space variability between hands indicating reason for differences in learning rate. (C) However, baseline task-space variability in the dominant hand and non-dominant hand reveal no differences in task-space variability between hands. (D) Comparison of the difference in null-space variability with the difference in learning rate between the dominant hand and non-dominant hand shows a significant positive relationship. The outlier subject data is shown as a dotted line (5A-C) and in green dot (5D).

lipse (angle of major axis) in starting of perturbation. We found that, orientation of ellipse was constant throughout the subjects (mean = 126 ± 9.3), which suggests that the same direction is difficult to learn in comparison to other directions across subjects. However, when we analyzed the eccentricity of ellipse in baseline, starting of perturbation and end of perturbation, we found significant differences in eccentricity. We found higher eccentricity of ellipse in the starting of perturbation in comparison of baseline and end of perturbation, which illustrated that leaning level is different in different directions (Figure 3.7B; $p = 0.02, t(9) = 3.6$). Similarly we also computed area of ellipse in baseline, starting of perturbation and end of perturbation, we found higher area in the starting of perturbation in comparison with area in the end of perturbation which is directly indicative of learning (Figure 3.7C; $p = 0.005, t(9) = 8.3$). Furthermore, we divided trails into block of 8 direction trails and fitted the ellipse in each block as illustrated in figure 3.7D, which shows how the error are decreasing in each direction and in end of perturbation ellipse become more closer to circle because eccentricity is small. However, when we plotted the eccentricity and area of ellipse across subjects (Figure 3.7C-D), we see drop in eccentricity and area as block progresses. Decrease in area indicates the learning in subjects but decrease in eccentricity of ellipse indicate that the brain is trying to remove the direction dependence of error. In other words, the natural anisotropy of errors with direction is being overcome during learning.

3.3.5 Neural substrates linking joint redundancy and motor learning

Since differences in the redundancy appear to reflect experience, we tested for possible neural substrates that allow joint redundancy to facilitate motor learning. We computed the null-space variability and motor learning in ataxia pa-

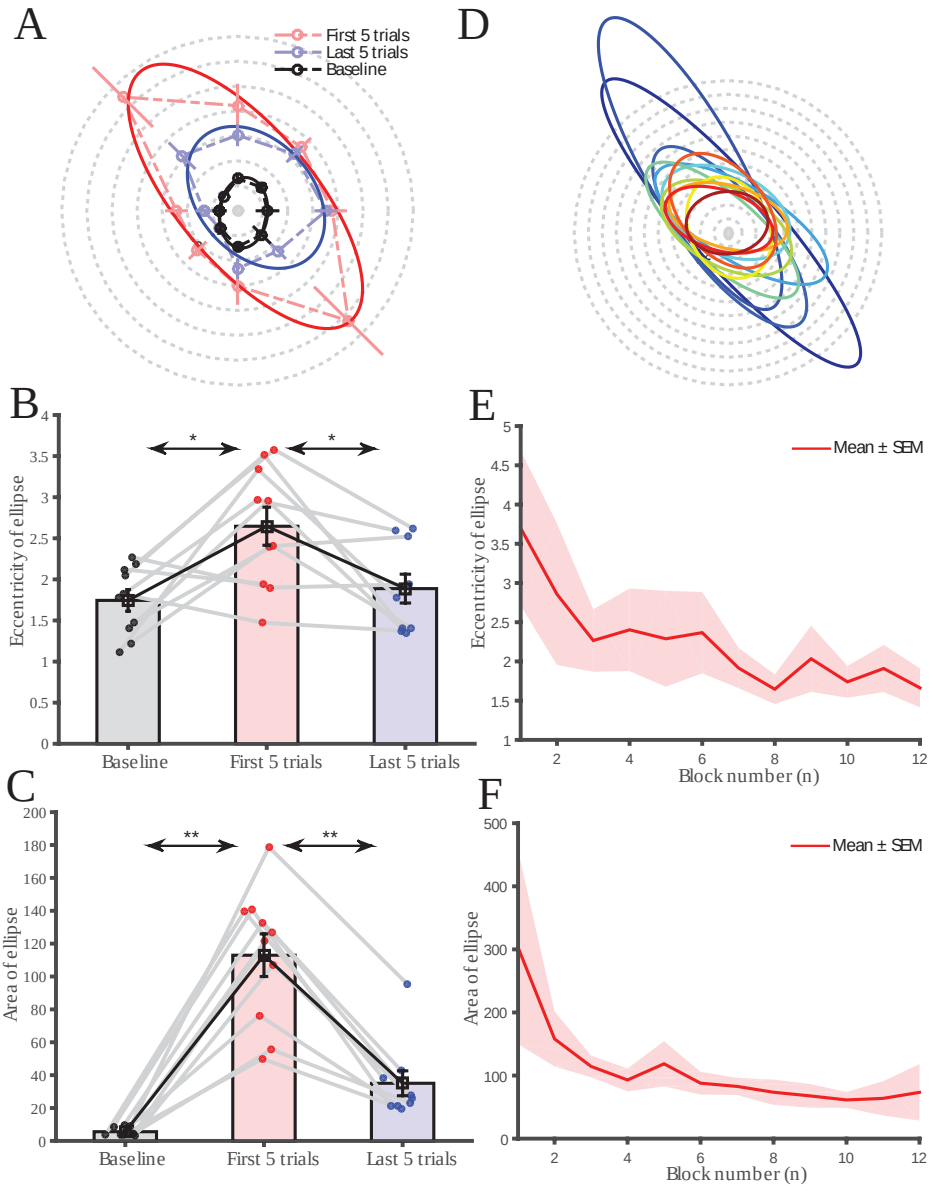

Figure 3.7: Joint redundancy and homogenization of workspace: (A) Representative subject directional error ellipse for the baseline (black), starting of perturbation (red) and end of perturbation (blue). (B) Comparison of directional error ellipse eccentricity in baseline (black), starting of perturbation (red) and end of perturbation (blue) reveal higher eccentricity in the starting of perturbation. (C) Comparison of directional error ellipse area in baseline (black), starting of perturbation (red) and end of perturbation (blue) reveal higher area in the starting of perturbation. (D) Representative subject directional error ellipse progression of toward more circular. (E) Mean SE across subjects (shading is SEM) showing the progression of change in ellipse eccentricity indicative of homogenous in equal in each direction. (F) Mean ± SE across subjects (shading is SEM) showing the progression of change in ellipse area indicative of learning.

tients and Parkinsons disease patients from the data presented and analyzed in Chapter 2. When the kinematic perturbation was applied in patients with cerebellar ataxia, we observed a similar degree of exploration of redundancy and also found a positive correlation between joint redundancy and motor learning (Figure 3.8A; $r = 0.60, p = 0.005, n = 20$), despite significantly reduced motor learning compared to controls (p = 3.3e-4, t (38) = 3.94).However, if we assume the dotted circle as an outlier in this analysis, The correlation between joint redundancy and motor learning is weak but still positively correlated ($r = 0.35, p = 0.14, n = 20$). Patients with Parkinsons disease (PD) ON and OFF medication also showed a similar degree of exploration of redundancy compared to controls as well [F(2,77) = 0.83, p = 0.44], while motor learning was only impaired in the OFF-medication condition compared to controls [F(2,77) = 16.8, p = 8.8e-7]. Interestingly, in contrast to ataxic patients, PD patients showed no significant correlation between joint redundancy and motor learning (Figure 3.8C; OFF-Medicine, $r = 0.34, p = 0.142, n = 19$ and ON-Medicine, $r = 0.32, p = 0.166, n = 20$). The results from both cerebellar and PD patients indicate that the degree of exploration of redundancy does not explain the reduced motor learning in these patients. However, we did find interesting differences between the correlation of redundancy and motor learning that was selectively impaired in PD patients but not cerebellar impaired patients, possibly pointing to a role of the basal ganglia in enabling the exploration of redundancy.

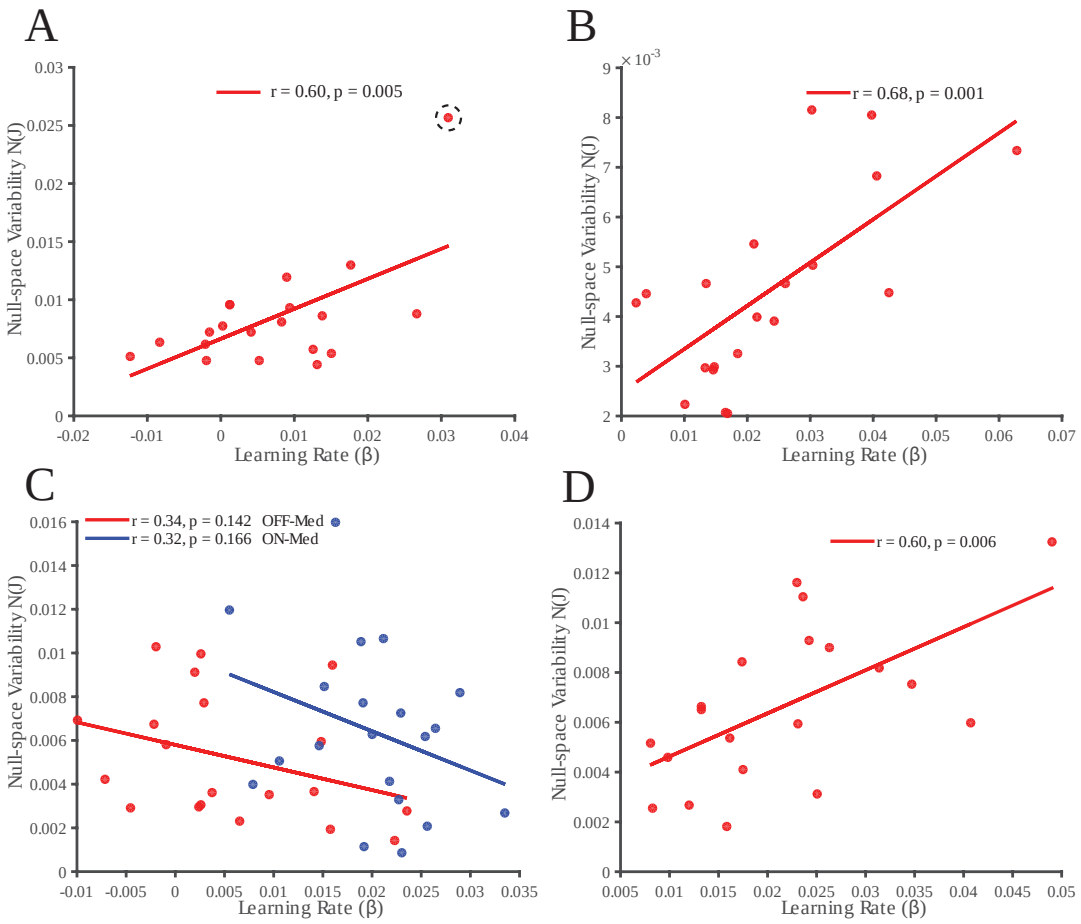

Figure 3.8: Joint redundancy in a cerebellum and basal ganglia disease patients: (A) Comparison of ataxia patients at baseline null-space variability at maximum error with learning rate shows positive relationship. (B) Comparison age matched healthy subjects at baseline null-space variability at maximum error with learning rate shows significant relationship between variability and motor learning. (C) Comparison of Parkinsons disease patients at baseline null-space variability at maximum error with learning rate shows no significant relationship between variability and motor learning (red indicates OFF-medicine, blue indicates ON-medicine). (D) Comparison age matched healthy subjects at baseline null-space variability at maximum error with learning rate shows a significant relationship between variability and motor learning.

3.4 Discussion

In contrast to previous work that has studied joint redundancy and learning in isolation, this is the first study undertaken to test the relationship between these two variables under the assumption that the extra degrees of freedom conferred by the arm is used by the motor system to facilitate learning. We have shown that variability in reaching a target in task-space has low correlation with learning during perturbations, whereas the variability in the null-space, resulting from the redundancy in the human arm, aids in learning. We interpret these results as indicating that exploration of redundancy aids in motor learning when a force-field or a visuo-motor rotation perturbation is present.

3.4.1 Joint redundancy

The uncontrolled manifold hypothesis (UCM) that has its origin in the initial observations by Bernstein [121] is the dominant framework to understand and quantify joint space redundancy [114, 115, 116]. Such redundancy is now established as a ubiquitous feature of behavior observed across a variety of tasks [105, 106, 107, 108, 109, 110]. In the current study we followed the UCM framework to quantify joint space redundancy. However, unlike previous work, we quantified redundancy in individual subjects as opposed to measuring the group response and observed large variability, suggesting that redundancy might be an idiosyncratic feature that is unique to each subject. In addition, unlike past work where redundancy was quantified at the maximum peak velocity or at the target location, we restricted our computation to the former in case of visuo-motor perturbations. This was done because task-space variability is known to be highest at the maximum velocity of the trajectory and smallest at the end point (target), particularly when the targets are small. Thus, quantifying redundancy at the peak velocity is better suited to reveal the full scale of variability across subjects

which are essential to understand its bearing on motor learning.

Previous work has suggested that the degree of redundancy can be task specific and can be optimized such that motor system obeys the principle of minimum intervention in which the brain only controls task relevant variability but does not control task irrelevant or redundant variability. Although we did not explicitly study the control of redundant variability, we did observe interesting task specific differences indicating that redundancy or task irrelevant variability also maybe actively controlled and is not merely epiphenomena of having more degrees of freedom than required for the task. For example, in our pool of subjects we observed that redundant variability was on average greater in the dynamics condition (mean=0.11 ± 0.069) than in the kinematic condition (mean= 0.04 ± 0.022) even in the pre-adaptation period when the reaching task was identical. We believe that this difference may reflect the additional constraint of subjects having to follow the incremental cursor movements along trajectory in the kinematic condition, thereby containing the available redundancy. In the force-field experiments, the hand motion was considerably longer thereby allowing redundancy to show its effects. Our results also showed a significantly larger redundancy in the dominant hand in comparison to the non-dominant hand despite being bio-mechanically similar [122, 123] and performing the same task. The larger redundancy seen in the dominant hand provides a natural explanation of why learning might be more potent in the dominant hand and reaffirms the belief that redundancy not only reflects the bio-mechanical characteristics of the arm but may reflect active control from the brain.

3.4.2 Dynamic and kinematic learning

To study motor learning we followed previous work that has tested the ability of subjects to implicitly adapt their motor behavior in presence of dynamic and kinematic perturbations [8, 13, 124, 125]. In our learning paradigm subjects

learnt the perturbations while making movements in two directions and also to all 8 directions, picked at random. Hence, unlike some learning paradigms that emphasize specific learning in one direction our learning is expected to generalize across directions. This motivated the use of single exponential fit pooled across all directions to study the average rate of learning as a single variable even though our data suggest the presence of fast and slow learning phase that has been reported in the literature [125]. In future work we hope to study direction-specific motor learning to test whether joint redundancy better correlates with the fast versus slow learning phase.

Nevertheless, our results revealed learning rates that are comparable to the literature [8, 13, 14, 17]. We also observed that kinematic learning (mean= 0.007 ± 0.001) was faster than dynamic learning (mean= 0.006 ± 0.002), which might be idiosyncratic to the subjects who performed the respective experiments. However, the data also revealed novel facets of motor learning not reported earlier to the best of our knowledge. First, learning in the dominant hand was significantly faster than the non-dominant hand. Second, trends indicate that some directions appear to be easier to learn, and like joint redundancy there is a large subject specific variability in the data, whose implications will be discussed in the next section.

3.4.3 Relating joint redundancy and motor learning

The strong subject wise correlations observed in both the dynamic and kinematic learning tasks support the hypothesis that joint redundancy supports motor learning. Although our data is fundamentally correlative in nature, we were able to exploit a novel feature in our experiment that involved the use of the dominant and non-dominant hand that resulted in differences in learning rates and redundancy. Lending further credence to the hypothesis, we found that the smaller redundancy in the non-dominant hand was associated with slower learn-

ing. Moreover, the differences in learning and redundancy were also correlated (Figure 3.6D;$r = 0.84, p = 0.003$). This notwithstanding, we do not claim that redundancy is the sole source of motor learning. This can be seen in kinematic and dynamic learning tasks where despite smaller redundancy in kinematic task compared to the dynamic task, the learning rate is higher during the former. This is likely to reflect differences in the mechanisms involved in learning these two perturbations and they may involve the learning of different internal models [17] with joint redundancy being a common factor that confers greater flexibility to explore motor space. Additionally, we also observed differences in the degree of redundancy and learning across directions. While these differences were not statistically significant (they were also poorly correlated), these results may suggest that redundancy not only possesses an active component that correlates with learning but also a passive component that reflects differences in the biomechanics.

Finally, we only observed strong correlations between joint redundancy and motor learning but not with task-space variability. These results, suggest that the minimum intervention model or the UCM framework needs to be extended to allow for active exploration of task relevant variability as well as joint redundancy [103]. Although it is not still mechanistically clear how joint space redundancy facilitates motor learning, we suggest that such active exploration of task irrelevant space maybe essential to motor learning, while simultaneously ensuring optimal motor performance by minimizing task space variability. In contrast, recent work by Wu et. al. [59] using both reinforcement learning and error based supervised learning emphasize the selective role of task relevant variability in motor learning.

3.4.4 Neural basic for linking joint redundancy and motor learning

To identify, the neural substrate responsible for potentially linking null-space variability and motor learning, we tested patients with impaired cerebellar (Ataxia) and basal ganglia (Parkinsons disease) function. The results from both cerebellar and PD patients indicate that the degree of exploration of redundancy does not explain the reduced motor learning in these patients. However, we did find interesting differences between the correlation of redundancy and motor learning that was selectively impaired in PD patients but not cerebellar impaired patients, possibly pointing to a role of the basal ganglia in allowing for the use of exploration in motor learning. Further research would be required to reconcile these points of view.

3.5 Summary

In this work, we explore motor variability and investigate its effect on supervised motor learning. We propose that the motor variability that arises from redundancy leads to faster learning across subjects. We observed this pattern in subjects learning novel dynamics and kinematics learning. Interestingly, we also observed differences in the redundancy between the dominant and non-dominant hand that explain differences in learning of novel dynamics, suggesting that redundancy maybe actively controlled by the nervous system. The results from ataxia and Parkinsons disease patients indicate that the basal ganglia maybe involved in the exploration of redundancy in motor learning. Taken together, these results provide support for the hypothesis that redundancy aids in motor learning and that the redundant component of motor variability is not noise.

Chapter 4

Conclusions

The key contributions of this thesis are in the area of supervised motor learning. The purpose of the thesis is to understand brain mechanisms and computations underlying supervised motor learning, its interaction with reinforcement learning and study its relation to motor variability. To address these issues, we have investigated factors influencing supervised motor learning such as neurological disease condition, the role of the reinforcement signal, motor variability and motor redundancy.

This thesis addressed two main questions:

- What is the role of basal ganglia in supervised motor learning?
- What is the role of motor variability in supervised motor learning?

4.1 What is the role of basal ganglia in supervised motor learning?

In this study, we made two significant observations. First, we demonstrated how the presence and absence of dopamine and STN stimulation influenced supervised

learning thereby implicating the role of basal ganglia in supervised learning. Second, we also showed that reinforcement at the end of the trial profoundly affected drug-induced (dopaminergic) learning in PD patients. The data and results obtained suggests, that the ability to learn from errors is also dependent on the basal ganglia and is driven by reinforcement of successful actions. Our data is best explained by a gain hypothesis in which, reward mediated at the end of a successful trial releases dopamine in the proportion that changes the extent of learning occurring in the cerebellum.

A potential unexplored implication of this finding is that reinforcement of corrective processes may also a play a role in motor learning. This aspect hitherto has been overlooked in computational models of supervised learning which has instead focused on the sensory error per se. In this work, we could not distinguish between error and error correction induced learning as all trials that produced errors automatically gave rise to successful error corrections in controls as well as patients. A caveat in our interpretation is, however, the surprising finding that the presence and absence of reinforcement appeared to have a profound effect on learning in PD patients while learning was unaffected in controls. Although we currently are unable to explain this finding in a straightforward manner, this apparent discrepancy only reinforces the complexities of attempting to infer brain function by observing the lack of it in patients with disease conditions. Given the plasticity that exists in the brain, adaptive changes are likely to reconfigure brain circuitry and function in patients with respect to controls rendering interpretations to be used with caution. Nevertheless, it is important to note that our main conclusions are based on comparisons between the same patients in different states (ON and OFF dopamine), and therefore our conclusions are justified. Another noteworthy, finding is the use of DBS patients to causally manipulate basal ganglia output in a more direct fashion than has been done before.

Taken together, these studies point to a more direct role of the basal ganglia and dopamine in modulating supervised learning.

Interestingly, the improvement of learning was independent of changes in reaction time (RT), suggesting that the STN may contribute to motor learning via a separate mechanism independent of inhibitory control. Thus we suggest that improvement in supervised learning occurs independently of executive processes and supervisory processes that involve more explicit cognitive strategies. While these data implicate basal ganglia circuitry (the STN) and dopamine, the detailed mechanisms that modulate motor learning are not clear and require additional experiments. In particular, the role of stimulation at subthalamic nucleus is not clear; does STN-DBS causes a dopamine release or does STN-DBS balance out the activity of the direct and indirect pathway in an impaired basal ganglia? In future, one can test while performing supervised learning task and DBS-OFF or DBS-ON stimulation in between the experiment. Taken together, these results indicate a link connecting reinforcement, dopamine and basal ganglia in the modulation of supervised learning.

4.2 What is the role of motor variability in supervised motor learning?

A fundamental concept in reinforcement learning theory is that the learning system must both explore the environment to gain better knowledge about it and exploit current knowledge. In line with this view, recent work claims that motor variability helps in motor learning. In contrast, theories of motor control propose that variability is noise that needs to suppress. We attempt to provide a framework to reconcile these apparently contradictory positions. In this study, our data and results suggest that motor variability has two components a part arising out of the redundancy and the other related to task-space variability. We show that

the motor variability component resulting from the redundancy determines learning ability across subjects without affecting end point. Although the results are fundamentally correlational, we also tested dominant and non-dominant hand because biomechanically both are thought to be similar. Interestingly the dominant and non-dominant hand showed differences in redundancy that explained the differences in the learning rate and suggest the possibility that the brain may actively control redundancy and enhance motor learning.

Although the mechanistic basis of how redundancy helps in motor learning is not clear, we surmise that the increased flexibility afforded by joint redundancy helps overcome the consequences of perturbations, resulting in faster learning. Perhaps, the increased redundancy allows more efficient mappings between neural activation and behavioral states, allowing different motor states to exist or be traversed with fewer changes in neural space.

To identify, the neural substrate responsible for potentially linking null-space variability and motor learning, we also tested patients with impaired cerebellar (Ataxia) and basal ganglia (Parkinsons disease) function. While the results from both cerebellar and Parkinsons disease patients indicate that the degree of exploration of redundancy did not explain the reduced motor learning in these patients, we did find interesting differences between the correlation of redundancy and motor learning in Parkinsons disease patients but not cerebellar impaired patients, possibly pointing to a role of the basal ganglia in enabling the use of exploration in motor learning.

Although in this study null-space variability was computed in joint space, the neuro-motor system has redundancy even at the level of muscles. In future, one can test the significance and role of muscle redundancy in motor learning. Furthermore, null-space variability was computed at peak velocity in the trajectory. In future, one can ask, how and which part of a feed forward and feedback con-

trol null-space variability contribute. One can also investigate the unaddressed question of how null-space variability influences reinforcement motor learning.

Bibliography

[1] K. Doya. "Complementary roles of basal ganglia and cerebellum in learning and motor control". In: *Current Opinion in Neurobiology* 10.6 (2000), pp. 732–739. DOI: 10.1016/S0959-4388(00)00153-7 (cit. on pp. 3, 22, 23).

[2] Daniel M. Wolpert, R.Chris Miall, and Mitsuo Kawato. "Internal models in the cerebellum". In: *Trends in Cognitive Sciences* 2.9 (1998), pp. 338–347. DOI: 10.1016/S1364-6613(98)01221-2 (cit. on pp. 2, 8).

[3] Mitsuo Kawato. "Internal models for motor control and trajectory planning". In: *Current Opinion in Neurobiology* 9.6 (1999), pp. 718–727. DOI: 10.1016/S0959-4388(99)00028-8 (cit. on p. 2).

[4] H Imamizu, S Miyauchi, T Tamada, Y Sasaki, R Takino, B Pütz, T Yoshioka, and M Kawato. "Human cerebellar activity reflecting an acquired internal model of a new tool." In: *Nature* 403.6766 (2000), pp. 192–5. DOI: 10.1038/35003194 (cit. on p. 2).

[5] R.C. Miall and D.M. Wolpert. "Forward Models for Physiological Motor Control". In: *Neural Networks* 9.8 (1996), pp. 1265–1279. DOI: 10.1016/S0893-6080(96)00035-4 (cit. on pp. 3, 22, 43).

[6] Konrad P Körding and Daniel M. Wolpert. "Bayesian integration in sensorimotor learning." In: *Nature* 427.6971 (2004), pp. 244–247. DOI: 10.1038/nature02169 (cit. on p. 4).

[7] Shadmehr and John W. Krakauer. "A computational neuroanatomy for motor control". In: *Experimental Brain Research* 185.3 (2008), pp. 359–381. DOI: 10.1007/s00221-008-1280-5 (cit. on pp. 4, 8, 43).

[8] Reza Shadmehr. "Control of movements and temporal discounting of reward". In: *Current Opinion in Neurobiology* 20.6 (2010), pp. 726–730. DOI: 10.1016/j.conb.2010.08.017 (cit. on pp. 4, 35, 43, 75, 76).

[9] S. T. Albert and Shadmehr. "The Neural Feedback Response to Error As a Teaching Signal for the Motor Learning System". In: *Journal of Neuroscience* 36.17 (2016), pp. 4832–4845. DOI: 10.1523/JNEUROSCI.0159-16.2016 (cit. on p. 4).

[10] Reza Shadmehr, Maurice a Smith, and John W Krakauer. "Error Correction, Sensory Prediction, and Adaptation in Motor Control". In: *Annual Review of Neuroscience* 33.1 (2010), pp. 89–108. DOI: 10.1146/annurev-neuro-060909-153135. arXiv: f (cit. on p. 5).

[11] Z Ghahramani, D M Wolpert, and M I Jordan. "Generalization to local remappings of the visuomotor coordinate transformation." In: *Journal of Neuroscience* 16.21 (1996), pp. 7085–7096 (cit. on p. 4).

[12] Zoubin Ghahramani and Daniel M. Wolpert. "Modular decomposition in visuomotor learning." In: *Nature* 386.6623 (1997), pp. 392–5. DOI: 10.1038/386392a0 (cit. on p. 4).

[13] J W Krakauer, Z M Pine, M F Ghilardi, and C Ghez. "Learning of visuomotor transformations for vectorial planning of reaching

trajectories." In: *Journal of Neuroscience* 20.23 (2000), pp. 8916–24. DOI: 20/23/8916[pii] (cit. on pp. 4, 55, 75, 76).

[14] Shadmehr and F A Mussa-Ivaldi. "Adaptive representation of dynamics during learning of a motor task." In: *Journal of Neuroscience* 14.5 Pt 2 (1994), pp. 3208–24 (cit. on pp. 6, 22, 76).

[15] K a Thoroughman and R Shadmehr. "Learning of action through adaptive combination of motor primitives." In: *Nature* 407.6805 (2000), pp. 742–7. DOI: 10.1038/35037588 (cit. on p. 6).

[16] Opher Donchin, Joseph T Francis, and Shadmehr. "Quantifying generalization from trial-by-trial behavior of adaptive systems that learn with basis functions: theory and experiments in human motor control." In: *Journal of Neuroscience* 23.27 (2003), pp. 9032–9045. DOI: 23/27/9032[pii] (cit. on p. 6).

[17] John W Krakauer, M F Ghilardi, and Claude Ghez. "Independent learning of internal models for kinematic and dynamic control of reaching." In: *Nature Neuroscience* 2.11 (1999), pp. 1026–31. DOI: 10.1038/14826 (cit. on pp. 6, 22, 26, 54, 76, 77).

[18] J. Randall Flanagan, E Nakano, H Imamizu, R Osu, Toshinori Yoshioka, and M Kawato. "Composition and decomposition of internal models in motor learning under altered kinematic and dynamic environments." In: *Journal of Neuroscience* 19.20 (1999), RC34. DOI: citeulike-article-id:406855 (cit. on p. 6).

[19] Christine Tong, Daniel M. Wolpert, and J. Randall Flanagan. "Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study." In: *Journal of*

Neuroscience 22.3 (2002), pp. 1108–13. DOI: 22/3/1108[pii] (cit. on p. 6).

[20] W. Thach. "The Cerebellum And The Adaptive Coordination Of Movement". In: *Annual Review of Neuroscience* 15.1 (1992), pp. 403–442. DOI: 10.1146/annurev.neuro.15.1.403 (cit. on pp. 7, 8).

[21] T a Martin, J G Keating, H P Goodkin, a J Bastian, and W T Thach. "Throwing while looking through prisms: I. Focal olivocerebellar lesions impair adaptation". In: *Brain* 119.4 (1996), pp. 1183–1198. DOI: 10.1093/brain/119.4.1183 (cit. on pp. 8, 23, 31).

[22] Y.-w. Tseng, Jörn Diedrichsen, John W Krakauer, R. Shadmehr, and Amy J. Bastian. "Sensory Prediction Errors Drive Cerebellum-Dependent Adaptation of Reaching". In: *Journal of Neurophysiology* 98.1 (2007), pp. 54–62. DOI: 10.1152/jn.00266.2007 (cit. on pp. 8, 23, 31, 43, 45).

[23] Matthias Maschke. "Hereditary Cerebellar Ataxia Progressively Impairs Force Adaptation During Goal-Directed Arm Movements". In: *Journal of Neurophysiology* 91.1 (2003), pp. 230–238. DOI: 10.1152/jn.00557.2003 (cit. on pp. 8, 43, 45).

[24] Maurice A Smith. "Intact Ability to Learn Internal Models of Arm Dynamics in Huntington's Disease But Not Cerebellar Degeneration". In: *Journal of Neurophysiology* 93.5 (2005), pp. 2809–2821. DOI: 10.1152/jn.00943.2004 (cit. on p. 8).

[25] Amy J. Bastian, T A Martin, J G Keating, and W T Thach. "Cerebellar ataxia: abnormal control of interaction torques across multiple joints." In: *Journal of Neurophysiology* 76.1 (1996), pp. 492–509 (cit. on pp. 8, 23, 31).

[26] Javier F. Medina. "The multiple roles of Purkinje cells in sensori-motor calibration: to predict, teach and command". In: *Current Opinion in Neurobiology* 21.4 (2011), pp. 616–622. DOI: 10.1016/j.conb.2011.05.025. arXiv: NIHMS150003 (cit. on p. 8).

[27] Lucio Marinelli, Domenica Crupi, Alessandro Di Rocco, Marco Bove, David Eidelberg, Giovanni Abbruzzese, and M. Felice Ghilardi. "Learning and consolidation of visuo-motor adaptation in Parkinson's disease". In: *Parkinsonism & Related Disorders* 15.1 (2009), pp. 6–11. DOI: 10.1016/j.parkreldis.2008.02.012 (cit. on pp. 8, 23, 43).

[28] Patrick Bédard and Jerome N. Sanes. "Basal ganglia-dependent processes in recalling learned visual-motor adaptations". In: *Experimental Brain Research* 209.3 (2011), pp. 385–393. DOI: 10.1007/s00221-011-2561-y (cit. on pp. 8, 23, 43).

[29] Li-Ann Leow, Andrea M. Loftus, and Geoffrey R. Hammond. "Impaired savings despite intact initial learning of motor adaptation in Parkinson's disease". In: *Experimental Brain Research* 218.2 (2012), pp. 295–304. DOI: 10.1007/s00221-012-3060-5 (cit. on pp. 8, 43).

[30] M. Ito, M. Sakurai, and P. Tongroach. "Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells." In: *The Journal of Physiology* 324 (1982), pp. 113–34. DOI: VL-324 (cit. on p. 10).

[31] S Pasalar, A V Roitman, W K Durfee, and T J Ebner. "Force field effects on cerebellar Purkinje cell discharge with implications for internal models". In: *Nature Neuroscience* 9.11 (2006), pp. 1404–1411. DOI: 10.1038/nn1783 (cit. on p. 10).

[32] K. Doya. "What are the computations of the cerebellum, the basal ganglia and the cerebral cortex?" In: *Neural Networks* 12.7-8 (1999), pp. 961–974. DOI: 10.1016/S0893-6080(99)00046-5 (cit. on pp. 10, 22).

[33] RS Sutton and a G Barto. *Reinforcement learning: An introduction*. vol. 1. MIT press Cambridge, 1998. DOI: 10.1109/TNN.1998.712192 (cit. on pp. 11, 49).

[34] Wolfram Schultz. "Behavioral Theories and the Neurophysiology of Reward". In: *Annual Review of Psychology* 57.1 (2006), pp. 87–115. DOI: 10.1146/annurev.psych.56.091103.070229 (cit. on p. 11).

[35] Jan Peters and Stefan Schaal. "Reinforcement learning of motor skills with policy gradients". In: *Neural Networks* 21.4 (2008), pp. 682–697. DOI: 10.1016/j.neunet.2008.02.003 (cit. on p. 11).

[36] B J Knowlton, J A Mangels, and L R Squire. "A Neostriatal Habit Learning System in Humans". In: *Science* 273.5280 (1996), pp. 1399–1402. DOI: 10.1126/science.273.5280.1399 (cit. on pp. 11, 45).

[37] Ashwin G. Ramayya, Amrit Misra, Gordon H. Baltuch, and Michael J. Kahana. "Microstimulation of the Human Substantia Nigra Alters Reinforcement Learning". In: *Journal of Neuroscience* 34.20 (2014), pp. 6887–6895. DOI: 10.1523/JNEUROSCI.5445-13.2014 (cit. on p. 11).

[38] Wolfram Schultz. "Multiple reward signals in the brain." In: *Nature Reviews Neuroscience* 1.3 (2000), pp. 199–207. DOI: 10.1038/35044563 (cit. on p. 11).

[39] Wolfram Schultz. "Behavioral Theories and the Neurophysiology of Reward". In: *Annual Review of Psychology* 57.1 (2006), pp. 87–115. DOI: 10.1146/annurev.psych.56.091103.070229 (cit. on p. 11).

[40] Jeffrey R Hollerman and Wolfram Schultz. "Dopamine neurons report an error in the temporal prediction of reward during learning." In: *Nature Neuroscience* 1.4 (1998), pp. 304–9. DOI: 10.1038/1124. arXiv: NIHMS150003 (cit. on p. 12).

[41] Paolo Calabresi, Barbara Picconi, Alessandro Tozzi, and Massimiliano Di Filippo. "Dopamine-mediated regulation of corticostriatal synaptic plasticity". In: *Trends in Neurosciences* 30.5 (2007), pp. 211–219. DOI: 10.1016/j.tins.2007.03.001 (cit. on p. 12).

[42] M. J. Frank. "By Carrot or by Stick: Cognitive Reinforcement Learning in Parkinsonism". In: *Science* 306.5703 (2004), pp. 1940–1943. DOI: 10.1126/science.1102941 (cit. on p. 13).

[43] D. Shohamy, C. E. Myers, J. Kalanithi, and M. A. Gluck. "Basal ganglia and dopamine contributions to probabilistic category learning". In: *Neuroscience and Biobehavioral Reviews* 32.2 (2008), pp. 219–236. DOI: 10.1016/j.neubiorev.2007.07.008 (cit. on p. 13).

[44] Takao Hashimoto, Christopher M Elder, Michael S Okun, Susan K Patrick, and Jerrold L Vitek. "Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons." In: *Journal of Neuroscience* 23.5 (2003), pp. 1916–1923. DOI: 23/5/1916[pii] (cit. on p. 13).

[45] Adrian M Haith and John W Krakauer. "Model-Based and Model-Free Mechanisms of Human Motor Learning". In: *Advances in experimental*

medicine and biology. Vol. 782. 585. 2013, pp. 1–21. DOI: 10.1007/978-1-4614-5465-6_1 (cit. on pp. 14, 22).

[46] M F Ghilardi, J Gordon, and C Ghez. "Learning a visuomotor transformation in a local area of work space produces directional biases in other areas." In: *Journal of Neurophysiology* 73.6 (1995), pp. 2535–2539 (cit. on p. 14).

[47] Hirokazu Tanaka and Terrence J. Sejnowski. "Motor adaptation and generalization of reaching movements using motor primitives based on spatial coordinates". In: *Journal of Neurophysiology* 113.4 (2015), pp. 1217–1233. DOI: 10.1152/jn.00002.2014 (cit. on p. 14).

[48] Eiji Hoshi, Léon Tremblay, Jean Féger, Peter L Carras, and Peter L Strick. "The cerebellum communicates with the basal ganglia." In: *Nature Neuroscience* 8.11 (2005), pp. 1491–3. DOI: 10.1038/nn1544 (cit. on pp. 14, 23, 45, 46).

[49] Andreea C Bostan, Richard P Dum, and Peter L Strick. "The basal ganglia communicate with the cerebellum". In: *Proceedings of the National Academy of Sciences* 107.18 (2010), pp. 8452–8456. DOI: 10.1073/pnas.1000496107 (cit. on pp. 14, 15, 23, 45, 46).

[50] Tao Wu and Mark Hallett. "The cerebellum in Parkinson's disease". In: *Brain* 136.3 (2013), pp. 696–709. DOI: 10.1093/brain/aws360 (cit. on p. 15).

[51] Vincent S. Huang, Adrian Haith, Pietro Mazzoni, and John W. Krakauer. "Rethinking Motor Learning and Savings in Adaptation Paradigms: Model-Free Memory for Successful Actions Combines with Internal Models". In: *Neuron* 70.4 (2011), pp. 787–801. DOI: 10.1016/j.neuron.2011.04.012 (cit. on pp. 15, 22).

[52] Ali A Nikooyan and Alaa a Ahmed. "Reward feedback accelerates motor learning". In: *Journal of Neurophysiology* 113.2 (2015), pp. 633–646. DOI: 10.1152/jn.00032.2014 (cit. on p. 15).

[53] Joseph M. Galea, Elizabeth Mallia, John Rothwell, and Jörn Diedrichsen. "The dissociable effects of punishment and reward on motor learning". In: *Nature Neuroscience* 18.4 (2015), pp. 597–602. DOI: 10.1038/nn.3956 (cit. on pp. 15, 16, 23, 44).

[54] K. van der Kooij and K. E. Overvliet. "Rewarding imperfect motor performance reduces adaptive changes". In: *Experimental Brain Research* 234.6 (2016), pp. 1441–1450. DOI: 10.1007/s00221-015-4540-1 (cit. on pp. 15, 44).

[55] C M Harris and Daniel M. Wolpert. "Signal-dependent noise determines motor planning." In: *Nature* 394.6695 (1998), pp. 780–4. DOI: 10.1038/29528 (cit. on p. 17).

[56] Emanuel Todorov and Michael I. Jordan. "A Minimal Intervention Principle for Coordinated Movement". In: *Advances in Neural Information Processing Systems* (2002), pp. 27–34 (cit. on p. 17).

[57] Evren C. Tumer and Michael S. Brainard. "Performance variability enables adaptive plasticity of crystallized' adult birdsong". In: *Nature* 450.7173 (2007), pp. 1240–1244. DOI: 10.1038/nature06390 (cit. on pp. 17, 48, 50).

[58] David J Herzfeld, Pavan A Vaswani, Mollie K Marko, and Shadmehr. "A memory of errors in sensorimotor learning". In: *Science* 345.6202 (2014), pp. 1349–1353. DOI: 10.1126/science.1253138 (cit. on p. 17).

[59] Howard G Wu, Y R Miyamoto, L N Gonzales Castro, Bence P. Ölveczky, and M a Smith. "Temporal structure of motor vriability is dynamically regulated and predicts motor learning ability". In: *Nature Neuroscience* 17.2 (2014), pp. 312–321. DOI: 10.1038/nn.3616 (cit. on pp. 17, 18, 22, 48, 50, 77).

[60] Bence P Ölveczky, Aaron S. Andalman, and Michale S. Fee. "Vocal Experimentation in the Juvenile Songbird Requires a Basal Ganglia Circuit". In: *PLoS Biology* 3.5 (2005). Ed. by Wolfram Schultz, e153. DOI: 10.1371/journal.pbio.0030153 (cit. on p. 17).

[61] B. P. Olveczky, Timothy M. Otchy, Jesse H. Goldberg, Dmitriy Aronov, and Michale S. Fee. "Changes in the neural control of a complex motor sequence during learning". In: *Journal of Neurophysiology* 106.1 (2011), pp. 386–397. DOI: 10.1152/jn.00018.2011 (cit. on p. 17).

[62] Kang He, You Liang, Farnaz Abdollahi, Moria Fisher Bittmann, Konrad Kording, and Kunlin Wei. "The Statistical Determinants of the Speed of Motor Learning". In: *PLOS Computational Biology* 12.9 (2016). Ed. by Jörn Diedrichsen, e1005023. DOI: 10.1371/journal.pcbi.1005023 (cit. on pp. 17, 49).

[63] David J Herzfeld and Shadmehr. "Motor variability is not noise, but grist for the learning mill". In: *Nature Neuroscience* 17.2 (2014), pp. 149–150. DOI: 10.1038/nn.3633 (cit. on pp. 19, 48, 50).

[64] Jordan a Taylor, John W Krakauer, and Richard B Ivry. "Explicit and Implicit Contributions to Learning in a Sensorimotor Adaptation Task". In: *Journal of Neuroscience* 34.8 (2014), pp. 3023–3032. DOI: 10.1523/JNEUROSCI.3619-13.2014 (cit. on p. 22).

[65] Gregory Dam, Konrad Kording, and Kunlin Wei. "Credit Assignment during Movement Reinforcement Learning". In: *PLoS ONE* 8.2 (2013). Ed. by Paul L. Gribble, e55352. DOI: 10.1371/journal.pone.0055352 (cit. on p. 22).

[66] Amanda S Therrien, Daniel M Wolpert, and Amy J Bastian. "Effective reinforcement learning following cerebellar damage requires a balance between exploration and motor noise". In: *Brain* 139.1 (2016), pp. 101–114. DOI: 10.1093/brain/awv329 (cit. on pp. 22, 23, 49, 50).

[67] Jun Izawa and Shadmehr. "Learning from Sensory and Reward Prediction Errors during Motor Adaptation". In: *PLoS Computational Biology* 7.3 (2011). Ed. by Konrad Körding, e1002012. DOI: 10.1371/journal.pcbi.1002012 (cit. on p. 22).

[68] Jun Izawa, Sarah E Criscimagna-Hemminger, and Shadmehr. "Cerebellar Contributions to Reach Adaptation and Learning Sensory Consequences of Action". In: *Journal of Neuroscience* 32.12 (2012), pp. 4230–4239. DOI: 10.1523/JNEUROSCI.6353-11.2012 (cit. on p. 23).

[69] David Mongeon, Pierre Blanchet, and Julie Messier. "Impact of Parkinson's disease and dopaminergic medication on adaptation to explicit and implicit visuomotor perturbations". In: *Brain and Cognition* 81.2 (2013), pp. 271–282. DOI: 10.1016/j.bandc.2012.12.001 (cit. on pp. 23, 43).

[70] Jennifer A Semrau, Joel S Perlmutter, and Kurt A Thoroughman. "Visuomotor adaptation in Parkinson's disease: effects of perturbation type and medication state". In: *Journal of Neurophysiology* 111.12 (2014), pp. 2675–2687. DOI: 10.1152/jn.00095.2013 (cit. on pp. 23, 43).

[71] Jing Chen, Shu-Leong Ho, Tatia Mei-Chun Lee, Richard Shek-Kwan Chang, Shirley Yin-Yu Pang, and Li Li. "Visuomotor control in patients with Parkinson's disease". In: *Neuropsychologia* 80 (2016), pp. 102–114. DOI: 10.1016/j.neuropsychologia.2015.10.036 (cit. on pp. 23, 43).

[72] Elsdon Storey, Kate Tuck, Robert Hester, Andrew Hughes, and Andrew Churchyard. "Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS)". In: *Movement Disorders* 19.2 (2004), pp. 190–192. DOI: 10.1002/mds.10657 (cit. on p. 24).

[73] A J Hughes, S E Daniel, L Kilford, and A J Lees. "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases." In: *Journal of Neurology, Neurosurgery & Psychiatry* 55.3 (1992), pp. 181–184. DOI: 10.1136/jnnp.55.3.181 (cit. on p. 24).

[74] Verna C Pangman, Jeff Sloan, and Lorna Guse. "An examination of psychometric properties of the Mini-Mental State Examination and the Standardized Mini-Mental State Examination: Implications for clinical practice". In: *Applied Nursing Research* 13.4 (2000), pp. 209–213. DOI: 10.1053/apnr.2000.9231 (cit. on p. 24).

[75] Dario Salmaso and Anna Maria Longoni. "Problems in the Assessment of Hand Preference". In: *Cortex* 21.4 (1985), pp. 533–549. DOI: 10.1016/S0010-9452(58)80003-9 (cit. on pp. 24, 51).

[76] David H Brainard. "The Psychophysics Toolbox." In: *Spatial vision* 10.4 (1997), pp. 433–6 (cit. on p. 25).

[77] Michael Dimitriou. "Enhanced Muscle Afferent Signals during Motor Learning in Humans". In: *Current Biology* (2016), pp. 1–7. DOI: 10.1016/j.cub.2016.02.030 (cit. on p. 26).

[78] Nicolò F Bernardi, Mohammad Darainy, Emanuela Bricolo, and David J Ostry. "Observing motor learning produces somatosensory change". In: *Journal of Neurophysiology* 110.8 (2013), pp. 1804–1810. DOI: 10.1152/jn.01061.2012 (cit. on pp. 26, 55).

[79] Kae Nakamura. "Role of Dopamine in the Primate Caudate Nucleus in Reward Modulation of Saccades". In: *Journal of Neuroscience* 26.20 (2006), pp. 5360–5369. DOI: 10.1523/JNEUROSCI.4853-05.2006 (cit. on p. 35).

[80] Jennie E S Choi, Pavan A Vaswani, and Shadmehr. "Vigor of Movements and the Cost of Time in Decision Making". In: *Journal of Neuroscience* 34.4 (2014), pp. 1212–1223. DOI: 10.1523/JNEUROSCI.2798-13.2014 (cit. on p. 35).

[81] Jonathan W. Mink. "The basal ganglia: Focused selection and inhibition of competing motor programs". In: *Progress in Neurobiology* 50.4 (1996), pp. 381–425. DOI: 10.1016/S0301-0082(96)00042-1 (cit. on pp. 39, 45).

[82] Adam R. Aron, Trevor W. Robbins, and Russell A. Poldrack. "Inhibition and the right inferior frontal cortex: One decade on". In: *Trends in Cognitive Sciences* 18.4 (2014), pp. 177–185. DOI: 10.1016/j.tics.2013.12.003 (cit. on pp. 39, 45).

[83] A. R. Aron, D. M. Herz, Peter Brown, B. U. Forstmann, and Kareem Zaghloul. "Frontosubthalamic Circuits for Control of Action and Cognition". In: *Journal of Neuroscience* 36.45 (2016), pp. 11489–11495. DOI: 10.1523/JNEUROSCI.2348-16.2016 (cit. on pp. 39, 45).

[84] Ausaf A. Farooqui, Neha Bhutani, Shrikanth Kulashekhar, Madhuri Behari, Vinay Goel, and Aditya Murthy. "Impaired conflict monitoring in Parkinson's disease patients during an oculomotor redirect

task". In: *Experimental Brain Research* 208.1 (2011), pp. 1–10. DOI: 10.1007/s00221-010-2432-y (cit. on p. 39).

[85] Erik E. Emeric, Joshua W. Brown, Leanne Boucher, Roger H.S. Carpenter, Doug P. Hanes, Robin Harris, Gordon D. Logan, Reena N. Mashru, Martin Paré, Pierre Pouget, Veit Stuphorn, Tracy L. Taylor, and Jeffrey D. Schall. "Influence of history on saccade countermanding performance in humans and macaque monkeys". In: *Vision Research* 47.1 (2007), pp. 35–49. DOI: 10.1016/j.visres.2006.08.032. arXiv: NIHMS150003 (cit. on p. 39).

[86] M. Desmurget, V. Gaveau, P. Vindras, R. S. Turner, E. Broussolle, and S. Thobois. "On-line motor control in patients with Parkinson's disease". In: *Brain* 127.8 (2004), pp. 1755–1773. DOI: 10.1093/brain/awh206 (cit. on p. 43).

[87] Jordan A. Taylor and Richard B. Ivry. "Cerebellar and Prefrontal Cortex Contributions to Adaptation, Strategies, and Reinforcement Learning". In: *Progress in Brain Research*. 1st ed. Vol. 210. Elsevier B.V., 2014, pp. 217–253. DOI: 10.1016/B978-0-444-63356-9.00009-1. arXiv: NIHMS150003 (cit. on p. 43).

[88] Joshua T. Dudman and John W. Krakauer. "The basal ganglia: from motor commands to the control of vigor". In: *Current Opinion in Neurobiology* 37 (2016), pp. 158–166. DOI: 10.1016/j.conb.2016.02.005 (cit. on p. 44).

[89] Henry H Yin and Barbara J. Knowlton. "The role of the basal ganglia in habit formation". In: *Nature Reviews Neuroscience* 7.6 (2006), pp. 464–476. DOI: 10.1038/nrn1919 (cit. on p. 45).

[90] Huiling Tan, Baltazar Zavala, Alek Pogosyan, Keyoumars Ashkan, Ludvic Zrinzo, Thomas Foltynie, Patricia Limousin, and Peter Brown. "Human subthalamic nucleus in movement error detection and its evaluation during visuomotor adaptation." In: *Journal of Neuroscience* 34.50 (2014), pp. 16744–54. DOI: 10.1523/JNEUROSCI.3414-14.2014 (cit. on p. 45).

[91] William J Gehring and Robert T Knight. "Prefrontal-cingulate interactions in action monitoring." In: *Nature Neuroscience* 3.5 (2000), pp. 516–20. DOI: 10.1038/74899 (cit. on p. 45).

[92] Matthew Michael Botvinick, Todd S Braver, Deanna M Barch, Cameron S Carter, and Jonathan D Cohen. "Conflict monitoring and cognitive control." In: *Psychological Review* 108.3 (2001), pp. 624–652. DOI: 10.1037/0033-295X.108.3.624 (cit. on p. 45).

[93] Shigehiko Ito. "Performance Monitoring by the Anterior Cingulate Cortex During Saccade Countermanding". In: *Science* 302.5642 (2003), pp. 120–122. DOI: 10.1126/science.1087847 (cit. on p. 45).

[94] M Jahanshahi. "The impact of deep brain stimulation on executive function in Parkinson's disease". In: *Brain* 123.6 (2000), pp. 1142–1154. DOI: 10.1093/brain/123.6.1142 (cit. on p. 45).

[95] Michael J Frank, Johan Samanta, Ahmed A Moustafa, and S.J. Sherman. "Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism". In: *Science* 318.5854 (2007), pp. 1309–1312. DOI: 10.1126/science.1146157 (cit. on p. 45).

[96] Ben Seymour, Michael Barbe, Peter Dayan, Tamara Shiner, Ray Dolan, and Gereon R. Fink. "Deep brain stimulation of the subthalamic nucleus modulates sensitivity to decision outcome value in Parkinson's disease".

In: *Scientific Reports* 6.September 2015 (2016), p. 32509. DOI: 10.1038/srep32509 (cit. on p. 45).

[97] Sarah E Criscimagna-Hemminger, Amy J Bastian, and Shadmehr. "Size of Error Affects Cerebellar Contributions to Motor Learning". In: *Journal of Neurophysiology* 103.4 (2010), pp. 2275–2284. DOI: 10.1152/jn.00822.2009 (cit. on p. 45).

[98] Opher Donchin, Kasja Rabe, Jörn Diedrichsen, Níall Lally, Beate Schoch, Elke Ruth Gizewski, and Dagmar Timmann. "Cerebellar regions involved in adaptation to force field and visuomotor perturbation". In: *Journal of Neurophysiology* 107.1 (2012), pp. 134–147. DOI: 10.1152/jn.00007.2011 (cit. on p. 45).

[99] Tao Wu and Mark Hallett. "The cerebellum in Parkinson's disease". In: *Brain* 136.3 (2013), pp. 696–709. DOI: 10.1093/brain/aws360 (cit. on p. 46).

[100] K A Flowers. "Movement Variability and Bradykinesia in Parkinson ' S Disease". In: (1990), pp. 1149–1161 (cit. on p. 48).

[101] Jeffrey M Hausdorff, Merit E Cudkowicz, and Rence Firtion. "Gait Variability and Basal Ganglia Disorders : Stride-to-S tride Variations of Gait Cycle Timing in Parkinson ' s Disease and Huntington ' s Disease". In: *Movement Disorders* 13.3 (1998), pp. 428–437. DOI: 10.1002/mds.870130310. arXiv: gerona/glp033 [10.1093] (cit. on p. 48).

[102] Bouwien C M Smits-Engelsman and Peter H. Wilson. "Noise, variability, and motor performance in developmental coordination disorder". In: *Developmental Medicine and Child Neurology* 55.SUPPL.4 (2013), pp. 69–72. DOI: 10.1111/dmcn.12311 (cit. on p. 48).

[103] Joshua G. a. Cashaback, Heather R. McGregor, and Paul L. Gribble. "The human motor system alters its reaching movement plan for task-irrelevant, positional forces". In: *Journal of Neurophysiology* 113.7 (2015), pp. 2137–2149. DOI: 10.1152/jn.00901.2014 (cit. on pp. 49, 50, 77).

[104] Andrew G Barto. "Reinforcement learning control". In: *Current Opinion in Neurobiology* 4.6 (1994), pp. 888–893. DOI: 10.1016/0959-4388(94)90138-4 (cit. on p. 49).

[105] David P. Black, Beth a. Smith, Jianhua Wu, and Beverly D. Ulrich. "Uncontrolled manifold analysis of segmental angle variability during walking: preadolescents with and without Down syndrome". In: *Experimental Brain Research* 183.4 (2007), pp. 511–521. DOI: 10.1007/s00221-007-1066-1 (cit. on pp. 50, 74).

[106] K J Cole and J H Abbs. "Coordination of three-joint digit movements for rapid finger-thumb grasp." In: *Journal of Neurophysiology* 55.6 (1986), pp. 1407–23 (cit. on pp. 50, 74).

[107] Patrick Haggard, Karen Hutchinson, and John Stein. "Patterns of coordinated multi-joint movement". In: *Experimental Brain Research* 107.2 (1995), pp. 254–66. DOI: 10.1007/BF00230046 (cit. on pp. 50, 74).

[108] J. Park, Y.-H. Wu, M. M. Lewis, X. Huang, and M. L. Latash. "Changes in multifinger interaction and coordination in Parkinson's disease". In: *Journal of Neurophysiology* 108.3 (2012), pp. 915–924. DOI: 10.1152/jn.00043.2012 (cit. on pp. 50, 74).

[109] Yaweng Tseng, J P Scholz, and Gregor Schöner. "Goal-equivalent joint coordination in pointing: affect of vision and arm dominance." In: *Motor Control* 6.2 (2002), pp. 183–207 (cit. on pp. 50, 74).

[110] Jeng-Feng Yang, J P Scholz, and Mark L. Latash. "The role of kinematic redundancy in adaptation of reaching". In: *Experimental Brain Research* 176.1 (2006), pp. 54–69. DOI: 10.1007/s00221-006-0602-8 (cit. on pp. 50, 74).

[111] Jörn Diedrichsen, Shadmehr, and Richard B. Ivry. "The coordination of movement: optimal feedback control and beyond". In: *Trends in Cognitive Sciences* 14.1 (2010), pp. 31–39. DOI: 10.1016/j.tics.2009.11.004 (cit. on p. 50).

[112] Emanuel Todorov. "Optimality principles in sensorimotor control". In: *Nature Neuroscience* 7.9 (2004), pp. 907–915. DOI: 10.1038/nn1309 (cit. on p. 50).

[113] Emanuel Todorov and Michael I. Jordan. "Optimal feedback control as a theory of motor coordination". In: *Nature Neuroscience* 5.11 (2002), pp. 1226–1235. DOI: 10.1038/nn963 (cit. on p. 50).

[114] Mark L Latash, John P Scholz, and Gregor Schöner. "Motor control strategies revealed in the structure of motor variability." In: *Exercise and Sport Sciences Reviews* 30.1 (2002), pp. 26–31. DOI: 0091-6631/3001/2631 (cit. on pp. 50, 74).

[115] Mark L Latash, J P Scholz, and Gregor Schöner. "Toward a new theory of motor synergies." In: *Motor Control* 11.3 (2007), pp. 276–308 (cit. on pp. 50, 74).

[116] J P Scholz and Gregor Schöner. "The uncontrolled manifold concept: identifying control variables for a functional task." In: *Experimental Brain Research* 126.3 (1999), pp. 289–306 (cit. on pp. 50, 74).

[117] Shoko Kasuga, Sebastian Telgen, Junichi Ushiba, Daichi Nozaki, and Jörn Diedrichsen. "Learning feedback and feedforward control in a mirror-reversed visual environment". In: *Journal of Neurophysiology* 114.4 (2015), pp. 2187–2193. DOI: 10.1152/jn.00096.2015 (cit. on p. 55).

[118] S. Telgen, D. Parvin, and J. Diedrichsen. "Mirror Reversal and Visual Rotation Are Learned and Consolidated via Separate Mechanisms: Recalibrating or Learning De Novo?" In: *Journal of Neuroscience* 34.41 (2014), pp. 13768–13779. DOI: 10.1523/JNEUROSCI.5306-13.2014 (cit. on p. 55).

[119] Jessica X Brooks, Jerome Carriot, and Kathleen E Cullen. "Learning to expect the unexpected: rapid updating in primate cerebellum during voluntary self-motion". In: *Nature Neuroscience* 18.9 (2015). DOI: 10.1038/nn.4077 (cit. on p. 55).

[120] Pietro Mazzoni, Anna Hristova, and John W. Krakauer. "Why Don't We Move Faster? Parkinson's Disease, Movement Vigor, and Implicit Motivation". In: *Journal of Neuroscience* 27.27 (2007), pp. 7105–7116. DOI: 10.1523/JNEUROSCI.0264-07.2007 (cit. on p. 55).

[121] Mark L. Latash. *Synergy*. Oxford University Press, 2008, p. 412. DOI: 10.1093/acprof:oso/9780195333169.001.0001 (cit. on p. 74).

[122] Leia B Bagesteiro. "Handedness: Dominant Arm Advantages in Control of Limb Dynamics". In: *Journal of Neurophysiology* 88.5 (2002), pp. 2408–2421. DOI: 10.1152/jn.00901.2001 (cit. on p. 75).

[123] R L Sainburg and D Kalakanis. "Differences in control of limb dynamics during dominant and nondominant arm reaching." In: *Journal of Neurophysiology* 83.5 (2000), pp. 2661–2675 (cit. on p. 75).

[124] John W Krakauer. "Adaptation to Visuomotor Transformations: Consolidation, Interference, and Forgetting". In: *Journal of Neuroscience* 25.2 (2005), pp. 473–478. DOI: 10.1523/JNEUROSCI.4218-04.2005 (cit. on p. 75).

[125] Maurice a. Smith, Ali Ghazizadeh, and Reza Shadmehr. "Interacting Adaptive Processes with Different Timescales Underlie Short-Term Motor Learning". In: *PLoS Biology* 4.6 (2006). Ed. by James Ashe, e179. DOI: 10.1371/journal.pbio.0040179 (cit. on pp. 75, 76).