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Investigating the neural substrates mediating visuomotor adaptation;

From beginner to expert

par

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Cette thèse intitulée :

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Résumé

L'objectif général de cette thèse était d'explorer et d'identifier les substrats anatomiques impliqués dans les différents stades de l'apprentissage d'une adaptation visuomotrice à l'aide de l'imagerie par résonance magnétique fonctionnelle (IRMf). Deux expériences ont été réalisées pour atteindre ce but. La première étude avait pour objectif l'investigation du stade automatique de l'exécution de l'habileté motrice, tandis que la deuxième expérience a exploré la rétention à long terme de cet apprentissage. Ces expériences ont utilisé des sujets normaux, et ont fait usage d'une tâche de poursuite visuelle requerrant l'utilisation d'une manette de jeux. Les résultats ont révélé qu'une réorganisation fonctionnelle des régions anatomiques a eu lieux au travers des phases d'apprentissages, et que ces changements ont suivi le model d'apprentissage moteur proposé par Doyon et collaborateur (2002, 2003, 2005). En effet, les résultats de notre série d'expériences ont mis en évidence l'implication des circuits cortico-cerebelleux (CC) et cortico-striatal (CS) au stage initial d'apprentissage, tandis que seul le circuit CC était impliqué dans le stade lent, la rétention, et l'automatisation de l'habileté motrice. De plus, nos résultats ont aussi mis en évidence l'importance de considérer et de contrôle la stratégie d'exécution utilisée par les sujets pour compléter la tâche et lors de l'interprétation des résultats de l'imagerie cérébrale.

Mots-clés : Apprentissage moteur, Adaptation visuomotrice, IRMf, Rétention, et Automatisation.

Abstract

The general objective of this thesis was to explore and describe the underlying brain circuits involved at different learning phases of a visuomotor adaptation skill through the use of functional magnetic resonance imaging (fMRI). Two experiments were designed to achieve this goal. The first study had for objective to investigate the automatic execution stage of learning, whereas the second experiment investigated the long-term retention of procedural memory. All experiments involved normal subjects, and employed a visually-guided adaptation skill requiring subjects to use a joystick to complete the task. The results reveal that functional neural reorganisations take place throughout the learning phases, and these changes follow Doyon and colleagues' (2002, 2003, 2005) model of motor learning. In fact, the results of our series of experiments revealed that both the cortico-cerebellar (CC) and the cortico-striatal (CS) systems play an important role during the early learning stage of motor learning, while only the CC circuit plays a pre-eminent role during the later learning stage, and is the only system implicated in the recall and automatic execution of the visuomotor adaptation skill. What's more, our results also suggest that the execution strategy used by subjects to complete the task has important consequences on the subcortical regions recruited for task completion, and is an important factor to consider when interpreting functional imaging data.

Keywords : Motor skill learning, Visuomotor adaptation, fMRI, Retention, and Automatisation.

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If the brain was simple enough for us to
understand, then we would be
too simple to understand it.
Arthur C. Clark

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It is with immense pleasure that I regard the past six years spent completing my graduate degree at the University of Montreal, a journey rippled with challenges, successes and turning points. The lessons I have learned throughout these past years have paved the way towards a greater understanding of the exciting world that is science, but also of my self. This journey, however, would have been impossible without the understanding and support of the many gifted professors, researchers, and staff members that have composed my environment, and that took time to care and share their knowledge with me. I am indebted to my thesis supervisor, Dr. Julien Doyon, for introducing me to the field of brain imaging, and grateful for his patience and moral support throughout my studies. His knowledge and know-how have served me well, and will continue to serve me throughout my career. I would also like to thank the rest of the professorial body, including Drs. Franco Leporé and Maryse Lassonde for their attention and interest in my progress, and researchers like Dr. Pascal Belin and Dr. Jorge Harmony who were friendly enough to tolerate my numerous office intrusions, and answer my never-ending stream of questions. One cannot forget Maria Sanchez and the late Susanne Lamothe, colleagues and friends who have made my stay at the University pleasant and generally more enjoyable. Finally, this thesis would have been impossible to complete if I did not have the technical support of a number of extremely talented group of engineers and research technicians such as Boalem Mensour, Vo An Nguyen, Yves Roy, Stéphane Denis, and Anne Bellio.

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Chapter 1. Introduction

Although the study of human memory dates back to Plato's work five centuries before this era, the subject matter was mostly limited to philosophical writings and introspective probing like the kind practiced by Sigmund Freud.

It was only in the 1930's that a resourceful researcher, by the name of Karl Lashley, began a systematic quest for the exact location of memory in the brain (Viney & Brett King, 1998). His approach was fairly simple, he taught rats and monkeys a variety of tasks, then destroyed a part of their brain. He reasoned that if the animals could not remember after the lesion, then he must have found the place where memories reside. After countless experiments, Lashley's results lead him to conclude that nothing short of near complete destruction of the cortex caused the animals to forget their tasks. Tired and frustrated, he concluded that the biological study of memory was impossible.

He was proven wrong less than 25 years later when, in 1953, twenty-seven year old Henry M. entered the hospital for radical brain surgery that was to cure his epilepsy. Living with debilitating epileptic seizures, H.M. was hopeful that the procedure would change his life for the better. Instead, it trapped him in a mental time warp where television is always a new invention and Truman is forever president of the United States of America. This devastating side effect made H.M. the most studied individual in the history of brain exploration and revolutionised the field of memory research. Following the resection of a large portion of his temporal lobes, H.M. was cured of his seizures, but was left with severe anterograde amnesia. Impressively however, H.M. did preserve some mnemonic abilities. For instance, he was able to hold some information in storage for very short periods of time (short-term and working memory), and he could still learn various motor skills (Milner, 2005). Such observations of HM's case have lead to some of the seminal findings about memory. Specifically, it was shown that the hippocampus is required for the formations of explicit long-term memories, but not for the short-term recall of these memories, nor for the acquisition of various motor skills. More importantly, H.M.'s case study had vividly illustrated that there is a biological basis for memory, and that it is possible to use biological techniques to study it.

Since then, a plethora of studies have given rise to a number of models suggesting that memory is not a single entity, but rather a heterogeneous phenomenon that can be broken down into different systems, each of which is sub-served by a distinct neural network (Cohen & Squire, 1980; Schacter, 1987; Squire, 1982; Tulving, 1985). Although all these researchers agreed that memory research should be understood as the study of various *systems of memories*, they disagreed on the classification scheme and terminology that should be used to describe and define all its components. Some researchers believe that a distinction should be made between "explicit" and "implicit" memories (Schacter, 1992a; Schacter, 1992b), "cognitive memories" and "habits" (Mishkin, Malamut & Bachevalier, 1984), "procedural" and "declarative" memories (Cohen, Eichenbaum, Deacedo & Corkin, 1985), or between "declarative" and "non-declarative" memories (Squire, 1992; Squire, Knowlton & Musen, 1993). Other models propose the existence of not two, but several distinct classes of memory: "semantic memories", "episodic memories", "procedural memories", "perceptual representation systems", and "working memory" (Schacter & Tulving 1994).

Despite these differences, the model proposed by Squire and colleagues (1992, 1993) is probably the conceptual framework that has gained the most recognition in neuropsychological research over the last decade. Part of its success is that in addition to dividing memories in two broad classes (declarative and non-declarative), their model goes a step further in decomposing memories into smaller subtypes (Fig. 1.1). Another reason for its success lies in the fact that this model is based on a wide variety of evidence, ranging from animal research to investigations in both normal and pathological human populations. A considerable amount of data now supports the existence of such functionally and neuroanatomically dissociable subsystems. This model, as well as the motor skill under investigation in this thesis, will be reviewed in some detail in the following lines.

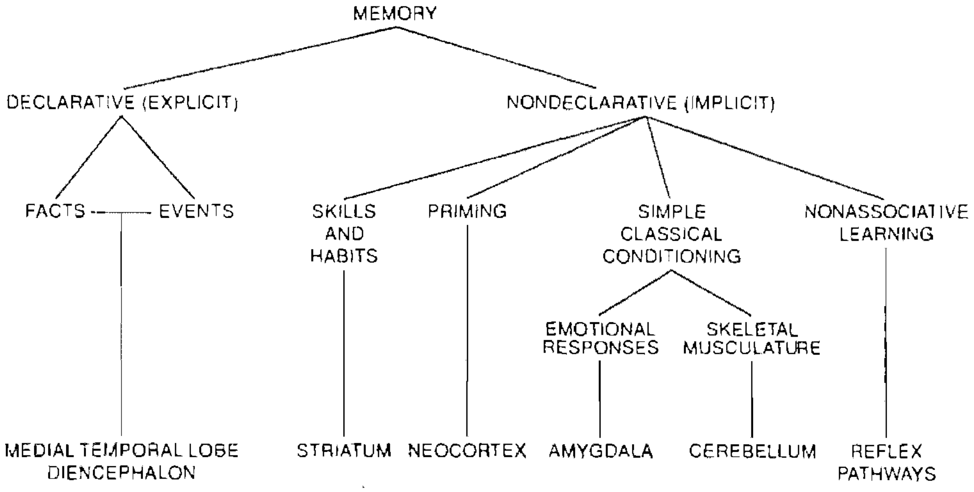

Figure 1.1 A taxonomy of memory and associated brain structures adapted from Squire & Knowlton (1995).

Briefly, Squire and colleagues propose that declarative memories are made up of facts and events that can be expressed in words. As such, two types of declarative memories have been distinguished: *semantic memories*, which refer to factual information that a group of people can share (e.g. who is the prime minister of Canada?), and *episodic memories*, which refer to autobiographical information for events (e.g. where you were on September 11th 2001?). The acquisition of these types of memories is rapid, as it often takes only a brief exposure for them to be acquired, and their expression is conscious and explicit, meaning that they require conscious thought to be learned or expressed (Cohen & Squire, 1980). In contrast, Squire & Knowlton (1995) define non-declarative memories as skills or habits that are acquired gradually with practice (priming and taste aversion conditioning are exceptions since they can be acquired after a single trial). In general, however, non-declarative memories are learned slowly and often require many repetitions over several training sessions to develop (Fitts, 1964). The acquisition of such abilities can be explicit and/or purely implicit, as they do not require conscious thought to be learned or expressed (Squire, 1992). The non-declarative memory system is comprised of four subtypes; skills and habits, priming, simple classical conditioning and non associative learning. Of particular importance for this work is the acquisition of skills. *Skill learning* refers to the learning of motor, cognitive or perceptual skills, whereby performance on a given task improves with repetition, such that after a critical amount of training, highly skilled performance levels can be attained (Mishkin, Malamut & Bachevalier, 1984; Squire & Knowlton, 1995; Squire & Zola, 1996).

As I will present in greater detail further, researchers differentiate between three general types of skills: cognitive, perceptual and motor skills. Motor skills themselves are subdivided into two smaller categories: sequence learning and motor adaptation. The work completed in this thesis has concentrated on studying a particular class of motor adaptation, namely visuomotor adaptation. Briefly defined, visuomotor adaptation skills refer to a set of abilities that allow an individual to change motor commands in response to alterations in sensory feedback. These motor capacities are essential to complete several everyday tasks, and actively contribute in such tasks as walking, driving, using a computer mouse, etc. In fact, their presence in our everyday functioning is ubiquitous, and researchers' interest in the learning of such skills is justifiable.

However, although the cerebral structures and circuits involved in the learning of declarative memories are well known (Meunier, Bachevalier, Mishkin & Murray, 1993; Squire, 1992; Squire, Knowlton & Musen, 1993), an analogous circuitry for motor skill learning is only beginning to be defined. Based on animal and human work, several brain structures, including the basal ganglia, cerebellum, and motor cortical regions of the frontal lobe are thought to be critical for the acquisition and/or retention of skilled motor behaviours (e.g. Bloedel, 1992; Nezafat, Shadmehr & Holcomb, 2001a; Della-Maggiore & McIntosh, 2005; Krebs et al., 1998; Doyon et al., 2002a; Ungerleider, Doyon & Karni, 2002; Doyon et al., 2004; Doyon & Benali, 2005). The exact nature of their involvement in motor skill learning, however, is far from being well understood. In fact, contradictory findings concerning the involvement of these structures in skill learning is quite common (Garavan, Kelley, Rosen, Rao & Stein, 2000). The general objective of the present thesis is thus to use modern neuroimaging tools to contribute to our current understanding of the memory system underlying motor skill learning. Based on the recent models presented by Doyon and collaborators (2002, 2003, 2005) that attempts to predict the involvement of the different brain regions during the learning of motor skills, we derived a-priory hypotheses concerning the automatisation and long-term retention of a visuomotor adaptation that we set out to test.

Chapter 2. The experimental study of motor adaptation

2.1. Defining and differentiating between motor skills

As was previously stated, our understanding of the memory system in the early part of the 1990s was of two broad categories of learning exists (i.e declarative and non-declarative), and that these two categories were further subdivided into smaller subcategories. The specific subcategory of interest in this thesis was referred to as skills and habits. It is generally agreed that three broad types of skill can be learned (cognitive, perceptual and motor) (Mishkin & Murray, 1994; Squire & Knowlton, 1995; Squire & Zola, 1996). Their acquisition is usually measured by a gradual reduction in reaction time, decrease in number of errors, and/or a reduction in the number of trials needed to reach successful completion criterion.

Cognitive skill learning can be defined as the process by which the procedures and strategies relevant to the performance of a task demanding mental operations come to be combined and used effectively following repeated practice (Ouellet, Beauchamp, Owen & Doyon, 2004). The learning and use of mathematics and arithmetic is a good example of cognitive skill learning in everyday life. On the other hand, visual-perceptual skills involve the ability to accurately interpret and give meaning to what is seen. A number of specific skills fall into this category. They include; visual discrimination -or the ability to distinguish one visual pattern from one another; and visual closure -or the ability to perceive a whole pattern when shown only parts of that pattern (R.Clay Reid, 1999).

The skill that has attracted most attention, and prompted the largest body of the research, including the experiments in this thesis, has been motor learning. The fact that motor learning has generated a great deal of investigations and deliberations is equitable to the amount of activities in everyday life that require the gradual acquisition of motor skills. Simply brushing our teeth necessitates the co-articulation of arm, hand and finger movements into specific and smoothly executed sequences of action. Motor skill learning can be operationally defined as the process by which movements, either produced alone or in a sequence, come to be performed effortlessly through repeated practice (Willingham, 1998). As one can readily recognise, this operational definition is rather vague and can encompass a wide variety of tasks that are quintessentially different. For instance, although knitting and playing consol games can be regarded as tasks that require the gradual acquisition of motor skills, they are essentially very different in nature. Just as memory research has invariably lead us to consider memory as a wide architecture of complex and distinguishable subtypes, so has the specific study of motor skills directed investigators to dissociate various forms of motor skills subtypes. Although varying in their complexity and nature, investigators agree to distinguish between two general categories of motor skill tasks: motor sequences and motor adaptation tasks.

Knitting is considered a *motor sequence tasks* because it requires the incremental acquisition of movements into a well-executed behaviour. To study the neural substrates mediating our agility to learn motor sequences, investigators have used a number of different experimental procedures. Researchers have tested subjects as they learned to repeat sequences of fingers or limb movements (Karni et al., 1995; Doyon et al., 2002), to move a pen through a cut-out maze by trial and error (Van Mier, Tempel, Perlmutter, Raichle & Petersen, 1998), and even while subjects knit (Doyon, pers comm).

On the other hand, consol games are considered *motor adaptation tasks* because they require subjects to map new representations between the various motor commands and the sensory feedback involved in the tasks' execution (Klassen, Tong & Flanagan, 2005). In order to study motor adaptation learning, researchers have employed a number of different paradigms. For instance; tasks requiring subjects to maintain contact between a metal stylus and a small target located on a disk that can be adjusted to rotate at different velocities (rotor pursuit task) (Maquet, Schwartz, Passingham & Frith, 2003; Smith & Smith, 2003), or asking subjects to draw figures through the reflection of a mirror (mirror-drawing task) (Gabrieli, Stebbins, Singh, Willingham & Goetz, 1997), or to adapt to changes in the relationship between the movements of a joystick and those of a cursor on a screen (tracking task) (Della-Maggiore & McIntosh, 2005; Contreras-Vidal & Kerick, 2004; Krakauer, Ghez & Ghilardi, 2005; Graydon, Friston, Thomas, Brooks & Menon, 2005), or even to adapt to changes created by a force field applied to a robotic arm when pointing to visual targets (force field adaptation task) (Diedrichsen, Hashambhoy, Rane & Shadmehr, 2005; Smith, Brandt & Shadmehr, 2000; Smith & Shadmehr, 2005; Shadmehr & Wise, 2005).

Learning from the errors of our predecessors, we can now recognize that comparing the results obtained while subjects learn to manipulate a joystick in a novel movement relationship to that of subjects learning a sequence of finger movements, is probably not very valid and clearly should be avoided. Ghilardi and his colleagues (2000) have argued that the different kinematic features and performance criteria of these tasks should discourage investigators from comparing the patterns of brain activity measured through one task to the other (Ghilardi et al., 2000). As these authors have pointed out, the simple act of reaching for an object requires the learning of both the sensorimotor representations of external space and of internal models of the dynamic properties of the musculoskeletal system. This kind of learning is believed to occur without the conscious awareness on the part of the subjects since they cannot describe the individual feedback events, the precise sequence of motor responses or the nature of the learned behaviour. On the other hand, subjects are generally aware of the specific responses during the learning of ordered sequences of required movements (Ghilardi et al., 2000).

Just as these researchers have suggested, we now know that different patterns of brain activations follow the acquisition of these different type of motor learning. Furthermore, recent evidence has also suggested that motor adaptation themselves should be further subdivided into two distinct categories (kinetic vs. kinematic adaptation), and that each form of motor adaptation constitute distinct processes that may require the use of separate neural substrates (Shadmehr & Wise, 2005).

This idea has stemmed from work completed by Krakauer and collaborators (1999) where in they elaborated a simple yet elegant series of experiments in which it was hypothesised that, should the processes underlying their acquisition be distinct, learning a novel dynamics adaptation should not interfere with the consolidation of a previously learned kinematic transformation. In addition, they hypothesised that, if distinct, these processes should be learned in parallel (Krakauer, Ghilardi & Ghez, 1999). In line with their hypotheses, they observed that the learning of novel dynamics does not interfere with the consolidation of a newly learned kinematic transformation, whereas the learning of another kinematic or dynamic interferes with the consolidation of a previously learned transformations of the same type. They also concluded that novel kinematic and dynamic transformations can be learned in parallel, supporting the idea that their acquisition is independent (Krakauer, Ghilardi & Ghez, 1999). One can therefore predict that these different forms of motor adaptation would involve separate regions of the motor system. Functional imaging data are consistent with a separation in the systems that mediate the different motor adaptations. In fact, kinematic learning has been associated with activations in posterior parietal areas , whose inputs are predominantly visual, whereas Kinetic adaptation has been associated with activations in the anterior regions of the parietal cortex (Stickgold, 2005; Walker & Stickgold, 2005).

In a more recent imaging study, Diedrichsen et al. (2005) investigated the neural responses evoked by these two adaptation tasks using fMRI and concluded that kinetic and kinematic transformations are not performed in two anatomical separate areas but rather in one continuous, overlapping cascade (Diedrichsen, Hashambhoy, Rane & Shadmehr, 2005). This issue certainly requires further investigation, however, one can readily assert the relevance of closely considering the type of motor adaptation tasks when interpreting imaging data, and when comparing our results to previous findings of brain imaging.

Although important in the context of skill learning, the acquisition of motor sequences constitutes, in itself, a vast domain of research which exceeds the aim of this thesis. For a more complete review on the matter, review the work of such authors as Ashe, Lungu, Basford & Lu (2006). Moreover, motor skill learning has been empirically studied for more then 70 years to date, and over 15 400 studies have been completed on this specific subject since 1935. These research endeavours include animal experiments in rodents and non-human primates, as well as research efforts in healthy humans and humans suffering from a range of debilitating conditions such as strokes and neurodegenerative diseases. More recently, the emergence of new imaging technologies have allowed researchers to expand this search and investigate the in-vivo implications of different brain structures in healthy humans. Considering the scale and magnitude of this research effort in the domain of motor skill learning, the short review that follows will focus on the contribution of modern imaging techniques to our state of knowledge regarding motor adaptations.

2.2. The neuroimaging of motor adaptations

A brief Pubmed review of articles published since 1990 reveals that over 4000 imaging studies concerned with motor adaptations have been completed. All of these studies have suggested the implication of a number of brain structures believed to be critical for the learning and the execution of the motor adaptations. Not surprisingly, most of these studies have reported very different results, some were even contradictory. The objective of the following sections is to review some of the seminal studies in the field of motor adaptation learning, to list and explain the contradictory findings, and discuss the important lessons we keep from them.

It is a well known fact that people demonstrate an impressive ability to acquire an almost unlimited repertoire of complex motor skills. The skills of musicians and athletes are good examples of such incredible learning feats. However, in the early 1990s, little was known about the neural systems that are required for motor control and task execution. Although the involvement of the cortical motor areas, the cerebellum and the striatum were derived from medical knowledge (i.e. stroke and neurodegenerative diseases), their implication and that of other brains structures was not well understood.

Grafton and colleagues (1992) completed some of the very first work specifically aimed at identifying the functional anatomy of the initial stages of motor skill acquisition (Grafton et al., 1992). Their study was designed to distinguish activations associated with the execution of the visuomotor task from the longitudinal changes associated with learning of the skill. These authors scanned six healthy subjects using positron emission tomography (PET) while they learned to perform a rotor pursuit task with their dominant right hand. The experiment was carried out during a single scanning session in which six scan runs were completed. Between each of these runs, a short practice period was given so as to accelerate learning of the pursuit performance. Grafton and colleagues (1992) reported that motor execution was associated with the activation of a widely distributed set of cerebral areas that included the left and right primary motor cortices and supplementary motor areas (SMA), the left putamen, globus pallidus and substancia nigra, the middle and left parasaggital zones of the cerebellum, as well as bilaterally within the visual systems of the occipital lobes (Grafton et al., 1992). As the subjects' performance became smooth and continuous, and learning of the task had improved significantly, the authors measured increases in relative cerebral blood flow in only three regions: left SMA, left motor cortex and left thalamus. They concluded that early learning of the visuomotor task occurs within this small subset of the neural network where the behaviour is actualised (Grafton et al., 1992). Although the authors found it interesting that no longitudinal changes of activity were measured in the cerebellum and in the motor cortex during the learning of the visuomotor skill, they conclude that their implication may be relate to the consolidation of skill following additional practice.

The cerebellum's role during the learning of a visuomotor adaptation tasks was specifically investigated by Flament and his colleagues a few years later (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996). These authors used functional magnetic resonance imaging (fMRI) to study the changes in cerebellar activation that occur during the acquisition of a pointing task. In this study, the experimenters scanned fourteen right handed healthy subjects while they used a joystick to superimpose a cursor onto a visual target. Two variations of this visuomotor adaptation task could be performed: 1) while the joystick and cursor movement were reversed (reversed paradigm), and 2) while the joystick and cursor relationship changed randomly for every trial (random paradigm). As such, this random condition kept subjects from making any significant gains in their learning, and therefore subjects remained in the early learning stages. The experiment was carried out during a single scanning session in which four scan runs were completed. No practice period was given between the scanning runs. Imaging the cerebellum only, the authors of this study observed a clear relationship between the activation in the cerebellum and the learning of the motor skill. They reported the cerebellum's involvement was highest during the entire random paradigm and during the early learning stages of the reversed paradigm. Inversely, cerebellar activation decreased when the subjects learned to perform the reverse paradigm more efficiently and smoothly (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996). As such, the authors reported a negative correlation between the cerebellum's involvement and amount of learning on the visuomotor adaptation task; as learning progressed, the cerebellum became less involved in the task's execution. In line with this statement, the authors reported that repeated practice on the random condition paradigm did not produce improvements in performance and cerebellar activity remained high. Flament and his colleagues (1996) concluded that their results were consistent with the role of the cerebellum in error detection and correction during tasks in which there is a need to remap sensory and motor information (i.e. visuomotor adaptation) (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996).

A prism-adaptation task was used to investigate visuomotor adaptation by Clower and his colleagues in 1996 (Clower et al., 1996). In their experiment, seven right handed healthy subjects wore goggles over each eye that created a visual displacement field of 17°. The subjects' task was to reach a visual target presented on a touch screen using their right index finger while viewing the distorted visual image. Using PET to investigate the underlying brain structures involved in the acquisition of this task, subjects were scanned in one session composed of several runs. During these scanning runs, subjects completed one of three different conditions of the above mentioned task. In four of these runs, subjects were asked to complete the experimental task described above. In another four runs, subjects were asked to complete a control condition in which the target's location was randomly displaced to either the left or the right while the subject was in mid-reach. In the final condition, subjects were simply asked to passively view the visual targets without making any reaching movements. These researchers reported that the net effect of the adaptation process was associated to selective activations limited to the left posterior parietal cortex (Clower et al., 1996). Surprisingly, no activation in other regions were identified as being involved in the adaptation process per se, as activations in other cerebral areas were cancelled out by their control procedures. The authors therefore argued that these other areas were probably implicated in the error correction that typically accompanies prism adaptation, a mechanism that could be anatomically and functionally distinct from the coordinative remapping between the visual and proprioceptive representations (Clower et al., 1996).

In a series of experiments conducted by Shadmehr and Brashers-Krug in 1997, it was suggested that the formation of human long-term memory for motor skills proceeds through functional stages that are anatomically distinguishable (Shadmehr & Brashers-Krug, 1997). These authors employed a robotic manipulandum that produces a force field to the arm holding the handle. The subjects' task was to grip the handle of the robot and try to make reaching movements in order to move a cursor presented on a computer screen to attain a target. In effect, the subjects had to adapt to the task by compensating the forces produced by the robot. These authors gathered evidence that argues for a distinct change in the state of resistance of a motor memory within a few hours after its acquisition. In fact, their data suggested that the ability to learn a second task (similar to the first) dependent on the time elapsed since the learning of the first. They therefore argued that it is possible that neural basis of motor memory changes after its acquisition (Shadmehr & Brashers-Krug, 1997).

A few months later, Shadmehr and colleagues (1997) used positron emission tomography (PET) to investigate the neural correlates of early, late and delayed recall of the same force field adaptation task (Shadmehr & Holcomb, 1997). In their study, 16 healthy subjects were asked to execute rapid reaching movements to a series of targets while holding the handle of a robot that produces a force field. Their experiment was carried out on a single day and was divided into two sessions separated by a 5.5 hour period. Shadmehr et al. (1997) measured significant increase in activity in the right thalamus, medial occipital gyrus and dorsal prefrontal cortex during the early stages of learning. No significant differences where observed in brain activations as subjects progressed to the late learning stage. However, when subjects were required to recall the newly learned skill 5.5 hours later, these researchers observed a shift from the prefrontal cortical regions to the premotor, posterior parietal, and the anterior cerebellar cortex (Shadmehr & Holcomb, 1997). They interpret this shift in brain region activation as specific to the recall of an established motor skill, and conclude that there is a change in the neural representation of the internal model that accompanies the passage of time.

A study undertaken by Krebs and colleagues (1998) had a similar goal, and used PET with the same force field adaptation task to investigate the early and late phases of adaptation learning (Krebs et al., 1998). They scanned 8 healthy subjects in a single session that lasted only a few hours. These investigators observed a very different pattern of results as their subjects progressed from the early to the late stage of learning. In fact, the early learning stage was associated with increased activity in the right striatum and right parietal area, as well as in the left parietal and primary sensory cortex, whereas the late learning stage resulted in increased activity in the left motor and premotor cortex, as well as in the right cerebellar cortex (Krebs et al., 1998). Although these researchers identified different cortical and subcortical regions than those reported by Shadmehr and colleagues (1997), their conclusions are similar in that they suggest a shift in neural structures that accompanies the progressive stages of motor learning.

In 1998, Inoue and colleagues designed an imaging study to examine where in the human brain visual feedback of hand movement is processed and utilised to permit the accurate pointing required in visuomotor adaptation (Inoue et al., 1998). This team of researchers use PET to measure the regional cerebral blood flow in nine right handed healthy subjects as they completed two different version of a visually guided reaching task. In one version of the task, subjects had to point to the target with their right index finger while their right hand was visible to them (with visual feedback). In the other version, the same task was completed, but the subjects' hand was not made visible to them (without visual feedback). According to the authors, both conditions yield increased activity in the supramarginal cortex, the premotor cortex and the posterior cingulated cortex of the left hemisphere, as well as in the right caudate nucleus, thalamus and cerebellum. Interestingly, however, the authors report identifiable fields of activation within these regions that are specific to the visual feedback condition (Inoue et al., 1998). According to Inoue et al. (1998), these patterns of activity suggest that specific regions within a larger network may play important roles in integrating visual feedback from hand movements and execution of right hand pointing (Inoue et al., 1998).

In an effort to better understand the cerebellum's role in the acquisition and maintenance of a visuomotor adaptation task, Imamizu and colleagues (2000) used fMRI to try to identify regions within the cerebellum that are specifically involved in the maintenance and storage of the internal model representing the motor task (Imamizu et al., 2000). These experimenters scanned ten healthy right handed subjects in six scanning runs in which they completed two versions of a tracking task using a computer mouse. In between these scanning runs, subjects completed a practice sessions on the tasks to accelerate learning and improve performance to an almost asymptotic level. In the visuomotor adaptation version of the task, the relationship between the mouse's movement and those of the cursor it controlled included a rotational transformation of 120°, while the second version was a control task in which the computer mouse normally controlled the cursor. As a result, the authors observed two types of activations in the cerebellum. One was spread out over wide areas of the cerebellum and was proportional to the error signal that guides the acquisition of internal models during learning. The other was confined to the area near the posterior fissure and remained after learning, when the error levels had reduced and were equalised (Imamizu et al., 2000). According to Imamizu and his collaborators (2000), their findings are poof that the cerebellum in not simply involved in the early phases of learning, but that specific sites within the cerebellum are involved in the creation and storage of an internal model representing the altered relationship between the cursor and mouse movements (Imamizu et al., 2000).

In 2001, Nezafat et al. also used PET and the same robot arm as the one used by Shadmehr et al. (1997) and Krebs et al. (1998) to investigate the learning and delayed recall of the adaptation skill. These researchers asked 8 subjects to complete 3 scanning sessions that were each separated by periods of two weeks, and reported on the involvement of the cerebellum during this period. Their results demonstrated an inverse relationship between the posterior regions of the right cerebellum and ipsilateral deep cerebellar nuclei (DCN). As learning progressed during the first session, decreased activity measured in the cerebellar cortex was accompanied by increased activity in the DCN. Across time, and with improvement in performance, the same negative correlation between regions was measured, and the strength of the latter significantly increased during the four-week period (Nezafat, Shadmehr & Holcomb, 2001).

Building on the results reported in their 2000 study, Imamizu and his colleagues (2003) investigated the cerebellum in more detail to determine if it could include a modular organisation for internal models (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). As such, Imamizu et al. (2003) asked whether or not the use of two separate tools could produce different patterns of activation within the cerebellum. Through the use of fMRI, the authors scanned seven healthy subjects while they performed three version of the same pointing task they employed in 2000. Two of the versions were identical to the ones used in 2000 (rotational mouse and control mouse), but the third computer mouse task did not create a rotational transformation, but rather a speed adaptation (velocity mouse). In this version of the task, the speed of the cursor's movements was determined by the mouse's position at the beginning of the trial. Following an extensive training period that was intended to make subjects proficient enough on both tasks so that they may easily switch between the two, subjects underwent four scanning runs: the rotated mouse followed by the control task, and the velocity mouse followed by the control task. Their results indicated that the two different tools were spatially segregated within the cerebellum (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). In fact, activations resulting from the use of the rotational mouse were more anterior and lateral to those resulting from the use of the velocity mouse, which were more posterior and medial (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). The authors do, however, bring up the difficulties in controlling and analysing the different kinetic components of the tasks, and conclude by stating that although these trends were common to all subjects, their precise location differed among them.

Similar to the work of Imamizu and colleagues (2003) with regard the multiplicity of internal models, and building on the psychophysical data accumulated throughout the better part of the 1990s, Krakauer and his colleagues (2004) investigated the possibility of separate anatomical substrates for the processing and storage of directional and extent errors needed for adapting to rotational and gain transformation. According to these authors, these two types of adaptation tasks are fundamentally different, and should therefore involve distinct functional and anatomical substrates (Krakauer et al., 2004). Furthermore, according to their hypothesis, activations measured in these substrates should change with the progressive learning from the rapid to the slow stages. To investigate their hypothesis, the authors used a reaching task in which subject manipulated a joystick in order to move a cursor displayed on a computer screen to a visual target in synchrony with a tempo. The adaptations were produced by changing the gain between the cursor and joystick movements (gain adaptation), or the direction of the cursor movement relative to the direction of the joystick movements (rotational adaptation). Learning on these tasks was manipulated by randomly altering the gain and rotation within blocs of trials. That is, when the changes are manipulated randomly, no learning is made and subjects should remain within the fast learning phase (Krakauer et al., 2004). Using PET and twelve right handed healthy subjects, Krakauer and his colleagues partly confirmed their theory. Firstly, the authors reported the regions activated in rotation adaptation were principally cortical for both rapid and slow learning phases. As such, activations were measured in the right posterior parietal cortex, right ventral premotor cortex and in the left lateral cerebellum during the slow learning phases. The fast learning of a rotation adaptation only revealed activation in the supplementary premotor area. In contrast, they found that the rapid phase of gain learning involves subcortical components; left medial cerebellum and bilateral putamen. No significant activation changes were measured outside of the areas with increased learning (Krakauer et al., 2004). Based on their imaging results, the authors come to two conclusions: 1) that the time course of rotation adaptation is paralleled by a frontoparietal shift in activated cortical regions, and 2) early gain adaptation involves only subcortical structures, which they suggest reflects a more automatic process of contextual recalibration of a scaling factor (Krakauer et al., 2004).

In 2004, Floyer-Lea and Matthews scanned fifteen subjects using fMRI to characterise the changes in brain activity that take place between early visuomotor learning and greater automaticity on the task (Floyer-Lea & Matthews, 2004). Unlike previous research exploring visuomotor adaptations, these experimenters used a task in which subjects had to visually track a moving target by varying the isometric force applied to a pressure plate held in the right hand. Also unlike previous work, this research tried to move beyond the early and late learning phases, and explored the changes in brain networks that accompany the later automatic execution stage. Their experiment was carried out in a single scanning session in which subjects completed ten scanning runs. The attainment of automaticity was verified in a separate experiment following the scanning session and used a dual task paradigm to validate the subjects' performance levels. The authors identified two distinct and time-dependent patterns of functional changes in the brain associated to the automatisation process. According to Floyer-Lea and Matthews (2004), the initial stage of learning, which was more attentionally demanding, was associated with the greatest relative activity in widely distributed cortical regions including the prefrontal, bilateral sensorimotor and parietal cortices (Floyer-Lea & Matthews, 2004). Activity at this stage was also measured in the caudate and ipsilateral cerebellar hemisphere. As learning progressed, the activity in these regions decreased, and activity increases were measured in subcortical motor regions including that of the cerebellar dentate, thalamus and putamen. These researchers interpreted their data by stating that the early performance gain in visuomotor adaptation rely strongly on prefrontal-caudate interactions, however as the task becomes automatic, activity increases in a subcortical circuit involving the cerebellum and the basal ganglia (Floyer-Lea & Matthews, 2004).

More recently, Della-Maggiore and her colleagues (2005) also used PET to investigate the time course of changes in brain activity and functional connectivity associated with the early and slow learning phase of a task that required a rotational transformation (Della-Maggiore & McIntosh, 2005). These researchers used a reaching task that required their twenty healthy subjects to adapt to distorted visual feedback similar to a mirror image. This study took seven days to complete, and subjects were scanned on the second and last day in order to monitor the brain plasticity mediating the early and slow learning stages. Early learning on the adaptation skill was associated with greater activity in bilateral dorso- and ventrolateral prefrontal cortices, frontal eye field, and the human homologue of area MT. As adaptation proceeded, however, the improvement in performance was associated with greater activity in the left sensorimotor cortex, bilateral anterior cerebellar regions, left cingulated, right putamen and middle temporal gyrus.

As we can see, although all of these studies focussed on the acquisition of a motor adaptation skill learning, and all studies dealt with the importance of specific brain regions during learning, their conclusions differ greatly. What are the reasons for such discrepancies? Can the differing pattern of results be explained away on methodological ground? The following section will be devoted to addressing this last question and enumerating some of these important experimental factors.

2.3. The discrepant factors in the imaging studies

2.3.1. Different imaging technologies

The first and most obvious discrepancy between the above reviewed studies is the imaging technology used to investigate the underlying brain structures. In fact, although fMRI and PET imaging are based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain, they measure activity in different manners. The source of the fMRI signal comes from the local reduction in deoxyhemoglobin that follows neural activity in a brain regions. It is this relative reduction in deoxyhemoglobin as compared to the oxyhemoglobin that is measured and analysed (Fox & Raichle, 1985). On the other hand, PET technology measures the decay of a short-lived radioactive tracer isotope after it has been injected into the bloodstream of a living subject. As such, PET measures the flow of this tracer through the blood stream into the brain areas that are more active during the task, whereas the fMRI measures the difference between deoxyhemoglobin and oxyhemoglobin in the activated region. Another factor to consider is the discrepancies within studies using PET technology; the different investigators used assorted tracers to monitor and measure regional cerebral blood flow. For instance, Krebs and colleagues asked subjects to inhale the tracer 15 O-CO2 30, while Nezafat and Della-Maggiore's groups used a bolus injection of mCi H2O15. Since radioactive tracers are designed to examine different aspects of brain functions, it follows that this divergence in PET methodology may have lead the researchers to measure dissimilar brain functions.

2.3.2. Different regions of interest

The second factor of importance is the regions visualised and investigated by the research teams. For instance, while researchers like Shadmher et al. (1997), Inoue et al. (1998), Floyer-Lea et al. (2004) and Della-Maggiore et al. (2005) looked at activity in the entire brain, other researchers like Flament et al. (1996), Krebs et al. (1998) and Imamizu et al. (2000, 2003) focussed on cerebellum's involvement in the learning process. One can readily understand the consequences of such a difference on the investigation of brain areas involved in the process.

2.3.3. Different methodological factors

Yet another factor to consider when interpreting the discrepancies between studies is the different methodological techniques used to analyse the data. It was previously thought that one of the most important limitations of modern neuroimaging is that the results are greatly underdetermined by the data, and that any particular finding is open to a number of interpretations. Going further, some authors have suggested that every data point can be disputed as being either real or artefactual (Poldrack, 2000; Ashe, Lungu, Basford & Lu, 2006). Although this may appear to be an extreme viewpoint, the fact remains that a number of data analysis approaches have been applied to identify plastic changes in neuroimaging data, and relatively little is known about their comparative virtues. Because learning the adaptation task includes components associated to visual perception, force production, attention and error reduction processes, subtracting the adaptation condition to the rest condition cannot reveal learning related activity per se. For instance, Although Shadmehr (1997) and Krebs (1998) used contrast analyses to interpret their data, they each used a different control task in the subtraction. Shadmehr and colleagues (1997) contrasted the adaptation condition to another adaptation condition (random field condition) that could not be learned. On the other hand, Krebs and his colleagues (1998) contrasted the motor adaptation task with a condition in which subjects completed the robot arm task while it did not produce any force field. It therefore follows that they each removed different condition-related activations from their data. For their part, Nezafat (2001) and Della-Maggiore (2005) employed a combination of contrast and parametric designs, and both were also interested in observing changes in the strength of functional connectivity between brain regions. These differences limit the interpretations and the conclusions researchers can come to concerning a region's role in the learning process, and therefore greatly undermines the consistency of the results reported in the literature.

Another methodological factor that we need to consider is the experiments' time line. In fact, because the studies described above varied in their learning time-line, the amount of sleep that subjects had is also likely to have varied across these studies. This may be an important factor since we now know that sleep is an important variable to consider when studying learning and it's consolidation (Stickgold, 2005; Walker & Stickgold, 2005). Interestingly however, recent data acquired in our laboratory confirms the importance of sleep in the consolidation of a motor sequence task, but the data also suggests that sleep has little effect in the consolidation of a visuomotor adaptation (Morin, pers comm).

2.3.4. Different experimental tasks

The fourth factor that can cause important discrepancies in the results of the different studies deals with the motor adaptation tasks investigated. In the studies reviewed above, we counted several different motor tasks that required subjects to adapt their movement to various kinds of distorted feedback. Some teams of researchers used reaching tasks in which the visual feedback was distorted through a rotational transformation (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996; Inoue. et al., 1998; Imamizu et al., 2000), through a gain in movement of the manipulated cursor (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003), or in its speed (Krakauer et al., 2004). Other tasks measure subjects' adaptation to miscalibration of dynamics in which subjects have to adapt to a change in force (Shadmehr & Brashers-Krug, 1997; Krebs et al., 1998; Nezafat, Shadmehr & Holcomb, 2001). The differences in the nature of these tasks is very important to consider since research has shown that not only is there a difference between kinetic and kinematic types of adaptation (Ghilardi et al., 2000), but that different kinds of kinematic adaptation also produce anatomically distinct patterns of brain activation (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). Other researchers have also suggested that visuomotor adaptation mechanisms engaged during perceptual recalibration (e.g. prism adaptation tasks) differ from those employed during visuomotor skill acquisition (e.g. pointing task with distorted visual feedback) (Clower & Boussaoud, 2000). Such a statement comes from findings that indicate that prism adaptation paradigms produce a shift in the entire visual field, including the targets, an may also engage recalibration of the visual system with respect to neck or trunk position (Ingram et al., 2000).

2.3.5. Different stages of learning

The amount of practice that subjects received prior to each stage of learning is the fifth point of contention. Even if we only consider the studies that investigated the earlier stages of acquisition, important differences exist in the way they defined and measured the attainment of the learning stages. For instance, when Shadmehr's (1997) subjects were said to have attained the slow learning stage, they had completed 800 trials on the adaptation condition, whereas Kreb's (1998) subjects had completed 640 trials on the task, and Nezafat's (2001) participants had completed 622 trials. Della-Maggiore (2005) and colleagues did not measure practice in terms of trials, but rather as time spent on the task, and when Della-Maggiore's (2005) subjects had attained the slow learning phase they had spent 168 minutes practicing the visuomotor adaptation task. As was made evident, even in studies examining within-session learning, there is little consistency in the amount of practice subjects have received and the degree to which the motor skill has been acquired (e.g. Jenkins, Brooks, Nixon, Frackowiak & Passingham, 1994b; Jueptner et al., 1997; Jueptner, Frith, Brooks, Frackowiak & Passingham, 1997).

Over the last decade, a large body of research has demonstrated that four main learning phases characterize the acquisition and execution of such skills: a highly attention-demanding early (fast) learning phase, an intermediate consolidation stage, a late (slow) learning phase, and an eventual automatic execution phase during which individuals are able to carry out these motor commands with little attentionnal resources needed for their successful completion. It is believed that considerable improvement in performance can be observed within a single trial or a few training sessions during the early (fast) learning stage. This is followed by a second (slow) stage in which further gains in motor skill can be observed with additional sessions of practice (Kalaska & Crammond, 1992; Korman, Raz, Flash & Karni, 2003; Karni et al., 1998; Luft & Buitrago, 2005). In addition to these two stages, there is an intermediate phase where spontaneous gains in performance can be observed and this without any additional practice on the task. This period is called the consolidated stage and it is dependent on the fact that little or no interference from a competing task is presented during a critical time window of 4-6 hours after the first training session has been presented (Appel, 1992; Korman, Raz, Flash & Karni, 2003; Krakauer, Ghez & Ghilardi, 2005; Karni & Sagi, 1993). Once the task has been well learned and consolidated, and subjects can, without any additional practice, recall and carry out the skill at a similar level at a future date, retention of the skill is believed to have occurred (Della-Maggiore & McIntosh, 2005; Hikosaka et al., 2002; Nezafat, Shadmehr & Holcomb, 2001a). Finally, once the task is over-learned and subjects are capable of executing it with minimal demands on cognitive resources, the skilled behaviour is believed to have reached the automatisation stage (synonymous to expert, easiful and efficient behaviours) (Anderson, 1990; Floyer-Lea & Matthews, 2004; Lang & Bastian, 2002; Logan, 1992).

However, much controversy remains with regards to what is the true definition of automatic learning stage, and thus will be specifically reviewed in the following Chapter. Nonetheless, our series of experiments went to great length to define the different learning phases, and therefore assure that the imaging data specifically represented the brain circuits implicated in the execution of a visuomotor adaptation skill at a very particular learning phase.

2.3.6. Different cognitive factors

Another source of variability that contributes to the inconsistency in imaging results, even when the same task is used, is the condition that elicits the different cognitive processes. As was mentioned previously, the acquisition of skills can either be explicit or purely implicit, as they do not require conscious thought to be learned or expressed (Squire, 1992). For example, in motor sequence learning studies, some investigators have used an implicit form of learning during which they must acquire a sequence of movements through practice without knowledge of the sequence, whereas others have employed an explicit form of learning during which subjects are practicing a motor sequence for which they have complete declarative knowledge (Grafton, Waters, Sutton, Lew & Couldwell, 1995; Rauch et al., 1995b). Recent data has demonstrated that subjects learning a task explicitly engage a very different set of brain regions than subjects learning the same task implicitly (Grafton, Hazeltine & Ivry 1995a; Hazeltine, Grafton & Ivry, 1997). Such findings suggest that well-designed supplemental behavioural tasks or questionnaires and open ended questions, to determine if the execution is based on explicit or implicit knowledge, may often be necessary to fully understand the results of imaging studies. Another possibility is to control such factors by making the subjects explicitly aware of the task being executed, and the strategy they should use to complete the task. For instance, in our series of experiments, subjects were presented the task in detail, the dependent variables used to calculate their performance were explained to them, and they were asked to complete the task putting equal emphasis on speed and precision. In this way, we attempted to control for differences in awareness and strategy, and consequently, we are more confident in the interpretation of our imaging results as representing similar cognitive processes.

2.4. Conclusion

This chapter reviewed the important variables that need to be considered when investigating skill learning in the laboratory. Taking the methodological differences between these studies into account can help us appreciate the reasons that may lead to discrepancies in imaging results reported in the literature. In fact, previous works have generally paid little attention to the experimental task used in the study, assuming that all motor skills are, by and large, similar and that they therefore recruit identical brain circuits during their execution. We now know this to be false. Furthermore, we integrated the concepts of cognitive processes and learning phases into our research by controlling subjects' awareness of the task used and the overall goal they sought. Finally, we also controlled the learning phase during which we acquired the imaging data by firstly defining the learning phases in a manner of task performance, and secondly, by manipulating the amount of practice subjects received on the experimental task in order to reach the specific performance criteria previously defined.

The following chapter will focus on one of the particular learning phase under study in this thesis (automaticity), and will provide the operational definition used to recognise and measure its attainment. In fact, this will help us differentiate between brain circuits involved in the long term retention of a consolidated skill and those involved in the retention of an automatised skill.

Chapter 3. Automaticity reviewed

Since there is much confusion regarding the definition of automaticity, this chapter has the important role of clarifying the terms and concepts surrounding this critical learning phase. As will be made clearer in this chapter, automaticity can refer to a number of very different processes, most of which were not studied in this thesis. The important point this chapter makes is that the type of automaticy investigated in our first experiment is explicitly sought after by conscious subjects who are trying to achieve a stage of expertise on a specific task. This kind of automatic execution is referred to as goal-dependent process.

At the turn of the century, automaticity was defined as the process in which there is a rapid increase in the speed of performance, a lack of memory for the automatically processed events, and most importantly, a significant reduction in the amount of effort and attention required to perform the task (Roth et al., 1996). The present day understanding of automaticity has changed enormously, yet our definition of it has changed very little. Automaticity, however, is much more complex than the previous definition suggests. In fact, many assumptions have been circulating about automaticity and its defining qualities, leading to no small confusion and muddying of the waters. This chapter's primary goal is to clarify the concept of automaticity, and to dissipate any confusion regarding its fundamental characteristics. In the following paragraphs, we will explore the different definitions that are advocated for this term, what they imply, where automaticity fits into the various learning stages, and finally how to use the dual-task paradigm to measure it in the laboratory.

3.1. What is automaticity?

Automaticity can be understood as a level of performance that is expert-like, over-learned, and/or executed to perfection. Researchers have traditionally believed automatic behaviours could occur without the need of an act of will from the individual, and that this automatic behaviour did not interfere with other concurrent processes (Decety, 1996b; Shiffrin & Schneider, 1977). On the other hand, these same researchers referred to controlled (or conscious) processes as under intentional control, flexible in responses to novel environmental conditions, and their occurrence were believed to be effortful and limited by the availability of processing resources (Decety, 1996a; Decety & Jeannerod, 1996).

According to these definitions, the two types of processes (automatic and controlled) exhausted the universe of possible procedures executed by man. Under this dual-mode model, researchers working up until the mid-eighty's classified every possible process as either controlled or automatic, i.e. possessing all of the features of one and none of the other (Bruyer, 1982). The problem with this unitary (all-or-none) definition of automatic and controlled processing is that they have been repeatedly disconfirmed empirically over the years. Reviews by Bargh (1989) and Zbrodoff & Logan (1986) have demonstrated that the defining features just do not hang together in an all-or-none fashion, but rather seem to be able to co-occur in just about any combination.

In addition to the empirical demonstrations, this mutually exclusive conceptualisation of automatic and controlled processes has run into logical difficulties. As Logan & Cowan (1984) have noted, people must intend to engage in any of these activities, and they can stop them whenever they want to. In fact, all of the common examples of automatic processes -such as reading, driving, walking and typing- are in reality highly controlled. In addition, people are usually aware of engaging in the activity, even though such routine actions sequences are autonomous. Therefore, the four defining features of automaticity —attention-demanding (vs. highly efficient), awareness (vs. phenomenally outside awareness), intentional (vs. unintentional), and controlled (vs. uncontrolled)— do not co-occur perfectly, but instead, are relatively independent qualities.

3.2. Different kinds of automaticity

As we have seen, there are roughly four pairs of core components that combine to define an automatic process —attention-demanding (vs. highly efficient), awareness (vs. phenomenally outside awareness), intentional (vs. unintentional), and controlled (vs. uncontrolled)—. Unfortunately, researchers have tended to assume the existence of all these characteristics, simply by observing the presence of one of them.

Bargh (1992) proposed that this practice ends, and be replaced by a more empirical approach. Namely, taking these four fundamental characteristics as the starting point for a definition of automaticity, we should classify varieties of automaticity in terms of these components' necessary preconditions. Bargh suggested that there are three important reasons for describing automatic processes as being composed of these fundamental characteristics. First and foremost, to avoid miscommunicating our beliefs about the phenomenon we are studying. Secondly, if we routinely classified processes in terms of which of the several features we have evidence for, and which we do not, it would leave open the question of whether any of the non-manipulated features are essential for the automatisation to occur. Finally, this knowledge pertaining to the necessary conditions for automatisation is essential if we are to generalise our findings from the laboratory to the "real world".

Basically, Bargh recommended that we avoid the danger of assuming implicitly the presence of an automatic feature given the presence of other features. Therefore, classified according to what is necessary for their occurrence, three major forms of automaticity have been suggested by Bargh (1992). Although finer discrimination of varieties of automaticity can be made within these three basic types, they will not be discussed in this paper (for more details see Bargh, 1989 & 1992).

1-Preconscious automaticity. As the term insinuates, for preconscious processes to occur, only the relevant (or triggering) stimulus event is needed. That is, these processes do not require the individual's conscious awareness. In fact, preconscious processes operate autonomously, involuntarily, nearly effortlessly, uncontrollably, and prior to and even in absence of conscious awareness of the stimulus event (Bruyer, 1982). As such, it can be said that it incorporates the preattentive processes concepts described by Triesman et al. (1992). However, whereas preattentive processes are largely innate or developed early in life, preconscious processes also include those that have developed through extensive practice. Also, unlike preattentive processes, preconscious processes may require some spatial attention to the triggering stimulus event; i.e. preconscious processes are also *post*attentive. Moreover, whereas preattentive processes appear limited to the coding of simple physical features such as colour, size, and shape orientation, the more general class of preconscious processes has been shown to be capable of performing interpretations and evaluations of complex social stimuli (Isaac & Marks, 1994). Finally, in regard to its occurrence, preconscious processes are understood as being the most common form of automatic process in the natural environment.

2-Postconscious automaticity. The classical example of postconscious automaticity is the priming effect. In other words, for postconscious events to occur, recent conscious experience (or thought) in the same stimulus domain as the automatic process is needed, or as Bargh (1989) puts it, "the unconscious consequence of conscious thought". Ultimately, postconscious and preconscious automaticity are comparable effects, the only difference between them is the necessity of priming (or preactivation) of the relevant construct for a preconscious process to become a postconscious process.

3-Goal-dependent automaticity. Just as we now believe that prior conscious thoughts affects the processing of a stimulus (postconscious automaticity), one can conclude that an experimental design that gives subjects the explicit goal to engage in a task invariably affects the processing needed to execute the task. Automatic processes of this kind require the guidance of the processing goal plus the presence of the relevant triggering stimulus. The best example of a goal-dependent automatic process is the over-learning of a procedural skill such as knitting or riding a bicycle. In sum, the fact that someone has a goal to achieve when performing a task cannot be overlooked and dismissed as being irrelevant.

All in all, Bargh (1989, 1992) distinguishes between a *preconscious* automatic process that is independent of attention and intention, *postconscious* automaticity that is independent of intention but not of attention, and *goal-dependent* automaticity that depends on both attention and intention.

3.3. The dual-task paradigm

Although most experiments in the field of motor learning use proficiency-based criteria measures (time and errors) to qualify performance on a motor task, these measures may not provide the most accurate assessment of performance (Maggill, 2004). In fact, the performance of two individuals may be indistinguishable based on measures of time, errors and precision, but significantly different when other metrics are used, such as limb kinematic, psychophysical measures, and measures of mental workload. Therefore, subjects may demonstrate an "automatic" level of performance based on time, errors or precision, but may fall short of true automaticity because these measures are not sensitive enough to reveal differences between automatic and near automatic performances.

As we have seen, the most important characteristic of an automatised process is its requirement for attentional resources; the less attention a task requires to be completed, the more automatic it is believed to be. Experts (i.e. automatic performances) can often perform multiple tasks simultaneously with little or no performance decrement. In contrast, beginners often struggle with new and difficult tasks, and their performance is severely impaired if they attempt to engage in another task at the same time. Consequently, the ability to effectively time-share attention among multiple tasks provides an index of automaticity and is a standard method for assessing skilled performances across a variety of domains (Logan, 1988). The dual-task paradigm allows researchers to measure the attentional resources that are spared, as the task is being over-learned. The dual-task paradigm involves performing the primary task simultaneously with a secondary task. The rational being that the dual-task methodology allows researchers to test for the attentional resources that can be devoted to a second task, as subjects are becoming more efficient at performing the initial learned behaviour. As skills develop, more attentional resources are available to perform the secondary task. Thus, performance on the secondary task provides an index of automaticity on the primary task (Logan, 1988).

Stefanidis and his colleagues (2007) have recently tested this automaticity theory by testing surgical students' expertise while they used a simulator (Stefanidis, Scerbo, Korndorffer & Scott, 2007). These researchers wanted to identify true experts on a suturing task. Their subjects counted novices, surgery residents, suturing experts, and subjects trained on the simulator without any surgery experience. Using the dual-task paradigm, Stefanidis et al. (2007) reported that only the expert in suturing were able to allocate attentional resources to complete the secondary task, whereas all other subjects quickly abandoned the secondary task to concentrate on the primary suturing task. In fact, although all subjects could perform the task at similar levels as based on suturing scores (time and errors), the dual-task paradigm allowed them to identify true automatic performances.

3.4. Conclusion

We now find ourselves in a very murky pool of concepts and insights. Research groups have tested an extensive amount of subjects, and identified many important factors concerning automaticity. The problem with all these researches is that, while they all called the concepts under study automaticity, they all evaluated very different things. We can now understand that the term automaticity has been, and is still being used to qualify a wide range of cognitive and motor processes. In fact, automatic processes have referred to tasks that are attention-demanding or highly efficient, tasks that require some awareness or that lie outside of it, to tasks that are controlled or uncontrolled, and finally, to tasks that subjects intend to perform or that are unintentional. What's more, an automatic process can be composed of any combination of these previous four pairs of criterion. This clearly is problematic for a number of reasons, the most obvious one being the communication of results; what exactly do researchers mean when they refer to the automatisation of a skill?

Bargh (1992) was evidently on to something very pertinent when he advocated the use of more terms to differentiate between all the different kinds of automatic processes possible. His three terms and their definition seem pertinent, and should be used in developing an even clearer and more elaborate lexicon for the vast theme automaticity encompasses. In regards to *pre & post* attentive processes, Logan (1992) argues that it would be possible to capture the main property of preattentive processes with the words "independent of attention" instead of automaticity, and reserve this last term for postattentive processes. This would allow researchers to communicate with a much more concise vocabulary the concept and idea under study. I would go further and suggest that the term automaticity not be used to define any particular process, but rather the term *automatic* should be part of the characteristics referring to the over-learned process.

All things considered, what we need is to develop a new vocabulary concerned with the over-learning of various skills, a vocabulary that does not need to be economical with terms, and a vocabulary that clearly expresses the process we are measuring. Perhaps the first terms of this new automaticity lexicon could be *goal-dependent-automatic-motor-adaptation-skill,* which would strictly refer to: attention demanding, intentionally learned motor adaptation skill, at the fourth and final phase of motor skill learning. Although not economical in words, they state with precision the exact topic under study in the first experiment composing this thesis.

Chapter 4. Doyon and colleagues' model

The nature of modern neuroimaging techniques brings us to discuss about the basic need of hypothesis driven experiments. Indeed, neuroimaging has advanced by leaps and bounds in the past decade, with a number of analysis tools and techniques being introduced on an almost monthly basis. This results in a steady increase of methods available for researchers to analyse their data, and consequently results in a greater ways the same data can be interpreted. This, of course, is not a good outcome of advancement, and the issue must be addressed by having researchers apply a hypothesis driven methods to their analysis. As such, we developed experimental hypothesis from Doyon and colleagues' models of motor skill learning, which we then set out to test.

When the model was first elaborated, these researchers considered the fact that much of the variability reported in neuroimaging studies can be accounted for if one considers two important factors. The first being the type of motor task studied, and a second being the learning phase at which subjects are scanned. According to Doyon and Ungerleider (2002), the acquisition of motor skills produces representational changes in different cerebral structures over the course of learning (Doyon & Ungerleider, 2002). Their model of cerebral plasticity suggested that representational changes depend not only on the stage of learning, but also on whether subjects are required to learn a new sequence of movements or learn to adapt to environmental perturbations (Fig. 4.1). They proposed that early in learning, during the fast learning phase, both motor sequence and motor adaptation tasks recruit similar cerebral structures: the striatum, cerebellum, motor cortical regions, as well as prefrontal and parietal areas. As learning progresses, however, representational changes can be observed, so that when a task is well learned and asymptotic performance is achieved, the representation of the motor skill may be distributed in a network of structures that involves either the cortico-striatal (CS) or the cortico-cerebellar (CC) circuit, depending on the type of learning acquired (Doyon &

Ungerleider, 2002). They suggested that, at this final stage of motor adaptation, the striatum is no longer necessary for the retention and execution of the acquired skill; regions representing the skill will involve the cerebellum and related cortical regions. By contrast, a reverse pattern of plasticity is proposed to occur in motor sequence learning, such that with extended practice, the cerebellum is no longer essential, and the long-lasting retention of the skill will involve representational changes in the striatum and its associated motor cortical regions.

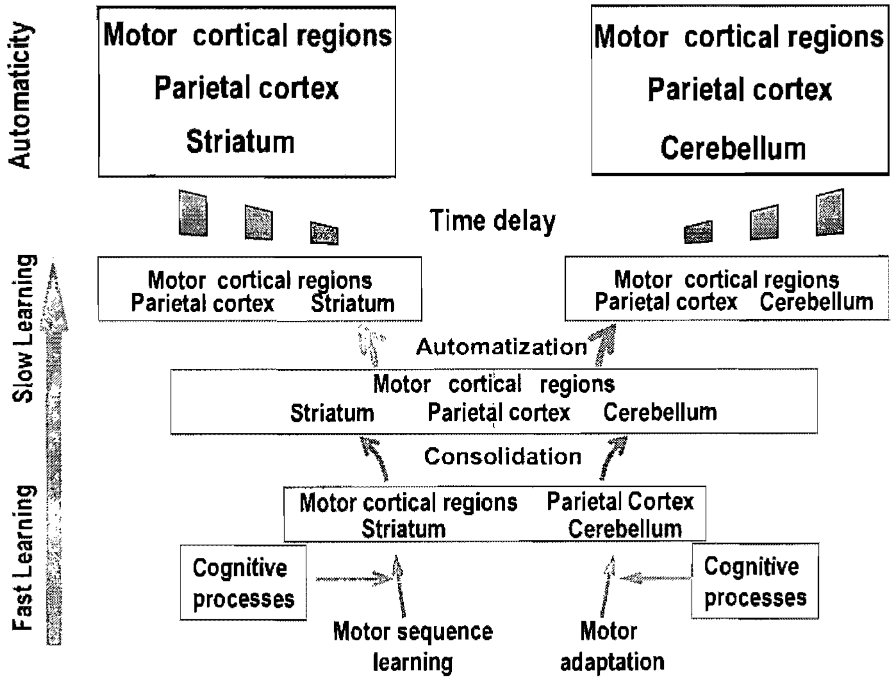

Figure 4.1. Model presented by Doyon and Ungerleide (2002) describing the cerebral plasticity within the cortico-cerebellar and cortico-striatal circuits during the course of learning. Adapted from Neuropsychology of Memory, 3rd Edition.

The authors stipulate that dynamic interactions between the structures are likely to be critical for establishing the motor routines necessary to learn the skilled motor behaviour. This idea is at the center of their model, and suggests that the learning and maintenance of the motor skills is not the responsibility of a specific region, or set of regions, but rather that active interaction between regions are critical for establishing the motor routines underlying the skilled behaviours. The exact nature and process by which these interactions occur is still not well established. However, research strongly suggests that learning, including motor learning, is dependent on the basic cellular mechanism described by Hebb in 1949 (Dudai, 2004). This basic Hebbian principle suggest that synaptic plasticity is modulated by a cascade of neurochemical signals that either amplify the post-synaptic response (long-term potentiation) or diminish it (long-term depression) (Stanton, 1996).

Although the precise mechanism by which these interactions occur are not completely understood, the learning process is now considered as emergent properties of interacting neural networks, rather then an effect of local variations of neural properties alone (McIntosh, 2000). It was therefore postulated that learning must be accounted for, not just in terms of synaptic plasticity, but also in terms of the information flow across specific cerebral networks (Toni, Rowe, Stephan & Passingham, 2002). Since the inception of such the idea, a number of studies have specifically investigated the use of structural equation modeling in the investigation of learning-related dynamics among the neural elements composing brain circuit (Varela, Lachaux, Rodriguez & Martinerie, 2001; Horwitz, Tagamets & McIntosh, 1999; Marrelec et al., 2006; Bellec et al., 2006). It is now widely accepted that this direct, indirect and stimulus-locked interactions between spatially remote brain regions can be measured by correlation of their fMRI time series. This correlation procedure has been called functional connectivity. Although connectivity maps have proved to be a powerful tool, its use to explore the functional networks relies heavily o the choice of the *seed* region (for more detail see Bellec et al., 2006). However, the use of these *seed* regions allow modellers to get insight only into networks associated with these particular regions. A more reliable and proven method to investigate the pathways or interconnectivity between cortical and subcortical structures is through the use tracer injections.

Using this method, investigators have been able to map the pathways linking the cerebellum and basal ganglia to each other and to other cortical structures (Middleton & Strick, 2000; Graybiel, 1998). These regions have been thoroughly investigated, and large numbers of cortical neurons have been found to project to both the inputs stages of the basal ganglia (the caudate and putamen) and the cerebellum (pontine nuclei). In a similar way, the output nuclei of the basal ganglia (internal globus pallidus and substancia nigra) and the cerebellum (deep cerebellar nuclei) project to subdivisions of the thalamus, which then project back to the cerebral cortex (Percheron, Francois, Talbi, Yelnik & Fenelon, 1996). A major architectural feature of these circuits is the formation of multiple "loops" between cerebral cortex and basal ganglia and cerebellum, which Doyon and colleagues refer to as the CC and CS circuits.

Since its original publication, new evidence called for a revision of Doyon and Ungerleider's (2002) model of motor learning. First, recent evidence from a fMRI study conducted at 3.0 Tesla has shown that both implicit and explicit motor sequence learning measured with the serial reaction time task does not only activate the usual cortical and subcortical motor regions in the early learning phase, but also the hippocampus and related cortices (Schendan, Searl, Melrose & Stern, 2003). These findings suggest that, in addition to the CS and CC systems, the limbic structures of the medial temporal lobe contribute to the acquisition of sequential movements, regardless of the subject's awareness. It should be noted, however, that the limbic involvement might not be necessary for the learning to occur and to be maintained over time, because contrary to lesion studies in clinical populations with striatal or cerebellar dysfunctions, amnesic patients with damage to the limbic system can typically acquire habits and motor skills normally.

Second, cerebral functional plasticity within the striatum and the cerebellum has also been observed during motor learning. Indeed, in collaboration with colleagues (Lehericy et al., 2005), it has recently been demonstrated in a fMRI study at 3.0T that there is a shift of motor representations from the associative to the sensorimotor territories of the striatum during the explicit learning of motor sequences, supporting the notion that motor skills are stored in the latter territory of the basal ganglia. Furthermore, a transfer of activity from the cerebellar cortex to the dentate nucleus has also been observed as subjects are acquiring implicit knowledge of a declaratively known sequence of movement (Doyon et al., 2002b), learning to track a continuously changing force target using a pressure sensor (Biernaskie & Corbett, 2001), or adapting to a force field in a target reaching task (Nezafat, Shadmehr & Holcomb, 2001b). Taken together, these findings thus suggest that in the fast learning phase, functional and physiological changes occur at both intra- and inter-system levels, and that this plasticity is necessary to build the motor routines that will then be consolidated over time as well as after additional practice (see Fig. 4.2).

In sum, new evidence confirms that interactions among cortico–striatal, cortico–cerebellar and limbic (hippocampal) structures are crucial for building the motor memory trace, which will then be consolidated and maintained over time within a more specialized subsystem depending on the type of motor skilled behaviours (i.e. motor sequence versus motor adaptation) acquired through repeated practice. It should be noted, however, that the model reviewed here is specific to conditions that require the acquisition of new spatio-temporal motor sequences or the modification of an internal motor representation necessary to adapt to environmental manipulations. Indeed, one would hypothesize that different forms of visuomotor learning, that are more cognitive and associative in nature, are going to recruit slightly different cerebral networks which will then undergo other patterns of cerebral plasticity with learning. New perspectives, in line with the previous statement, will be discussed in detail in the concluding chapter. Meanwhile, the models proposed by

Doyon and colleagues allow experimenters to develop a-priory hypotheses which they can set out to disconfirm.

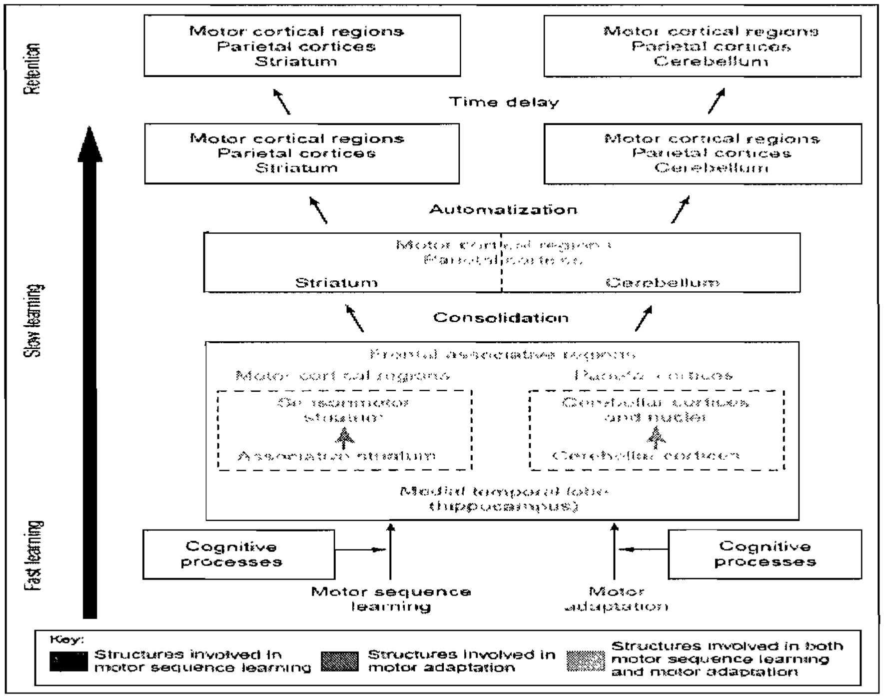

Figure 4.2. Revised model presented by Doyon and Underleider (2002) describing the cerebral plasticity within the cortico-cerebellar and cortico-striatal circuits during the course of learning. Adapted from Current.Opinion in Neurobiology(15), page 164.

Chapter 5. The thesis' objectives and hypotheses

There is a considerable amount of data suggesting that the striatum, cerebellum, and other related structures that form the cortico-stiatal (CS) and cortico-cerebellar (CC) systems are important for the learning and execution of various motor learning skills. Yet, despite these empirical data, the exact nature and extent of their involvement is far from being fully understood, and the contribution of the striatal and cerebellar circuits in this process is still unclear. For instance, we do not know if these systems participate in a redundant manner to the same operations, or if they operate in complementary fashion to different aspects of the same task. The available evidence to answer the questions is rather limited, and contains numerous inconsistencies and controversies. It was proposed that this is a result of a lack of knowledge and control procedures regarding the important variables that need to be considered. In an effort to reconcile the results of brain imaging investigations, Doyon and colleagues (2002, 2003 & 2005) have proposed a model that makes predictions with regards to the cerebral networks believed to be implicated at different learning phases of new movement adaptations (Doyon & Ungerleider, 2002; Bruyn, Dots & Dom, 1979; Bustini et al., 1999). The major advantage of this theoretical framework is that it makes several testable predictions with regards to the contribution of the neural circuits based on the stage (fast, slow, consolidation and automatisation) and nature of the motor learning process (motor sequence vs adaptation learning). Little research has investigated the acquisition of motor adaptation skills as compared to motor sequences. In addition, a number of studies have identified the neural system involved in the early phases of motor adaptation learning (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996b; Imamizu et al., 2000; Krebs et al., 1998; Shadmehr & Holcomb, 1997a; Shadmehr & Holcomb, 1999), whereas little is known of the circuitry mediating the later learning phases (retention and automatic), as subjects are rarely given enough practice trials to reach such a level of expertise (Della-Maggiore & McIntosh, 2005; Lang & Bastian, 2002). The objective of this thesis is to describe the neural activity that accompanies the attainment of a goal-dependent-automatic-visuomotor-adaptation-skill learning and long term retention of a new visuomotor adaptation skill, and consequently test and validate a part of Doyon and colleagues' model.

The visuomotor adaptation task used in the experiments comprising this thesis was a laboratory version of a well known tracking task (Hadj, Blanchet & Doyon, 2004). It required subjects to use a joystick in order to move the cursor positioned at the centre of a computer screen to one of eight possible targets, following an elliptic trajectory. At the beginning of every trial a starting point emerged in the middle of the computer screen and the cursor, a cross-shaped figure, appeared superimposed on top of the starting point. At the same time, the target represented by a red circle appeared some distance from the starting point. Simultaneously, a line which indicated the ellipse shaped trajectory the subjects should follow to reach the target with the cursor came to view. The subjects' task was to reach the targets with the cursor following the curved path as fast and as accurately as possible while adapting to a novel directional bias. In fact, this represents a visuomotor adaptation task because the cursor's movements were made opposite to those produces by the joystick; moving the joystick to the top right caused the cursor to move towards the bottom left part of the screen.

5.1. Experiment 1: Automatisation of a visuomotor adaptation skill

This first study was designed to describe the functional cerebral plasticity that accompanies the automatisation of a motor adaptation skill. Briefly, subjects were introduced to the experimental conditions on Day 1 (baseline performance) and scanned immediately thereafter. Beginning on Day 2, and for as long as they needed, subjects were asked to practice the motor adaptation task. In addition to these practice sessions, subjects completed a dual-task paradigm in which they were required to complete a tone discrimination task (TDT) administered either alone, or while simultaneously completing the motor adaptation task. Automaticity on the adaptation task was believed to have been attained when subjects executed the motor adaptation task with minimal interference generated by the secondary tone discrimination task being completed simultaneously (Passingham, 1996). Finally, subjects underwent a second fMRI scanning session after automatisation had been confirmed. Based on Doyon and colleagues' (2002, 2005) model, it was hypothesised that early learning of a motor adaptation skill would engage neural activity in both CC and CS systems, while automatic performance of the skill would only implicate the CC circuit.

5.2. Experiment 2: Retention of a consolidated visuomotor adaptation skill

In the second experiment we asked whether with the passage of time, and with no additional practice, there is a change in the neural representation underlying the retention of the consolidated visuomotor skill, and if these regions differed from those involved in the long-term maintenance of the task once automatised. Eight subjects were contacted two months after they completed a previous study in which they had completely consolidated the visuomotor adaptation skill, and after a very brief reminder session on the experimental tasks, were asked to complete a fMRI scanning session. The brain activity measured in this experiment is therefore believed to represent the brain structures mediating the long term retention of the consolidated motor adaptation skill. Based on Doyon and colleagues' (2002, 2005) model, it was hypothesised that the retention of a motor adaptation skill would engage neural activity in CC only.

Chapter 6. Experiment 1: Differential contributions of the cortico-cerebellar and cortico-striatal circuits in the automatisation of a motor adaptation skill

6.1. Abstract

This study used functional magnetic resonance imaging (fMRI) to explore the underlying brain structures implicated in the automatisation of a visually guided motor adaptation skill (kinematic adaption). Subjects were introduced to the experimental tasks on Day 1 (baseline performance) and scanned immediately thereafter. Beginning on Day 2, and for as long as they needed, subjects practiced the motor adaptation task until they reached automatic performance. Once automatisation on the motor adaptation task had been reached, subjects underwent a second fMRI scan identical to the first. Our results revealed that the progress from early learning to automatic execution stage was associated with a reorganisation of the functional anatomy underlying kinematic adaptation with decreased activity in the striatum and increased activity in the cerebellum and its related cortical structures. In addition to confirming the essential role of the cerebellum in the automatisation of a kinematic adaptation skill, between subject correlation analyses revealed that distinct cerebellar regions are involved in different execution strategies used to completed the adaptation task. As such, our results suggest that the anterior cerebellar regions are involved in the rapid execution of the automatised skill, whereas the posterior regions are recruited to complete the task with more precision.

6.2. Introduction

When subjects adapt their movements to compensate for perturbations in visual feedback they are said to produce a kinematic adaptation. Although trivial in appearance, these skills are essential to complete visually-guided tasks such as walking, driving and using a computer mouse. However, to complete these tasks as efficiently and expertly as in everyday life, one needs to automatise them. Once automatised, the subject needs to devote much less attentional resources to complete it, and can attend to another piece of work in the immediate environment. In the laboratory, automaticity is measured through the use of a dual-task paradigm (DT). The dual-task paradigm involves performing the primary task simultaneously with a secondary task. The rational being that DT allows researchers to quantify attentional resources devoted to a secondary task, as subjects are becoming more efficient at performing the primary task (Bucher, 1993). Although previous imaging studies have identified a number of motor structures involved in the early phase of kinematic adaptation (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996; Imamizu, Kuroda, Miyauchi, Yoshioka, & Kawato, 2003; Della-Maggiore & McIntosh, 2005; Krebs et al., 1998; Imamizu et al., 2000), comparatively little is known with respect to the circuitry mediating the automatic stage of learning.

In an effort to reconcile the results of brain imaging investigations looking at motor adaptation, Doyon and colleagues (2002, 2003 & 2005) have proposed a model that differentiates the structures implicated in the learning of different motor skills, and that makes predictions with regards to the cerebral networks believed to be involved at the different phases of the acquisition process (Doyon & Ungerleider, 2002; Doyon & Benali, 2005; Doyon, Penhune & Ungerleider, 2003). This model proposes that during the fast learning phase, the acquisition of a new motor adaptation skill recruits several structures within the CS and the CC. At this stage, dynamic interactions between these circuits are thought to be critical for establishing the motor routines necessary to learn this skill.

However, when performance has become automatic, the neural representation of the adaptation skill is then believed to be distributed in a network of structures that mainly involves the CC circuit.

The present study was designed to describe the functional cerebral plasticity that accompanies the automatisation of a kinematic adaptation skill, and thus test the model's predictions. Kinematic adaptation was created by inverting the spatial correspondence between the direction of movements made by the hand and the location of the cursor reflected on the screen (Inversed Mode or IM). In addition, a motor control task was also completed by the subject, in this task the hand and cursor movements were kept normal (Direct Mode or DM).

Briefly, subjects were introduced to the experimental conditions on Day 1 (baseline performance) and scanned immediately thereafter. Beginning on Day 2, and for as long as they needed, subjects were asked to practice the adaptation task and to complete a tone discrimination task (TDT) administered either alone, or while simultaneously completing the IM task (dual-task sessions). Once automatisation on the adaptation task was confirmed, subjects underwent a second fMRI scanning session. Based on Doyon et al.'s model of motor adaptation, it was hypothesised that as subjects progressed from the early learning to the automatic execution stage, we would observe a reorganisation of functional activations from the CC and CS systems towards the CC system.

6.3. Materials and methods

6.3.1. Subjects

Ten university students (4 males) between 20-23 years of age (mean = 21.5 years, SD = 1.18 years) participated in the study. All were strongly right-handed as assessed by the Edinburgh Handedness Inventory. They were screened to ensure that none suffered from medical complications, or neurological difficulties that could impede learning and execution of the motor skill. All of the subjects were recruited at the University of Montreal according to the review board guidelines, provided written informed consent, and received financial compensation for their participation.

6.3.2. Materials

The Spike 4 software and CED 1401 data acquisition peripheral (both from Cambridge Electronic Design Inc.) were respectively used to generate the computer programs necessary to present the sequence of targets in both motor adaptation and control tasks, and to record the subjects' performance. Subjects used a MRI compatible joystick (Resonance Technology Inc) to reach the targets, which were displayed onto a screen behind the subject's head via a LCD projector (NEC MultiSync MT 1030+). They were able to observe the screen through its reflection on a mirror embedded within the head coil. During the laboratory sessions, subjects were also asked to practice the IM task in the supine position using the same MRI-compatible joystick. In the tone discrimination task (TDT) performed either alone or in dual-task condition, the sounds were generated by two piezo electric speakers placed near the subject's head.

The BOLD signal was acquired using a standard head coil with a 1.5 Tesla Siemens Sonata magnetic resonance system located at Hôpital Notre-Dame of the Centre Hospitalier de l'Université de Montréal. Using scout images of the midline sagital plane, 35 slices were positioned on the axial plane so as to cover the entire brain. First, T2*-weighted functional scans were acquired using a mosaic sequence (TR 3000 msec, FOV 256 mm, in-plane resolution 64 x 64 mm, 4 mm voxel size, and 4 mm slice thickness with no separation), and a standard high resolution T1-weighted scan was obtained last.

6.3.3. Experimental Tasks

The IM and DM tasks were completed using a version of the eight-target tracking task designed in our laboratory (Flament, Ellermann, Kim, Ugurbil & Ebner, 1996). Both tasks required subjects to use the joystick in order to move the cursor from a starting point positioned in the center of the computer screen to a distant target following an elliptical trajectory. At the beginning of every trial, a starting point, represented by a white circle (0.75 cm in diameter), appeared in the middle of the computer screen. The cursor, a cross-shaped figure, appeared superimposed on top of the starting point. At the same time, the target represented by a red circle (1.5 cm in diameter), appeared 10 cm from the starting point. Appearing simultaneously was a line (0.5 cm in thickness) indicating the ellipse-shaped trajectory the subjects had to follow (radius of 2.5 cm) to reach the target with the cursor. The use of an elliptic trajectory, as opposed to a straight line, obliged subjects to implement a more complicated spatial transformation to complete the task, and therefore allowed us to rule-out the possibility that task improvement could have been due to learning an explicit reversal rule (i.e. move hand in opposite direction). Contrary to the IM, which served in both scanning and laboratory training sessions, the DM only served as a motor control condition during fMRI scanning sessions, and was therefore not administered in the laboratory sessions. The subject's performance on the IM and the DM were measured by computing a precision index based on the distance between the cursor's trajectory and the ideal curved path leading to the target, as well as a speed index based on the time subjects took to complete each trial. These indices were then combined to calculate a global performance index (GPI). All these indices ranged from 0 to 1, and can be interpreted as the probability distribution for the subject's performance on both the spatial and/or temporal aspects of the task (Fig. 6.1ABC). Expressed mathematically, the latter index can be described as:

$$GPI = exp(-dS/S * (TT(ms)-T_0)/T_a)$$

Where *exp* is the value given to the trial (1 for successful and 0 for failed), the *dS* represents the differential surface area between the actual path followed to reach a target and the optimal path of the curved line, *S* is defined as the differential surface area between the optimal path of the curved line and a straight line between the starting point and the target center, TT constitutes the total time, T_0 the minimal time needed (500 ms), and T_a the time allowed (2,900 ms) to reach the target.

Insert figure 6.1

In addition, subjects were tested in two other conditions: (1) a tone discrimination task (TDT), and (2) a dual-task paradigm combining the IM and TDT tasks. In the TDT, streams of audible sounds composed of high (3600 Hz) and low (300-500 Hz) pitch tones were presented to the subjects who were asked to respond, as quickly as possible, to every tone by saying whether they were of high or low pitch. The sequences of tones were composed of 50% high and 50% low pitches, and were presented randomly every 4 sec. Two dependent variables were measured in this task: the correctness of the response, and the subject's reaction time. Although mean reaction times were calculated for successful trials only, subjects rarely failed any trials in either the single or the dual-task conditions (average number of trials failed during TDT blocks = 0.96, SD = 0.71). When the TDT was completed as a secondary task in the dual-task condition, the tones were presented 900 ms after the targets appeared, therefore ensuring that subjects did not simply wait to give the verbal answer to the TDT before completing the IM trial. Along with the TDT, the dual-task condition was only employed in the laboratory training sessions to evaluate the subjects' level of performance at different time points during the study, and was therefore not used as an experimental condition in fMRI scanning sessions.

It is important to understand that the goal of the training sessions was to have subjects practice the experimental task until they had reached the automatic execution level. As such, the practice schedule was subjects tailored and did not count a specific number of training sessions. What's more, the TDT was only completed a few times during this training schedule, not more then once a week. This was decided early on in the experiment because we did not want subjects to become better at the TDT, but rather simply use the TDT to measure the subjects' level of performance on the primary task.

6.3.4. Procedure

The experiment was broken up into three phases. In Phase 1, subjects were given a brief introduction to the experimental tasks, followed by the first series of fMRI runs. The fMRI scans lasted approximately 75 min, during which subjects underwent ten runs. These runs included 4 randomly presented blocks of 8 trials on the IM and 4 blocks of 8 trials on the DM, separated by rest (5 sec) and instruction (3sec) periods. We used a mixed fMRI paradigm that combined both block and event-related designs to acquire the functional data. To sample the BOLD signal at different moments during the execution of the task, jittering within each run was achieved by varying the inter-trial intervals during both motor blocks (Visscher et al., 2003). Therefore, in addition to the 3000 msec given to a subject to complete a trial (i.e., 2900 msec given to reach the target and the 100 msec needed to validate the target), one of 5 possible time intervals (500, 750, 1000, 1250, 1500 msec) was insert between trials. In Phase 2, subjects practiced the motor adaptation task for an extended time period in order to reach automatisation of the skill. During this phase, training on the task was subject-tailored, i.e. the subject's performance on the tasks determined how much practice was needed for them to reach the automatic execution criterion. During each day of practice, subjects completed five runs composed of 64 trial of the IM. The dual-task condition was completed during this period at a frequency of not more then one session per week. Finally, in Phase 3, subjects had reached complete automatisation and were asked to complete a second and final series of ten fMRI runs identical to the first scanning session.

6.3.5. fMRI data analysis

The functional data were analysed using statistical parametric mapping (SPM2) (www.fil.ion.ucl.ac.uk/spm). Data pre-processing included slice timing, EPI and MPRAGE realignment, as well as EPI and MPRAGE spatial normalisation according to the Montreal Neurological Institute (MNI) space. The data was then convolved with a three-dimensional

Gaussian Kernel (12 mm FWHM) to enhance the signal-to-noise ratio. The fMRI acquisition runs were analysed as a mixed block and event-related paradigm, with 5 variables defined and measured in every run: (1) successful IM trials; (2) failed IM trials; (3) successful DM trials; (4) failed DM trials; and (5) rest period. Since no motor output was required during the instruction periods, they were combined to the actual rest period and modelled as a block, whereas the 4 other variables were modelled as event-related. The data were then convolved with a canonical hemodynamic response functions, and a high-pass filter was applied for filtering low frequency noise (cut off, 128 sec). Finally, realignment parameters (translation and rotation in x, y, z dimensions) were included as covariates of no interest to correct for head movements. In order to determine the pattern of activations in the various conditions, three different contrast images were calculated per subject, and all of the contrasts used events associated to successful trials only. Two contrasts were calculated to reveal the cerebral regions implicated in the learning of the motor adaptation *per se* at both the early and automatic execution stage [IM VS DM]. Because visuomotor adaptation requires various cognitive processes such as visual perception, attention, sensory integration, and motor control for its execution, activations associated with these processes need to be removed in order to assess brain activation patterns specifically related to learning of the adaptation skill *per se*. Thus, functional data acquired while subjects completed the motor control task (DM) were contrasted to those of the visuomotor adaptation (IM). The third and final contrast was calculated to reveal the regions differentially involved in the automatisation process of the motor adaptation skill [(IM *vs* DM in the automatic learning stage) VS (MI *vs* DM in the early learning stage)]. The corresponding images were then entered into a second level random-effects analysis for group comparisons, as calculated by a one-sample t-test model. Based on predictions derived from Doyon and colleagues' (2002, 2003. 2005) model of motor adaptation learning, as well as results of previous fMRI studies (Doyon & Ungerleider, 2002; Doyon, Penhune & Ungerleider, 2003; Doyon & Benali, 2005; Nezafat, Shadmehr & Holcomb, 2001; Della-Maggiore & McIntosh, 2005; Smith & Shadmehr, 2005; Ghilardi et al., 2000;

Shadmehr & Brashers-Krug, 1997), a statistical threshold of $P^{uncorrected} < 0.001$ in brain structures composing the CS and CC circuits (with a spatial extent of 3 voxels for subcortical structures, and 6 voxels for cortical structures) was considered to show significant activations.

Lastly, to examine the association between subjects' behavioural performance on the task and the brain structures, we conducted correlation analyses coupling the mean behavioural performance (i.e. precision and speed indices) per session with the effect size at every voxel in individual statistical maps derived from relevant motor adaptation-related contrasts [IM *vs* Rest]. As such, the correlation analyses looked at brain structures involved in the automatic execution of the motor adaptation for which BOLD responses (as assessed by statistical effect size at the random effect level) were specifically correlated with average precision or speed during the scanning session.

6.4. Results

6.4.1. Behavioural results: Training sessions

Figure 6.2 (A, B) displays the behavioural results measured in the laboratory for both the IM and TDT, executed alone (blue) or in the dual-task condition (red). Although completed an average 20 sessions (SD = 1.1) of practice, only seven laboratory training sessions are presented in this figure. As such, we had to present the data on another time scale. We chose to represent the number of sessions in percentage, and expose the subjects' performance at every 14%. As expected, the data revealed weak and variable performance in the IM condition during the early learning stage (Day1). However, this performance rapidly improved as shown by a sharp progress in performance across the two blocks of trials completed alone, and with the additional two blocks completed in the dual-task condition. Immediately starting on Day 2, and as subjects learned the IM during the extended practice stage, their performance stabilised, quickly reaching an asymptotic level of performance. An analysis of variance (ANOVA) for repeated measures confirmed this behavioural trend, the results revealing a significant improvement in performance between the first and last training sessions ($F(1,9) = 112.92$, $P < 0.001$), a difference between the single and dual-task conditions ($F(1,9) = 46.18$, $P < 0.001$), as well as a significant session by condition interaction ($F(1,9) = 53.42$, $P < 0.001$). Most importantly, at the end of the experiment, the subjects' performance on the IM executed in the dual-task condition was identical to their performance on the IM when executed alone ($F(1,9) = 0.72$, $P = 0.418$).

Insert figure 6.2

The dual-task paradigm involves performing the primary task simultaneously with a secondary task. The rational being that the dual-task methodology allows researchers to test for the attentional resources that can be devoted to a second task, as subjects are becoming more efficient at performing the initial learned behaviour. As skills develop, more attentional resources are available to perform the secondary task. Thus, performance on the secondary task provides an index of automaticity on the primary task (Logan, 1988). Consequently, subject tested on the TDT in the dual-task condition were expected to show an improvement in performance that would gradually approach the values obtained when they completed the TDT alone. Consistent with this hypothesis, a repeated measures ANOVA revealed significant effects between the first and last session ($F(1,9) = 74.72$, $P < 0.001$), between the single and dual-task conditions ($F(1,9) = 58.26$, $P < 0.001$), as well as a significant session by condition interaction ($F(1,9) = 25.34$, $P < 0.001$). Simple effect analyses also showed that during the early learning stage, subjects' reaction times in the TDT executed alone differed significantly from their performance in dual-task condition ($F(1,9) = 40.28$, $P < 0.001$). With additional practice, differences in reaction time between the TDT in the single and dual-task conditions gradually decreased, reaching almost identical level in the automatic execution stage (43 msec difference on average). Although the latter difference remained significant ($F(1,9) = 49.81$, $P < 0.001$), the overall results on the TDT and IM strongly suggest that automaticity on the motor adaptation task had been attained.

6.5. Behavioural results: Scanning sessions

Figure 6.2C displays the average behavioural results for all subjects measured on both the IM and the DM tasks in the ten runs of each of the two scanning session. Similar to their pattern of results during the introductory session, subjects' performance on the IM and DM tasks was variable at first but then rapidly improved throughout the runs. In fact, subjects showed a great deal of learning during this first session as confirmed by a repeated measures ANOVA that revealed a significant effect between the subjects' performance in the first and last runs ($F(1,9) = 17.14$, $P < 0.003$), but no effect between the IM and DM tasks ($F(1,9) = 0.001$, $P > 0.98$), nor a run by task interaction ($F(1,9) = 4.14$, $P > 0.072$). By contrast, the subjects' performance during the second scanning session (i.e., following the extensive training period) was much more stable, as they performed at an asymptotic level. An ANOVA for repeated measures on these results confirmed the trend as it yielded no significant effect of runs (first and last) ($F(1,9) = 4.21$, $P > 0.70$), of task (IM and DM) ($F(1,9) = 5.062$, $P > 0.51$), nor any interaction during this session.

6.6. Imaging results

Early learning stage. The first contrast was intended to uncover brain regions implicated in the early stage of the skill's acquisition. Contrary to our hypotheses, subtracting the DM from the IM revealed activations limited to the striatum in the left putamen and right caudate nucleus (Fig. 6.3A and Table 6.1), and none in the CC system.

Insert Figure 6.3 and Table 6.1

Automatisation process. Here we sought to uncover regions involved in the automatisation process by contrasting the BOLD signal obtained during the second scanning session from that of the first. However, because non-specific related factors might influence metabolic activity of the brain on different days, comparisons between days of scanning are difficult to interpret (Rajah, Hussey, Houle, Kapur & McIntosh, 1998). To overcome this limitation, we contrasted the neural activity obtained by subtracting the DM from the IM in the early learning stage from that of the same subtraction obtained during the automatic stage; the reasoning being that non-specific factors present during the execution of the adaptation skill would also be present during the control condition. The results yielded activations in the left cerebellar crus I and the right parahippocampal gyrus, hence suggesting that these structures play a critical role in this process (Fig. 6.3B and Table 6.1).

Automatic execution. Finally, to reveal brain activation patterns related to the automatic performance of the motor adaptation skill, we subtracted the DM from the IM obtained during the second series of images. Consistent with Doyon et al.'s model, our results revealed activation located bilaterally in cerebellar lobules V-VI, and in the supplementary motor areas (SMA), as well as in the left superior parietal lobule, left primary motor cortex (M1), and left dorsal premotor region (PMd) (Fig. 6.3C and Table 6.1).

Correlation analysis: Precision index. To investigate better (or poorer) performances associated with the automatic execution of the adaptation skill, the subjects' precision at following the curved path during task execution was correlated with the BOLD response in this condition. The between-subject correlation analysis revealed that subjects completing the adaptation task with better precision showed greater activations in the posterior region of the cerebellum, more precisely in the right crus I area (32 -64 -32, T= 5.3, r= .88) (Fig. 6.4A). Conversely, poorer precision was correlated with increased activity in the anterior region of the cerebellar cortex involving the left lobule IV (-20 -32 -24, T= 6.32, r= -.91) and lobule V (-20 -44 -24, T= 5.06, r= -.87) (Fig. 6.4B and Table 6.2).

Insert Figure 6.4 and Table 6.2

Correlation analysis: Speed index. Similar correlation analyses using the speed index during the automatic execution stage of the motor adaptation task, revealed that subjects who completed the task fastest had increased BOLD signals in the anterior region of the cerebellar cortex located in the left lobule IV (-20 -32 -28, T= 4.92, r= .87) (Fig. 6.5A). Conversely, BOLD activity that correlated negatively with speed performance was seen in the posterior region of the cerebellar cortex, that is in the right lobule IX (12 -40 -44, T= 4.87, r= -.86) (Fig. 6.5B and Table 6.2).

Insert Figure 6.5

6.7. Discussion

Our results indicate that experience-dependent neural activity was limited to striatal regions during the early learning stage of a visuomotor adaptation skill, but then shifted and remained circumscribed to the CC circuit once the skill was automatised. Further analyses revealed that the process of automatising the adaptation skill predominantly implicated the cerebellum and the parahippocampal gyrus. Additional correlation analyses coupling the subjects' behavioural data with the BOLD signal acquired during the automatic stage demonstrated that distinct regions of the cerebellum are differentially involved in the speed and precision with which subjects execute the task.

Early motor adaptation learning. Although similar striatal activations were measured in previous imaging studies investigating the early stages of acquisition, these researchers employed a different, kinetic adaptation as their experimental task (Krebs et al., 1998). With the exception of Seidler et al. (2006) and Krakauer et al. (2004), the BOLD signal measured in the left putamen and right caudate nucleus are novel findings with respect to the striatums' involvement in the early learning phase for this kind of adaptation (Seidler, Noll & Chintalapati, 2006; Krakauer et al., 2004). In fact, while a number of previous experiments investigated the early learning phase of a kinematic adaptation

(Clower et al., 1996; Inoue et al., 1997; Ghilardi et al., 2000; Imamizu et al., 2000), they did not measure any activations in these regions.

Several reasons can be advanced to explain this discrepancy. For one, the majority of the prior studies used PET rather than FMRI, which may have limited their temporal and spatial resolution. Second, some studies did not scan these brain regions, and focused mostly on the cerebellum's contribution. Although these data suggest that the neural bases of early kinematic adaptation are similar to those for kinetic adaptation and sequence learning, it is not clear that the underlying contributions of the striatal system have to be the same for all types of learning. This topic requires further investigation.

From early learning to automatic execution. To identify brain structures specifically implicated in the *process* of automatising the adaptation skill, we subtracted the BOLD signal obtained in the early learning phase from that in the automatic execution stage. This contract revealed activations limited to the left lateral cerebellar region and the right parahippocampal gyrus. These results are consistent with the idea that the cerebellum is needed for motor performance to shift from an attention demanding state to an automatic mode (Doyon et al., 1998; Jenkins, Brooks, Nixon, Frackowiak & Passingham, 1994; Thach, 1998). Similar conclusions concerning the cerebellum's contribution to movement automaticity have been reported by Floyer-Lea and Matthews (2004). Indeed, using a motor task combining sequence and isometric force adaptation, the latter investigators have reported that the development of movement automaticity is particularly associated with greater recruitment of the cerebellum (Floyer-Lea. & Matthews, 2004). Additional corroborating evidence concerning the role of the cerebellum in this process has come from a clinical study completed by Lang and Bastian (2002), who showed that patients with cerebellar damage can learn to coordinate their arm and shoulder to make a figure-8 movement, but cannot perform the skill at an automatic level (Lang & Bastian, 2002).

Although unexpected, the activation observed in the parahippocampal gyrus suggests that this structure contributes to the automatiation process. In fact, functional activations in the vicinity of this structure have been associated with the consolidation of a visuomotor tracking task (Maquet, Schwartz, Passingham & Frith, 2003), and with the integration of a motor network representing a consolidated motor adaptation skill (Della-Maggiore & McIntosh, 2005). Moreover, the later findings are in accord with recent fMRI studies conducted at 3 Tesla, which have demonstrated that in addition to the CS and CC systems, the limbic structures of the medial temporal lobe also contribute to the acquisition of motor sequences (Schendan, Searl, Melrose & Stern, 2003a; Schendan, Searl, Melrose, & Stern, 2003b). Such results suggest that in addition to the potential reliance on the declarative memory system to acquire and consolidate motor skills, this region may also be involved in the latter process of automatisation. However, this issue requires further investigation, as damage to the limbic structures does not impede amnesic patients from learning various motor tasks.

Automatic skill execution. In line with our *a priori* hypothesis, automatic execution of the adaptation skill only engaged structures composing the CC circuit. This level of execution was associated with increased activity in cerebellar lobules V-VI bilaterally, along with significant activations in M1, SMA, PMd, and superior parietal lobule. Our results are corroborated by a series of studies that reported increases in cerebellar activations as motor adaptation learning progressed (Della-Maggiore & McIntosh, 2005; Imamizu et al., 2000; Krebs et al., 1998; Shadmehr & Holcomb, 1997). In fact, similar lateral cerebellar regions have been identified by Imamizu et al. as being involved in the maintenance of the acquired internal model of an analogous visuomotor adaptation task (Imamizu et al., 2000; Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003).

As was hypothesised, our results also show that the M1, SMA, PMd, and superior parietal lobule contribute to the execution of the automatised adaptation skill. In fact, the increase of BOLD signal in M1 is consistent with other imaging studies that reported a progressive increase of activity in this region during motor sequence and adaptation learning (Grafton et al., 1992; Hazeltine, Grafton & Ivry, 1997; Karni et al., 1995; Karni et al., 1998). Although conjectural, this result thus agrees with the notion that M1 may be the storage site for motor memories that are highly overlearned. The PMd activation is in line with previous studies, which have shown that this cortical area plays a role in the temporal aspect of motor planning (van Mier, Tempel, Perlmutter, Raichle & Petersen, 1998), and in the execution of smooth automatic movements (Krebs et al., 1998). The bilateral activity in SMA is also consistent with suggestions that it contributes to the organisation of sequential movements (Jenkins, Brooks, Nixon, Frackowiak & Passingham, 1994; Jueptner, Frith, Brooks, Frackowiak & Passingham, 1997; Jueptner et al., 1997), as well as in the timing of internally generated actions (Rao et al., 1997). And finally, increased activity in the parietal cortex may be attributed to its involvement in somatosensory processing, with the anterior regions playing a role in motor preparation based on sensory information, and the posterior regions participating in the correct selection of the movements based on spatial attention (Deiber, Ibanez, Sadato & Hallett, 1996; Della-Maggiore & McIntosh, 2005). Although the exact contribution of these structures requires further investigation, these results are in accord with Doyon and colleagues' model of motor adaptation learning, and suggest that the cerebellum and its related motor structures are important for the execution of an automatised visuomotor adaptation skill.

Different execution strategies and the cerebellum. Although specific instructions were given to the subjects to complete the motor task as fast and as accurately as possible, once debriefed at the end of the study, most of them declared having used one of two strategies to complete the adaptation task. They either focussed on performing the trials as fast as they could, or completing them as accurately as possible. Correlation analyses using the speed and precision indices revealed that the strategy employed during automatic execution generated two general patterns of cerebellar activity. Activations in the left anterior cerebellar regions were linked to a strategy based on fast performances, but low precision, whereas activations in the right posterior cerebellar regions were common to subjects executing the task with high precision, but slow execution. These results are in agreement with conclusions presented by Hikosaka et al. (2002) who stated that motor skills are acquired and retained in two different forms within the basal ganglia (Hikosaka et al., 2002). They proposed that the anterior parts of the basal ganglia are responsible for accurate performance, whereas more posterior regions of the putamen are responsible for speedy performances. These researchers thus maintained that at least two neural mechanisms operate independently to represent a motor skill. A similar finding regarding the segregation of specific execution strategies in the cerebellum was reported by Imamizu and his colleagues in 2003 (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). Using visuomotor adaptation tasks that required subjects to either adaptation to a rotational transformation or to a difference in speed, Imamizu and his colleagues (2003) identified to distinct regions within the cerebellum that were significantly and differentially activated by the two different kinds of adaptations. Their results indicated that the use of the rotational mouse were more anterior and lateral to those resulting from the use of the velocity mouse which were more posterior and medial (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). Our results agree with this statement, and further support the functional dissociation between speed and precision execution within the cerebellum.

6.7.1. Conclusion

First, this study confirms the importance of using a dual-task paradigm to measure automatic execution on a motor task, as evidenced by the fact that subjects required several more weeks of practice from the moment they had attained the asymptote, to when they reached an automatic level of performance. Second, although the striatal activity observed during the early learning stage partially fit Doyon and colleagues' model of motor adaptation learning (Doyon & Ungerleider, 2002; Doyon, Penhune & Ungerleider, 2003; Doyon & Benali, 2005), our results follow very closely their hypothesis concerning the role of the CC in the automatic execution of this skill. Moreover, in addition to confirming the essential role of the cerebellum in the automatisation of a visuomotor adaptation skill, our results suggest the involvement of the limbic structures in the learning process. Finally, our correlation analyses reveal that distinct cerebellar regions are involved in different execution strategies used to complete the task, and consequently, future investigations of motor skill learning should pay close attention to the various strategic approaches subjects may use to complete the experimental paradigm.

6.8. Acknowledgments

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6.9. Specific contributions by authors

Raby Bouras : doctoral student; significant contribution to all stages of the present work including : subject recruitment, task development and administration, data acquisition and analyses, principle writer.

Julien Doyon : director; supervising all the above mentioned stages.

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Table 6.1 Brain areas activated at different learning stages of a motor adaptation skill.

Contrast	Brain region	MNI coordinates			T-value
		X	Y	Z	
IM vs DM during early learning					
	Putamen (L)	-20	-12	12	5.23
	Caudate (R)	20	12	16	5.03
([IM vs DM early] VS [IM vs DM auto])					
	Cerebellar crus I (L)	-48	-52	-36	9.10
	Parahippocampal gyrus, BA 36 (R)	32	-36	-12	7.67
IM vs DM during automatic execution					
	Cerebellar lobule VI (L)	-16	-64	-16	7.82
	lobule VI (R)	20	-60	-20	5.15
	lobule V (L)	-28	-52	-20	6.21
	lobule V (R)	32	-52	-20	6.53
	Superior parietal lobule, BA 7 (L)	-28	-56	64	5.18
	SMA, BA 6 (L)	-4	-26	76	6.69
	SMA, BA 6(R)	8	-4	76	9.82
	M1, BA 4 (L)	-56	-8	44	5.75
	PMd, BA 6 (L)	-24	-20	76	5.59

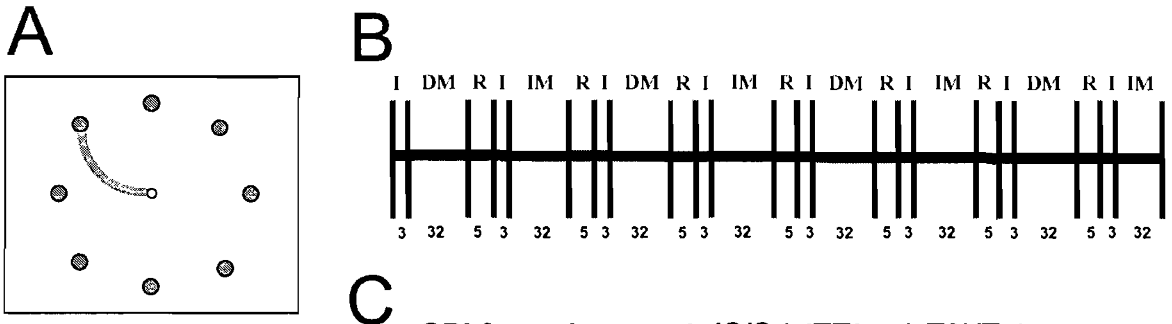
Table 6.1 Activation peaks are given using the MNI coordinates. All coordinates are significant as defined by $P^{uncorrected} < 0.001$. Abbreviations; L: left, R: right, PMd: dorsal premotor cortex, SMA: supplementary motor area, M1: primary motor cortex, BA: Broadman's area.

Table 6.2 Brain areas significantly correlated with the precision and speed performance indices during automatic execution of the motor adaptation skill.

Correlation Brain region	MNI coordinates X	Y	Z	T-value	r
Positive corr b/w PI and BOLD signal					
Cerebellar crus I (R)	32	-64	-32	5.30	0.88
Negative corr b/w PI and BOLD signal					
Cerebellar lobule V (L)	-20	-44	-24	5.06	-0.87
lobule IV (L)	-20	-32	-24	6.32	-0.91
Positive corr b/w SI and BOLD signal					
Cerebellar lobule IV (L)	-20	-32	-28	4.92	0.87
Negative corr b/w SI and BOLD signal					
Cerebellar lobule IX (R)	12	-40	-44	4.87	-0.86

Table 6.2 Activation peaks are given using the MNI coordinates. All coordinates are significant as defined by $P^{uncorrected} < 0.001$. Abbreviations; b/w: between; r: correlation coefficient; PI: precision index, SI: speed index.

Figure 6.1: A B & C



C

$\textbf{GPI formula} = \exp(-dS/S * (TT(ms)-T0)/Ta)$

Figure 6.1 **(A)** Visual interface of the Eight Target Tracking task (ETT). At the beginning of every trial, a starting point, represented by a white circle (0.75 cm in diameter), appeared in the middle of the computer screen. The cursor, a cross-shaped figure, appeared superimposed on top of the starting point. At the same time, the target represented by a red circle (1.5 cm in diameter), appeared 10 cm from the starting point. Appearing simultaneously was a line (0.5 cm in thickness) indicating the ellipse-shaped trajectory the subjects had to follow (radius of 2.5 cm) to reach the target with the cursor. **(B)** Timeline describing a possible configuration for one of the ten runs in one of the two scanning sessions. Subjects completed 2 tasks in these runs: ***DM*** stands for eight target tracking in direct mode, ***IM*** stands for eight target tracking in indirect mode, ***I*** stands for instructions, and ***R*** stands for rest. Total duration of a run was 315 seconds. Each bloc was composed of 8 trials, and each trial was separated by a pseudo-randomly varied interval ranging from 500 to 1500 msec. This is known as a jittered design, and has the advantage of combining both the block and event-related run configurations. **(C)** Formula used to calculate the global performance index (GPI) on ETT trials. The GPI was calculated by combining the precision *(dS/S)* and speed performances *([TT-T0]/Ta)* on the ETT. In the formulas *exp* is the value given to the trial (1 for successful and 0 for failed), the *dS* represents the differential surface area between the actual path followed to reach a target and the optimal path of the curved line, *S* is defined as the differential surface area between the optimal path of the curved line and a straight line between the starting point and the target center, TT constitutes the total time, T_0 the minimal time needed (500 ms), and T_a the time allowed (2,900 ms) to reach the target.

Figure 6.2: A, B & C

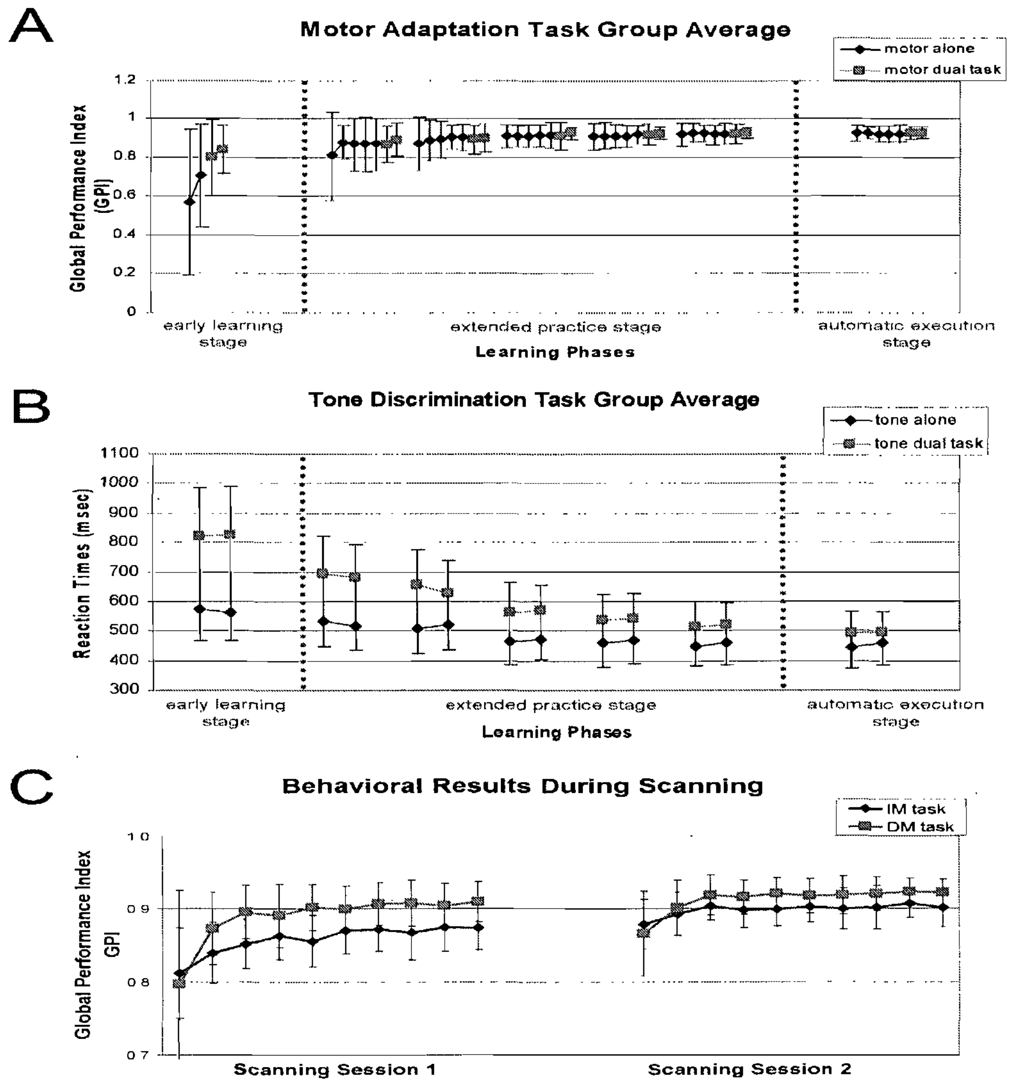


Figure 6.2 Average group performance across-subjects (mean ± SD) on **(A)** the visual-tracking task in the inversed mode (IM) executed alone (blue diamonds), and in the dual-task condition (red squares); **(B)** the Tone Discrimination Task (TDT) completed alone (blue diamonds), and in the dual-task condition (red squares); and **(C)** the visual-tracking task in the inversed mode (IM, blue diamonds) and direct mode (DM, red squares) measured during the two scanning sessions. In both figures A & B, every data point corresponds to the subjects' performance during a bloc of trials, whereas in figure C, each data point corresponds to the subjects' performance during an fMRI run.

Figure 6.3: A, B & C

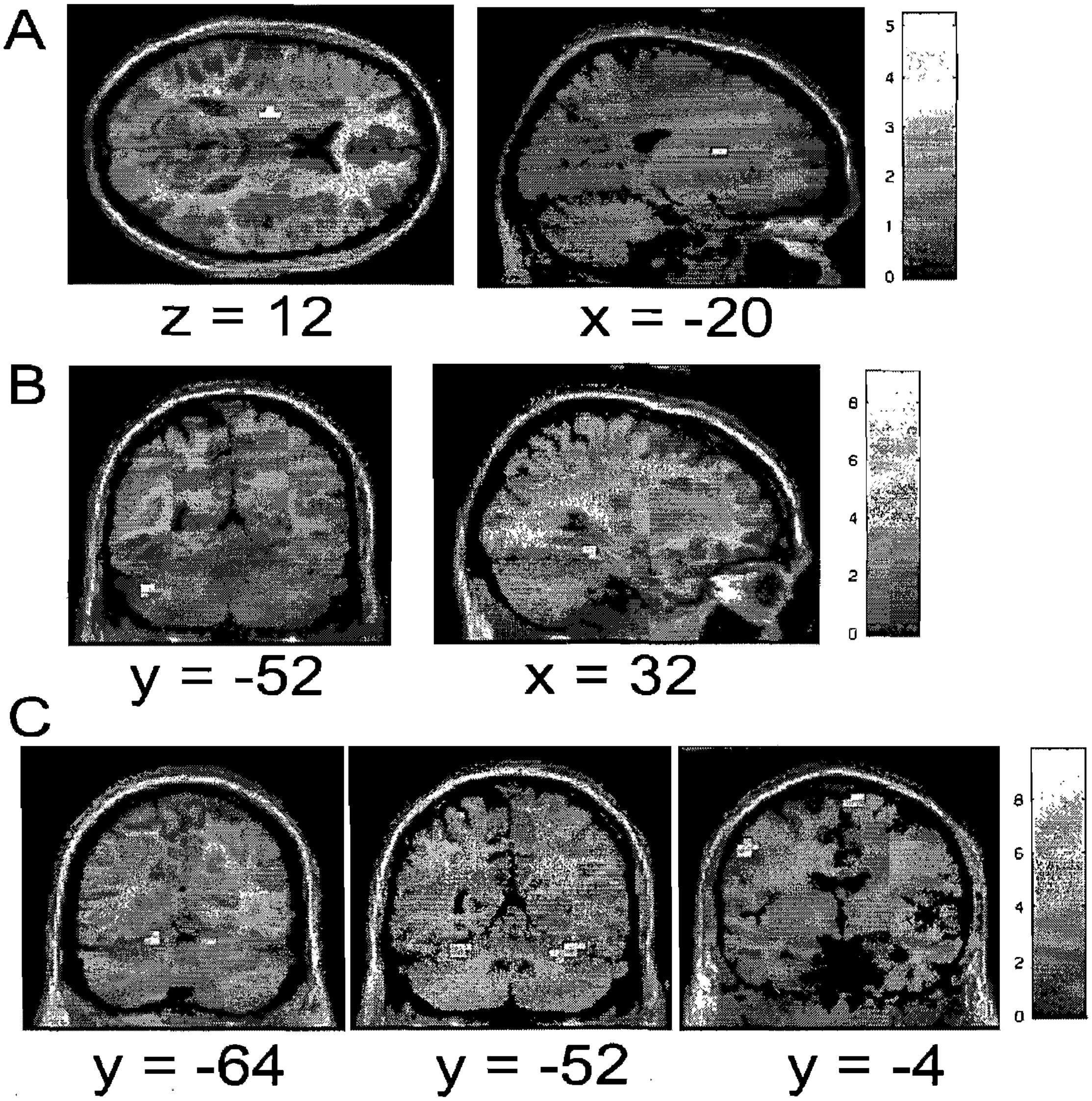


Figure 6.3 Statistical parametric maps of brain activity during motor adaptation. **(A)** Brain regions activated during the early learning phase (IM *vs* MD in the early stage). **(B)** Results of the contrast ([IM *vs* DM] early stage *vs* [IM *vs* DM] automatic stage) revealing the brain structures involved in the automatisation process. **(C)** Brain regions activated during the automatic execution of the task (IM *vs* MD in the automatic stage). All contrast images were obtained for subject individually and then used in the second level random-effects analyses as calculated by a one-sample t-test model, a statistical threshold of $P < 0.001^{\text{uncorrected}}$ was considered to show significant activations. Color bars code for the value of the *t* statistic associated with each voxel. Right side of the image corresponds to the right side of the brain.

Figure 6.4: A & B

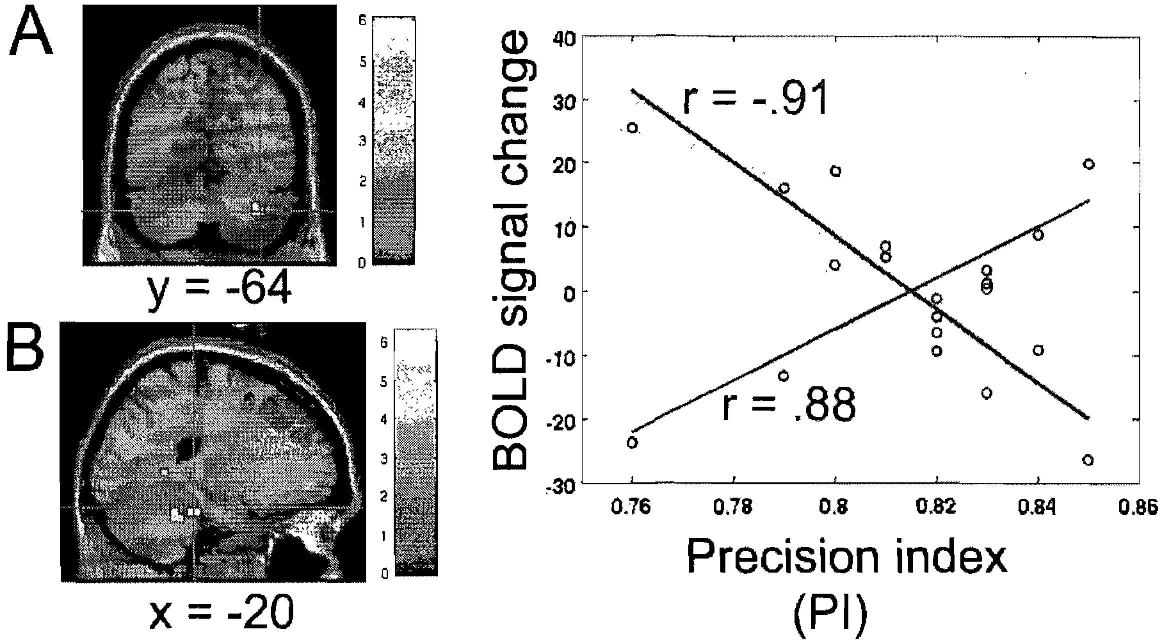


Figure 6.4 Between-subjects regression analyses coupling the subjects' average precision index (PI) and the BOLD signal measured during the automatic execution stage of the motor adaptation skill. **(A)** Blue crosshair: right cerebellar crus I (32 -64 -32). The scatter plot shows that the brain response at this coordinate was positively correlated with precision (blue; *r* = .88). **(B)** Red crosshair: left cerebellar lobule IV (-20 -32 -24). The scatter plot shows that the brain response at this coordinate was negatively correlated with precision (red; *r* = -.91). Note that a negative correlation was obtained for the left lobule V (-20 -44 -24, r= -.87), but that it is not plotted on the graph.

Figure 6.5: A & B

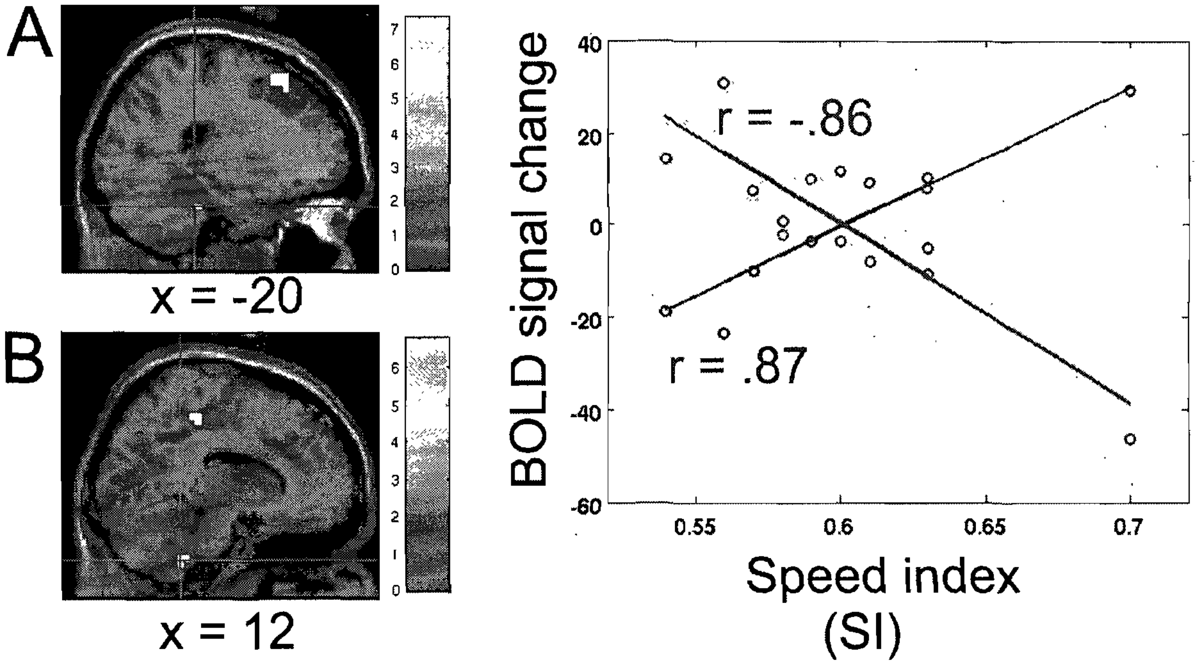


Figure 6.5 Between-subjects regression analyses coupling the average subjects' speed index (SI) and the BOLD signal measured during the automatic execution stage of the motor adaptation skill. **(A)** Blue crosshair: left cerebellar lobule IV (-20 -32 -28). The scatter plot shows that the brain response at this coordinate was positively correlated with speed (blue; $r = .87$). **(B)** Red crosshair: right cerebellar lobule IX (12 -40 -44). The scatter plot shows that the brain response at this coordinate was negatively correlated with speed (red; $r = -.86$).

Chapter 7. Experiment 2: The long-term retention of a visuomotor adaptation skill: a fRMI study

7.1. Abstract

In a previous experiment completed in our laboratory, eight healthy volunteers were scanned using fMRI (3.0 Tesla) on two consecutive days: first while learning to complete a kinematic visuomotor adaptation task (Day 1), and after extensive practice was given such that subjects reached asymptotic performance (Day 2). In the present study, we intended to investigate the brain structures implicated in the long-term retention of this type of visuomotor adaptation skill by scanning the same eight subjects completing the same task approximately two months after the initial learning phase. Consistent with the model of motor learning proposed by Doyon and colleagues (2002, 2003, 2005), the results revealed that the functional reorganisation that take place during the slow learning phase (i.e. the functional specialisation of the cortico-cerebellar (CC) system) is reactivated when the skilled behaviour is recalled at a later time.

7.2. Introduction

In this past decade, a plethora of brain imaging studies interested in motor skill learning has demonstrated that activations in different brain regions depend on the learning phase in which subjects are scanned in (Grafton et al., 1992). As such, four learning phases have been identified; the early [fast] phase, consolidation, late [slow] phase, and automatisation (Doyon & Ungerleider, 2002; Karni et al., 1998; Doyon & Ungerleider, 2002; Doyon, Penhune & Ungerleider, 2003; Friston, Frith, Passingham, Liddle & Frackowiak, 1992; Karni et al., 1995; Doyon, Owen, Petrides, Sziklas & Evans, 1996; Doyon, 1997). Also, it has been demonstrated that the roles of the cortico-striatal (CS) and cortico-cerebellar (CC) systems can be dissociated in late phases of the acquisition process when subjects are either performing a learned motor sequence, or motor adaptation task (Doyon & Benali, 2005).

While the plastic changes associated with the learning and long-term maintenance of movement sequences have been studied extensively (Karni et al., 1998; Penhune & Doyon, 2002; Jueptner, Frith, Brooks, Frackowiak & Passingham, 1997; Toni, Krams, Turner & Passingham, 1998), our knowledge base of the neural structures mediating the retention of a motor adaptation skill remains largely incomplete. Indeed, most of the imaging work looking at the latter type of learning has focussed on the fast learning phase (Brashers-Krug, Shadmehr & Bizzi, 1996; Shadmehr & Holcomb, 1997; Shadmehr & Holcomb, 1999; Imamizu et al., 2000; Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003), while only a few experiments have scanned subjects after they attained the slow learning stage (Krebs et al., 1998; Nezafat, Shadmehr & Holcomb, 2001; Della-Maggiore & McIntosh, 2005). Amongst these studies, Krebs and colleagues (1998) did not investigate the long term retention of the skill, and Della-Maggiore and her colleagues (2005) only acquired behavioural data describing the skill's long-term retention. As for Nezafat et al. (2001), they obtained imaging data regarding the long term retention of a force field adaptation task, however their study employed positron emission tomography (PET) and they focused primarily on the cerebellum's involvement in the process. The objective of the present study was use functional magnetic resonance imaging (fMRI) of the entire brain to identify regions responsible the recall of a visuomotor adaptation skill, and to compare them to the structures implicated in the long-term retention of the skill.

In a recent model, Doyon and colleagues (2002, 2003, 2005) proposed that the fast acquisition of a new visuomotor adaptation skill depends upon dynamic interactions within the CS and the CC systems. However, once consolidated, the neural representation of the adaptation skill is believed to be distributed in a network of structures that involves the CC circuit only (Doyon & Ungerleider, 2002; Doyon, Penhune & Ungerleider, 2003; Doyon & Benali, 2005). In a previous investigation designed to test this hypothesis (Doyon et al., 2004), eight healthy volunteers were scanned using a 3.0 Tesla fMRI on two separate days, i.e. while subjects were learning to complete a visually-guided motor adaptation task on Day 1, and once subjects had attained the asymptotic level of performance on Day 2. The results of standard and functional connectivity analyses revealed that learning was first characterized by a transient overall increase within the CS and CC systems, followed by sustained activity limited to the CC structures on Day 2. In the present experiment, the same eight subjects were scanned again two months after completing the previous study. The results of this experiment are thus believed to reflect the brain networks mediating the retention of a consolidated visuomotor adaptation skill. Based on the model of motor adaptation, it was hypothesised that similar brain regions composing the CC system would be involved in long-term retention of the adaptation skill.

7.3. Materials & methods

7.3.1. Subjects

Eight right-handed healthy volunteers (5 males) participated in this study. The subjects were aged between 19 and 26 years (Mean: 23.1), with 13 to 20 years of education (Mean: 16.6). Subjects were screened to exclude those with expertise in video games, as well as those with a history of neurological, psychological or psychiatric disorder. All subjects provided written informed consent, and received financial compensation for their participation. The study was approved by the Local Ethic's Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, CCPPRB) in Paris.

7.3.2. Materials

The Spike 4 software and CED 1401 data acquisition peripheral (both from Cambridge Electronic Design Inc.) were respectively used to generate the computer programs necessary to present the sequence of targets in both motor adaptation and control tasks, and to record the subjects' performance. Subjects used a MRI compatible joystick (Resonance Technology Inc) to reach the targets, which were displayed onto a screen behind the subject's head via a LCD projector (NEC MultiSync MT 1030+). They were able to observe the screen through its reflection on a mirror embedded within the head coil.

7.3.3. Task Description

Subjects were scanned while completing two experimental conditions: a motor adaptation and motor control task. Both tasks were completed using a version of the eight-target tracking task designed in our laboratory (Hadj, Blanchet & Doyon, 2004). Subjects were required to use a joystick to move a cursor from a starting point positioned in the center of the computer screen to a distant target following an elliptical trajectory. Motor adaptation was measured by inversing (inversed mode [IM]) the relation between the joystick's movement and the cursor's direction (i.e. moving the joystick to the right caused the cursor to move to the left). In contrast, the relation between the joystick's movements and the cursor's direction were the same (direct mode [DM]) in the motor control condition. The subject's performance on the IM and the DM were measured by computing a precision index based on the distance between the cursor's trajectory and the ideal curved path leading to the target, as well as a speed index based on the time subjects took to complete each trial. These indices were then combined to calculate a global performance index (GPI). All these indices ranged from 0 to 1, and can be interpreted as the probability distribution for the subject's performance on both the spatial and/or temporal aspects of the task. Expressed mathematically, the latter index can be described as:

$$GPI = exp(-dS/S * (TT(ms)-T_0)/T_a)$$

Where *exp* is the value given to the trial (1 for successful and 0 for failed), the *dS* represents the differential surface area between the actual path followed to reach a target and the optimal path of the curved line, *S* is defined as the differential surface area between the optimal path of the curved line and a straight line between the starting point and the target center, TT constitutes the total time, T_0 the minimal time needed (500 ms), and T_a the time allowed (2,900 ms) to reach the target.

7.3.4. Procedure

The subjects were contacted approximately two months after they completed training in the previous study (Doyon et al., 2004), and were reacquainted with the motor tasks before scanning. This reminder session was composed of 24 trials in the DM and 48 trials in the IM condition. Subjects then completed a fRMI scanning session (i.e. retention scan) comprised of five runs that were identical to the ones completed in the previous study. Each of the five runs consisted of a buffer period of 12 sec, a block of 16 DM trials (64 sec), a block of 64 IM trials (256 sec), and a rest period of 20 seconds between the two experimental conditions to prevent accumulation of fatigue in subjects. The order of presentation of the two conditions was counterbalanced on every run. Finally, 4 sec instruction periods were included before each experimental condition to guide subjects, for a total run duration of 360 sec.

It is important to clarify that the five runs completed by subjects in the experiment reported here was originally accompanied by another five runs in which subjects performed a motor sequence task. This is important to keep in mind since the subject's fatigue while they were in the scanner needed to be considered. As such, we opted to limit the number of trial in the motor control condition so as to diminish a run's duration. Another reason for the important difference between the number of trials completed in the IM block versus the DM blocs was the need for supplementary IM data in order to complete connectivity analyses.

A mixed fMRI paradigm that combined both block and event-related designs was used to acquire the functional data. To sample the BOLD signal at different moments during the execution of the task, jittering within each run was achieved by varying the inter-trial intervals during the motor conditions (Visscher et al., 2003). Therefore, in addition to the 3000 msec given to a subject to complete a trial (i.e., 2900 msec given to reach the target and the 100 msec needed to validate the target), one of 5 possible time intervals (500, 750, 1000, 1250, 1500 msec) was insert between trials. In addition, since the number of trials in every block was a multiple of eight, every trial within a bloc was designed to last 4000 msec on average. Blood oxygenation level dependent (BOLD) signals were recorded in 103 volumes, which were acquired using a single-shot echo-planar imaging sequence (TR = 3,486 ms, TE = 35 ms, 64 x 64 matrix, 42 slices, FOV = 19.2 cm and flip angle = 90°) on a Bruker 3.0T system at the fMRI Center at La Timone hospital, Marseille, France.

7.3.5. fMRI data analysis

The functional data were analysed using statistical parametric mapping (SPM2) (on line at www.fil.ion.ucl.ac.uk/spm). Data pre-processing included EPI realignment and spatial normalisation according to the Montreal Neurological Institute (MNI) space. The data was then convolved with a three-dimensional Gaussian Kernel (12 mm FWHM) to enhance the signal-to-noise ratio. The fMRI acquisition runs were analysed as an event-related paradigm, with 4 variables defined and measured in every run: (1) successful IM trials; (2) failed IM trials; (3) successful DM trials; and (4) failed DM trials. The data set was then convolved with a canonical hemodynamic response function, and a high-pass filter was applied for filtering low frequency noise (cut off, 128 sec). Finally, realignment parameters (translation and rotation in x, y, z dimensions) were included as covariates of no interest to correct for head movements. In order to determine the pattern of activations in the various conditions, two contrast images were calculated per subject, using events associated to successful trials only. The first contrast was calculated to reveal the regions involved in the reactivation of the adaptive movements necessary to complete the reaching task two months post-consolidation, i.e. long-term retention ([IM VS DM] *on retention scan*). The second and final contrast was intended to reveal the regions specifically involved in the retention of the motor adaptation skill ([IM vs DM *on retention scan*] VS

[IM vs DM *on Day 2*]). The corresponding contrast images were entered into a second level random-effects analysis for group comparisons, as calculated by a one-sample t-test model. Based on the predictions derived from Doyon & colleagues' (2002, 2003, 2005) model regarding the involvement of the CC and CS circuits in motor adaptation learning, as well as results of previous fMRI studies (Nezafat, Shadmehr & Holcomb, 2001; Della-Maggiore & McIntosh, 2005; Krebs et al., 1998; Doyon & Ungerleider, 2002; Doyon, Penhune & Ungerleider, 2003; Doyon & Benali, 2005), a statistical threshold of $P^{uncorrected} < 0.005$ (with a spatial extent of 3 voxels for subcortical structures, and 10 voxels for cortical structures) was considered to show significant activations.

7.4. Results

7.4.1. Behavioural results

Figure 7.1 displays the subjects' average performance measured during the first two scanning sessions (Days 1-2) conducted previously by Doyon and colleagues (Doyon, J. et al., 2004), and that observed in the present experiment (retention). An ANOVA for repeated measures revealed a significant effect of task ($F(1,7) = 11.699$, $P < 0.011$). Although an improvement with time seems to occur, no significant effect of time ($F(2,14) = 6.694$, $P < 0.09$) or interaction effect was measured ($F(2,14) = 0.158$, $P < 0.855$). Subsequent Newman-Keuls post-hoc comparison, using an alpha level of 5%, showed that contrary to the performance improvement observed on the first two days of the experiment, subjects recalled the task two months later with no significant improvement or deterioration in performance.

Insert figure 7.1

7.4.2. Imaging results

Recall of the skill. The execution of a visuomotor adaptation requires various cognitive processes including visual perception, attention, and sensory integration for its execution. To assess brain activation patterns specifically related to recall of the adaptation skill *per* se, the latter processes were removed by subtracting the DM from the IM condition as measured on Day 3. Consistent with the hypotheses derived from Doyon and colleagues' model of motor learning (2002, 2003, 2005), contrasting these two conditions revealed activations bilaterally in cerebellar lobules VI and in the left lobule VIIIB. Increased activity was also observed in left parahippocampal gyrus, uncus, and dorsal premotor cortex (PMd) (see Fig. 7.2A and Table 7.1).

Retention of the skill. The second contrast sought to uncover regions differentially involved in the long-term retention of the motor adaptation skill by subtracting activations measured in the slow learning phase (Day 2) from those measured during recall (retention). However, because non-specific related factors can influence metabolic activity of the brain on different days, comparisons between days of scanning are difficult to interpret (Rajah, Hussey, Houle, Kapur & McIntosh, 1998). To overcome this limitation, we proceeded to contrast the neural activity obtained by subtracting the DM from the IM on Day 2, from those resulting of the same contrast at retention; the reasoning being that any non-specific factors present during the execution of the adaptation skill would also be present during the control condition. The results of this contrast (Fig. 7.2B) revealed significantly brain activations located in left cerebellar lobule V, left parahippocampal gyrus, and right fusiform gyrus (see Table 7.1).

Insert figure 7.2 and table 7.1

7.5. Discussion

This study sought to uncover the implication of different brain regions in the recall and long-term maintenance of a previously consolidated kinematic visuomotor adaptation task. As such, eight subjects were recruited who, two months prior, had practiced the same task until their performance had reached asymptote. In the present study, and with no additional practice, subjects were scanned through fRMI while they recalled the task. No significant improvement or deterioration in performance was measured, demonstrating that long-term maintenance of the skill had been achieved. As such, after contrasting the images acquired on this day, while subjects recalled the adaptation task with those acquired during the execution of a control task, revealed the implication of similar structures also identified as being involved in the slow learning phase during the previous experiment. Additionally, a between session subtraction was calculated to uncover the structures specifically implicated in the long-term maintenance of the skill. The results of this contrast revealed that a redistribution of activations took place, but that this reorganisation was limited within these same brain regions.

Brain circuits implicated at recall. The results of the present study reveal that the delayed recall of the visuomotor adaptation task is mediated by regions located bilaterally in cerebellar lobules VI, left lobule VIIIB, as well as in left parahippocampal gyrus, uncus, and PMd. This pattern of activity closely resembles the pattern associated to the slow learning of the task as measured in the previous experiment. Furthermore, it complies with Doyon's model, and suggests that only the CC circuit is involved in the maintenance of an adaptation skill beyond the slow learning phase. Another study completed by Nezafat and colleagues (2001) also examined the recall and long-term retention of dynamic motor adaptation skill through positron emission tomography (PET) (Nezafat, Shadmehr & Holcomb, 2001). These researchers, however, had subjects learn a force field adaptation task, and measured blood flow changes during three scanning sessions; on the first day, two weeks, and four weeks later. As compared to day 1, two weeks after initially learning the adaptation skill (day 15), only one region with significant increases in activity was identified in the medial gyrus of left temporal lobe. However, these researchers employed a time-by-condition interaction to identify this region, that is, they reported the difference between adaptation and a control on day 15 as contrasted by the same difference on day 1. They therefore did not present data that represent the recall of the skill, but rather brain structures that differed from those measured on the previous scanning session. In addition, and unlike our study, Nezafat and colleagues' (2001) subjects did not attain the asymptotic level of performance by the end of day 1, and therefore, they may still have been learning the skill when completing the scans two weeks later. In fact, on all three scanning days (days 1, 15 & 29), subjects were given additional practice on the adaptation task between scanning runs. Consequently, their results cannot be interpreted as the recall of an adaptation task in the same manner as our data.

Although we are not aware of other previous work that has explored and described the delayed recall of an adaptation skill, very similar results concerning the CC circuit were obtained by researchers who investigated late learning stages of a similar kinematic adaptation task (Della-Maggiore & McIntosh, 2005). Using PET, Della-Maggiore and colleagues reported that the gradual improvement in performance, and the eventual attainment of the slow learning stage (following 5 days of practice), was associated greater activity in the parietal and temporal regions, as well as in the cerebellum and striatum. In addition, and similar to (Doyon et al., 2004), functional connectivity results indicated that this later learning phase was related the functional links between the anterior cerebellum, left sensorimotor cortex and left middle temporal gyrus. Another study completed by Krebs et al. (1998) combined PET and a dynamic adaptation to study the functional changes in brain areas participating in the incremental learning of a motor adaptation (Krebs et al., 1998). In line with our results and with those reported by Della-Maggiore et al. (2005), these researchers reported that as subjects became skilled at performing the task, the pattern of neural activity implicated the left premotor, left primary motor, and sensory areas, as well as right cerebellar cortex (Krebs et al., 1998). Although these studies cannot attest to the involvement of these structures in the recall of the adaptation skill, their conclusions are in line with ours as they maintain that the interactions between cerebellar, and the temporal/parietal cortical areas are necessary to learn the visuomotor task beyond the fast learning phase.

Brain circuits implicated in long-term retention. Our results show that few changes occur in functional activity from the time the task is well learned (slow learning stage) to the moment the skill is recalled two months later. In fact, consistent with the model, when brain regions implicated on Day 2 were compared to those of the retention, activity was observed only in left cerebellar lobule V, left parahippocampal gyrus, and right fusiform gyrus. In Nezafat and colleagues' (2001) study, they examined the long-term retention of a dynamic motor adaptation four weeks after subjects were initially presented to the task (Nezafat, Shadmehr & Holcomb, 2001). In line with our results, they found no significant differences across weeks with regards to the cerebellar regions they had identified on the first training day, but as the weeks passed, there was a significant decrease in the regional cerebral blood flow (rCBF) in a region of the right anterior cerebellar cortex. This decrease in activation was interpreted as increased neural efficiency, which in turn, is believed to correspond to a sharpening of the response in a particular neural network representing the internal model (Poldrack, 2000). Interestingly, a cerebellar region in the vicinity of lobule V was also identified by Imamizu et al. (2000) as being involved in the maintenance of the acquired internal model of a kinematic visuomotor adaptation task (Imamizu et al., 2000). In fact, these researchers maintained that the specific internal model representing the altered relationship learned by the subjects to execute the adaptation task was maintained in the lateral regions of the cerebellum. Therefore, our results add to the growing literature confirming the importance of the cerebellum in the acquisition and long term maintenance of motor visuomotor adaptation (Shadmehr & Holcomb, 1997; Jueptner & Weiller, 1998; van Mier, Tempel, Perlmutter, Raichle & Petersen, 1998; Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003; Imamizu et al., 2000).

The measured activity in the parahippocampal gyrus is also consistent with data from brain imaging studies investigating visuomotor adaptation. In fact, a reliance on structures supporting the declarative memory system to maintain the motor skill has been suggested to account for such activity. This is corroborated by studies which demonstrate that declarative and procedural memories, although subserved by two different cerebral systems, may interact with one another on a given task (McDonald & White, 1993; Doyon & Benali, 2005). Therefore, the activation pattern reported in this study testifies to the involvement of this region in the long-term maintenance of a motor adaptation skill. However, this issue requires further investigation, since research has also demonstrated that the limbic structures are not required by amnesic patients to learn motor abilities.

Our results therefore suggested that once the task is well learned, the long-term maintenance is mediated specifically by the cerebellum and parahippocampal gyrus, while the other regions composing the CC circuit are involved in the execution of the learned task. In sum, our results are consistent with the model of motor learning proposed by Doyon and colleagues (2002, 2003, 2005), confirm the particular importance of the of the cerebellum and parahipocampal regions in the process of learning, maintaining and recalling a kinematic visuomotor adaptation skill.

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7.7. Specific contributions by authors

Raby Bouras : doctoral student; significant contribution to all stages of the present work including : data analyses and principle writer.

Amélie Morin : collaborator; involved in the data acquisition.

Jean-Luc Anton : collaborator; technical aide involved in the development of the motor tasks and data acquisition.

Habib Bénali : collaborator; significant aide in the development of the experimental protocol and subject recruitment.

Julien Doyon : director; supervising all the above mentioned stages.

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Table 7.1 ***Brain areas implicated in the long-term retention of a visuomotor adaptation skill***

Contrast	Brain region	MNI coordinates			T-value
		X	Y	Z	
[IM vs DM] Day 3					
	Cerebellar lobule VIII B (L)	-27	-57	-51	5.71
	Lobule VI (L)	-39	-66	-21	4.19
	Lobule VI (L)	-36	-45	-33	3.86
	Lobule VI (R)	33	-45	-33	5.19
	Parahippocampal gyrus, BA 36 (L)	-36	-36	-15	4.43
	Uncus, BA 28 (L)	-21	-9	-36	3.79
	PMd, BA 6, (L)	-18	3	60	11.64
([IM vs DM] Day 3 VS [IM vs DM] Day 2)					
	Cerebellar lobule V (L)	-6	-63	-12	4.05
	Fusiform gyrus, BA 37 (R)	39	-48	-15	6.94
	Parahippocampal gyrus, BA 36 (R)	-36	-36	-18	5.71

Table 7.1 The coordinates are given in MNI coordinates. All coordinates are significant as defined by $p^{uncorrected} < 0.005$. Abbreviations; L: left, R: right, PMd: dorsal premotor cortex, BA: Broadman's area.

Figure 7.1

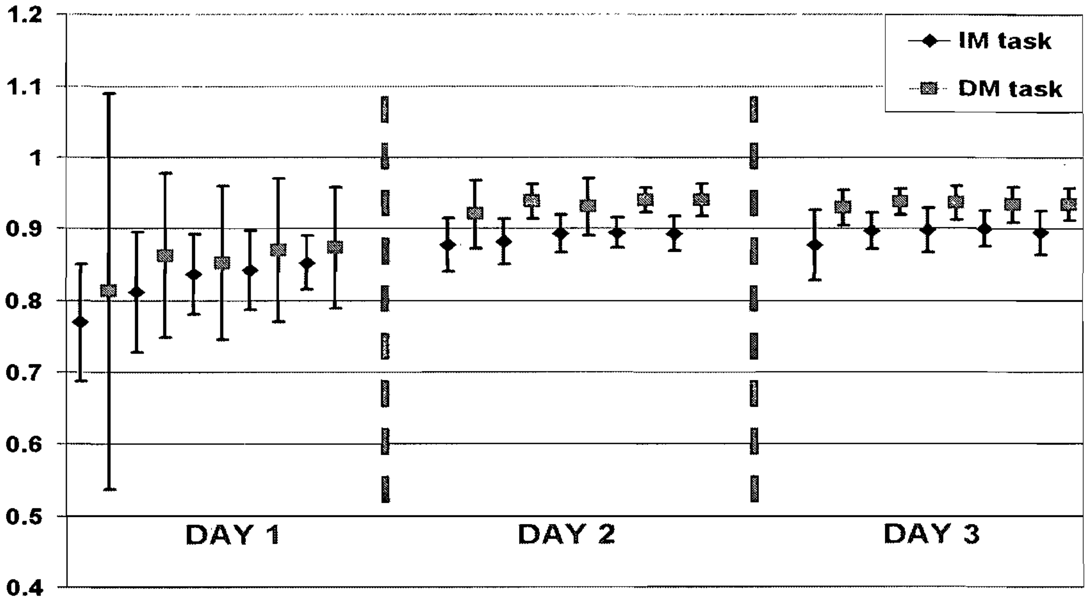

Figure 7.1 Average group performance (across-subjects mean ± SD) on the visual-tracking task in inversed mode (IM, blue diamonds), and in direct mode (DM, red squares). Every point corresponds to the average of trials completed during a scanning run, and the axe represents the three days of experimentation: Days 1 and 2 completed during the previous study, and the present retention experiment (Day 3).

Figure 7.2: A & B

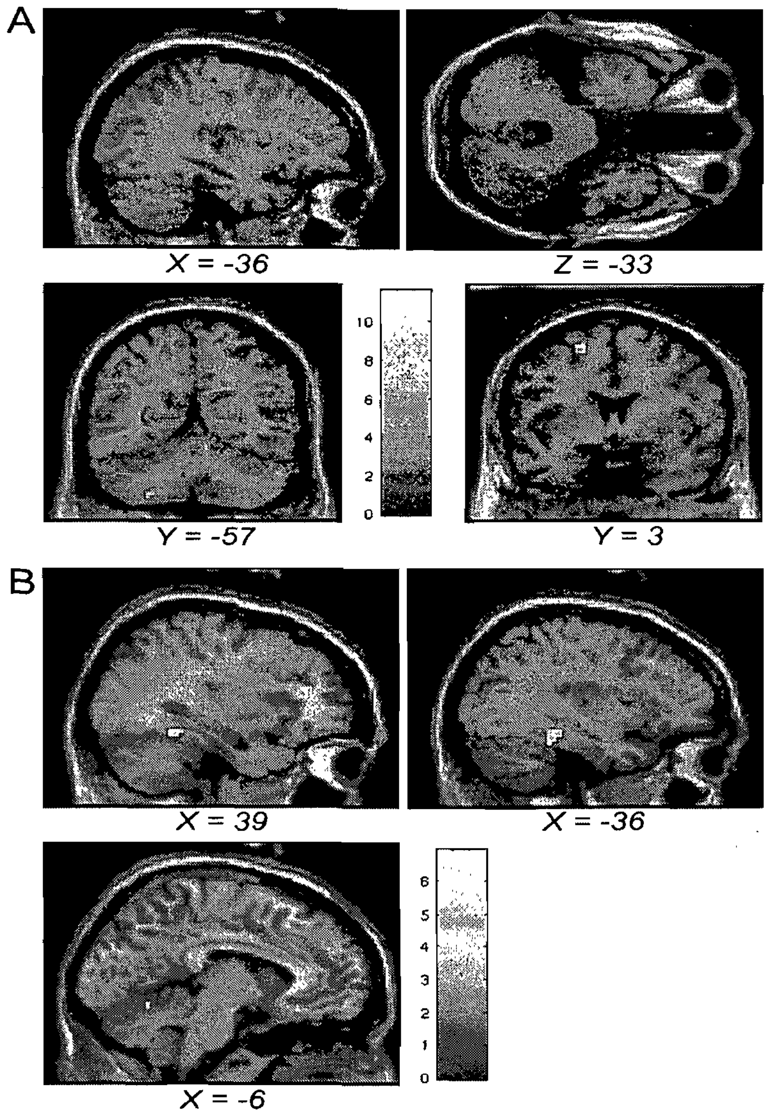

Figure 7.2 Statistical parametric maps of brain activity representing long-term retention of the visuomotor adaptation task. **(A)** Brain regions identified following the contrast subtracting the direct mode (DM) from the inversed mode (IM) during the delayed recall of the learned task (IM VS MD on Day3). **(B)** Brain regions identified following the contrast subtracting the direct mode (DM) from the inversed mode (IM) during the delayed recall on Day3 and the same contrast on fMRI data acquired on Day2 ([IM vs DM] Day3 VS [IM vs DM] Day2). All contrast images were obtained for every subject individually and then used in the second level random-effects analyses as calculated by a one-sample t-test model, a statistical threshold of $P < 0.005$ was considered to show significant activation. Color bars code the value of the *t* statistic associated with each voxel.

Chapter 8. General conclusion

8.1. Thesis overview

This concluding chapter contains a brief overview of the principle findings of the thesis in relation to the goals that were initially set, as well as an overview of the issues and questions that remain unanswered. The thesis' main objective was to contribute to our knowledge and understanding of visuomotor adaptation learning by examining the activation in the brain circuits underlying its acquisition and maintenance and those involved in its automatisation.

Just as initial concepts of a unitary memory systems evolved to include different kinds of memory subdivided into memory systems, our understanding of motor skill has evolved to include different types of skills. In the first chapter, we introduced the reader to early concepts and models of the memory system, and detailed the conceptual framework that has gained the most recognition in neuropsychological research over the last decade; Squire and colleagues' (1992, 1993) model. In chapter 2, we reviewed the three main types of skills learned by individuals (cognitive, perceptual and motor) and outlined how motor skill learning is itself further subdivided into motor sequence and motor adaptation skills. We then reviewed some of the most important factors that need to be considered and controlled for in the study of motor skill learning, and showed how not doing so has helped generate the contradictory findings reported in imaging studies. In chapter 3, we explored the topic of automatic execution of skills and the different operational definitions that have been given to this specific learning stage. We also detailed the rational behind the use of the dual-task condition in laboratory exploration of automatisation, and how it is really subjects' performance on the secondary task that provides an index of automaticity on the primary task being investigated. Chapter 4 examined the different models introduced by Doyon and colleagues (2002, 2003, 2005) that describe the implication of the cortico-striatal (CS) and cortico-cerebellar (CC) circuits during the learning and maintenance of the different motor skills. They take into consideration the important experimental variables described previously, and make predictions with regards to the cerebral networks involved at different learning phases during motor skill acquisition. The major advantage of this theoretical framework is that it makes several testable predictions with regards to the contribution of the neural circuits based on the stage of learning (fast, slow, consolidation, retention and automatisation), and the nature of the motor learning process (motor sequence vs. adaptation learning). In order to investigate the model's validity, we set out to test it in the two experiments reported in this thesis.

8.2. Overview of the experimental results and other recent experimental data

In the first experiment, the brain structures mediating the complete automatisation of a visuomotor adaptation skill were investigated. We examined subjects over several weeks while they learned to automatise the eight target tracking task, and used fMRI to monitor areas of increased cerebral blood flow both on their first day of practice and after they had reached an automatic level of performance. Based on Doyon and colleagues' (2002, 2003, 2005) model, it was hypothesised that early learning of the visuomotor adaptation skill would involve functional interaction of both the cortico-striatal (CS) and cortico-cerebellar (CC) circuits, while the retention and automatisation of the skill would engage neural activity in the CC only. In the second experiment we asked whether with the passage of time, and with no additional practice, there was a change in the neural representation underlying the retention of the previously learned skill. As such, eight young and healthy subjects were trained on the visuomotor adaptation task over a period of two consecutive days so as to reach a stable level of high performance. These same subjects were contacted approximately two months after they had learned the experimental adaptation task, and after a very brief reminder session on the same tasks, they were asked to undergo an fMRI scan. The brain activity measured in this latter experiment was therefore likely to represent the brain structures that mediate the long-term retention of a well learned visuomotor adaptation skill.

As hypothesised, our results revealed that a functional reorganisation took place among the brain structures composing the CC and CS systems throughout the learning process. First, a "true" reorganisation took place between structures from the moment the task was initially learned (early), to when it was performed at a more asymptotic level (late). There was a change in the location of activations from brain regions composing the CS system towards structures that form the CC circuit. This was followed by a second pattern of functional changes thought to reflect a "pseudo" reorganisation, or redistribution. This was exemplified by the pattern of brain activations observed on the long-term retention of the skill as compared to the late learning phase. This redistribution resulted in activations that generally contained similar brain areas at different phases of learning, although the level of activations changed within the CC system. Interestingly, and as expected, the CC system was engaged in the automatic learning phase and the long term retention of the adaptation skill. The results of our automatisation study also demonstrated that different cerebellar regions are activated during different execution strategies at the automatic phase. Correlational analyses using speed and precision indices revealed that the strategy employed during automatic execution generated two general patterns of cerebellar activity. On one hand, activity in the left anterior cerebellar regions was linked to a strategy based on fast performance, but low precision. The second pattern was associated with activations in the right posterior cerebellar region, and was most commonly observed in subjects executing the task with higher precision, but slow execution.

Our findings are therefore consistent with Doyon and colleagues' (2002, 2003, 2005) model of skill acquisition, and confirm that both the cerebellar and striatal systems sontribute to the early learning process, whereas only the cerebellar system contributes the later stages of retention and automatisation of the kinematic adaptation skill. These findings are consistent with imaging studies that have preceded and followed our own experiments, and confirm the different contribution of the cerebellum, striatum and their related circuits in the learning process (Clower et al., 1996; Shadmehr & Holcomb, 1997; Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003; Floyer-Lea & Matthews, 2004; Della-Maggiore & McIntosh, 2005; Seidler, Noll, & Chintalapati, 2006). The implication of these neural structures in motor control and learning is now well established in the imaging literature. However, the specific contribution of these circuits in the motor execution/learning process cannot completely be elucidated through imaging technologies alone. On the other hand, the study of the effects of human cerebral degenerative diseases, such as Parkinson's, Huntington's and cerebellar degeneration, provides interesting insights in this process.

Kinematic adaptation was investigated by Contrera-Vidal and his colleagues (2003) in Parkinson's disease (PD) patients (Contreras-Vidal & Buch, 2003). Using a pointing task that can produce a distorted visual feedback (90° counterclockwise rotation), these researchers compared the performance of PD patients to those of age-matched controls as they progressively learned the visuomotor adaptation task. Contreras-Vidal and his collaborators showed that PD patients displayed impairments in visuomotor adaptation to a 90° rotation distortion, when compared with age-matched controls. As such, PD subjects were not as efficient as the control to displace the cursor in the correct initial direction to reach the target. However, PD patients showed some adaptation in terms of the spatial variability of their movements, although not as important as that showed by the control subjects. Their results showed that with enough practice, PD patients were able to complete the adaptation task with some degree of precision, but their initial movement towards the target was never acquired. The authors used this data to argue that there are two processes operating during the course of adaptation learning. The first, rapid portion of the learning curve may be attributed to the initial acquisition and/or selection of the behaviourally appropriate internal model. On the other hand, the latter, linear component may involve processes that progressively fine-tune the selected internal model to the specific task condition. Considering the damage to the basal ganglia caused by PD, and their apparent inability to acquire this initial selection of internal model, the authors argued that the basal ganglia may be involved in the selection of appropriate movements based on external cues (Contreras-Vidal & Buch, 2003). Since no cerebellar damage is expected to occur in the course of PD, and subjects were able to demonstrate some adaptation to the distorted feedback during execution, the researchers suggested that the cerebellum is involved in the recalibration of motor commands through adjustment and optimisation of movement parameters (Contreras-Vidal & Buch, 2003). Their conclusion are in line with previous hypothesis concerning the basal-ganglia's and cerebellum's role in motor learning and execution (Jueptner & Weiller, 1998; Krakauer, Pine, Ghilardi & Ghez, 2000; Robertson & Miall, 1999).

Other researchers have found somewhat contradictory findings with regards to the role of the basal ganglia in motor adaptation learning. Investigating reaching movements through a kinetic adaptation task (miscalibration of dynamics through force-field) in patients suffering of Huntington's disease (HD), Smith and his colleagues (2000) observed a disturbance in error feedback control (Smith & Shadmehr, 2005). Unlike the findings of previous studies (Jueptner & Weiller, 1998; Krakauer, Pine, Ghilardi & Ghez, 2000; Robertson & Miall, 1999), Smith et al. (2000) reported that HD patients' errors made in the early part of the movement were poorly compensated by the motor commands in the remainder of the movement (i.e. feedback control). According to these authors, one of the many computational mechanisms that are involved in error feedback control was affected by damage to the basal ganglia (Smith & Shadmehr, 2005).

In a follow-up experiment, Smith and Shadmehr (2005) set out to investigate how the internal model with which subjects perform a subsequent movement is modified by the on-line feedback control mechanisms (Smith & Shadmehr, 2005). Testing HD and cerebellar patients with roughly comparable movement disorders during reaching, they studied how these patients adapted to the altered limb dynamic produced by the robot manipulandum. These authors found this ability to be intact in patients suffering from HD, but was profoundly impaired in cerebellar degeneration patients. Whereas control and HD groups used errors in a given trial to produce compensatory changes in the motor commands that initiated the next trial, the cerebellar damaged group changes in motor commands were unrelated to the errors in the previous trial. According to the authors, their data suggest that in HD, there is an intact ability of the motor system to respond to sensed errors from movement-to-movement but a reduced ability to form an appropriate response during the execution of the movement. In contrast, degeneration of the cerebellum does not affect in-flight error-correcting responses, but severely undermines the subjects ability to use this information to adjust motor output from trial to trial (Smith & Shadmehr, 2005).

Just as in the imaging literature, the clinical studies reviewed above report some contradictory findings that need to be addressed. What can account for the contradictions with regards to the roles the basal ganglia and cerebellum are hypothesised to play? One factor that could have helped generate the discrepancies may be the adaptation task employed; Smith and his colleagues (2000, 2005) used a kinetic adaptation as their experimental task, whereas Contrera-Vidal and his collaborators (2003) used a kinematic adapttion task. In fact, and as was previously described in detail, research has shown that not only is there a difference between kinetic and kinematic types of adaptation (Ghilardi et al., 2000), but that different kinds of kinematic adaptation also produce anatomically distinct patterns of brain activation (Imamizu, Kuroda, Miyauchi, Yoshioka & Kawato, 2003). Other researchers have also suggested that visuomotor adaptation mechanisms engaged during perceptual recalibration (e.g. prism adaptation tasks) differ from those employed during visuomotor skill acquisition (e.g. pointing task with distorted visual feedback) (Clower & Boussaoud, 2000). It is therefore possible that the distinct neural circuits employed to produce these kinds of adaptations are differently affected by the progression of the degenerative diseases.

Another important factor that could have contributed to the discrepancies is the nature of the degenerative disease the subjects presented. In fact, just as PD and HD are different neurodegenerative diseases that cause different patterns of atrophy in different structures of the basal ganglia, cerebellar degenerations can be brought about by either cardiovascular accidents, tumours and/or various accidents. What's more, the cognitive and motor dysfunctions associated with the cerebral atrophy that accompany the neurological conditions progress differently from one subject to the next (Thompson et al., 1988). As such, the patients composing the same experimental group may be at different stages of the degeneration, and patients between studies may also differ in the extent of their neurological damage.

Another important factor that could have contributed to the discrepancies between studies can be the presence of neural circuits that were not considered and/or appreciated in previous years. In fact, until very recently, more emphasis was placed on the dichotomy between the striatal and the hippocampal memory systems than on their eventual complementary/cooperative role (Packard & McGaugh, 1992; Teather, Packard, Smith, Ellis-Behnke & Bazan, 2005; Pych, Chang, Colon-Rivera & Gold, 2005). Direct anatomical connections between the hippocampus and the striatum have been recently documented (Voorn, Vanderschuren, Groenewegen, Robbins & Pennartz, 2004). According to these authors, the connections are abundant, complex and very well systemised. In addition, connections between the striatum and hippocampus via the entorhinal and prefrontal cortex have also been well studied (Christakou, Robbins & Everitt, 2004). Since we know that the hippocampus is involved in declarative memory, and that some motor task can be learned through cognitive strategies (explicit knowledge of the task demands), one can therefore speculate that the intact hippocampal memory circuit could have contributed to the learning of the adaptation tasks in the PD, HD and cerebellar degeneration patients.

This possibility has been recently investigated by Rossato and his colleagues (2006). Using the Morris water maze (MWM) as their experimental task, these researchers have made a solid case for the linkage between the striatal and hippocampal memory systems in the learning of a procedural task (Rossato et al., 2006). As Rossato et al. (2006) argue, the MWM is a form of learning that closely mimics human situations of daily life because it requires the formation of both a declarative component and the formation of a habit (Rossato et al., 2006). The cued version MWM requires rodents to learn to swim the shortest possible distance in a water tank to a hidden platform by learning the platform's position through visual cues external to the apparatus. This spatial version of the task is dependent on the hippocampus (Morris, 2006). There is also a non-spatial version of the MWM in which no external spatial cues are presented. This version is purely procedural, and depends on the striatum (Teather, Packard, Smith, Ellis-Behnke & Bazan, 2005). Using bilateral intra-CA1 (entorhinal cortex) infusion of anisomycin, or a placebo, to explore the acquisition, retention and reversal learning of the MWM, their results reveal that the declarative component of the task is changed, but the procedural component (to swim to safety) persists and needs to be re-linked with a different set of spatial cues. According to Rossato et al. (2006), their findings endorse the view that the borders between memory systems are not so clear that tasks or forms of learning may be defined as just "declarative" or "non-declarative". Such a suggestion has very important implications, particularly to clinical studies investigating learning in patients. In fact, a link between these systems (and possibly between others that have not yet been identified) might explain why in Parkinson's disease there may occur an amnesic syndrome that is remindful of temporal lobe amnesia, and why in Alzheimer's disease there may be disruptions of forms of memory usually considered non-declarative (Rossato et al., 2006). These findings also bring up interesting questions pertaining to the implication of the hippocampal memory system in motor learning, and how the circuitry between these regions needs to be considered in models of motor learning.

8.3. A critical review of our work

Although our findings help validate Doyon and colleagues' model, the results of our experiments suggest that, in addition to the three variables considered in the learning model we used (cognition, learning phase and motor skill), other factors need to be taken into account when designing and interpreting brain imaging studies of motor skill acquisition. With regards to the experiments carried out to complete this thesis, much effort was invested in creating a kinematic adaptation task with a valid motor control and precise performance indices which served in all our experiments. Also, the same subtractive technique was employed in both experiments for analysing the imaging data, assuring us reliable and valid comparison between studies. Thirdly, we set out to define the learning stages of interest and used behavioural measures of interest to assure their attainment. Finally, we developed subject tailored approaches to take into account inter subject variability and ensured that all subjects understood and were conscious of the task's execution. However, our experiences reveal that important questions remain which must be addressed before a comprehensive interpretation of brain circuits mediating motor skill learning can be advanced.

First among these factors is the kinematic adaptation and motor control task we used to investigate visuomotor adaptation. A close inspection of the behavioural data presented in our first experiment reveals that no significant performance difference between tasks was observed when subjects were performing the experimental and control tasks in the series of fMRI runs. That is, their level of performance, as measured by the global performance index (GPI), were relatively similar at both learning stages. This brings about questions pertaining to the task's difficulty level and the methods we have used to measure the subjects' performances. Using the results of the secondary task completed in the dual task condition, we can state with confidence that the subjects' performances on the adaptation task showed significant learning from the early to the automatic execution stage. However, the fact remains that this is not visible when we only consider the performances on the adaptation task alone. This therefore suggests that our performance index (GPI) was not sensitive enough to display this difference in performance. Future work should invest a good deal of time and resources to develop proper methods of measuring subject performances on experimental tasks. Work needs to be done to develop specific performance indices that are more sensitive, reliable and valid with respect to the different tasks; indices that reflect the acquisition and performance on the motor task under study, rather then simply expose the inevitable gains in speed and precision that follows practice. This is being actively pursued in our laboratory, and we are confident that a new performance index will be developed shortly.

With regards to our first experiment, another limitation of the study was the lack of activation in the CS circuit in the early stages of learning. The subtraction method we used (IM-DM) was believed to reveal brain regions specifically involved in learning *per se*, because it is hypothesised to control for non-specific factors confounding learning, such as the sensory and purely motoric components of the task. Based on Doyon and colleagues' model (2002, 2003, 2005), we hypothesised that this subtraction would reveal activations in both the CS and CC circuits. The missing activations are intriguing because they suggest that the control task we used was perhaps too complicated, and may have implicated more visuomotor adaptation in the early stages of learning then we anticipated. However, this is rather unlikely because subjects showed no learning effect across the block of trials, or across the extended practice period. It is therefore more likely that the missing activations result from the statistics used, and a greater number of subjects in our experiment would have revealed activations in those regions. Nevertheless, we have corrected this in the recent experiments completed in our laboratory, and all new investigations of visuomotor adaptation uses a simpler version of the motor control task which requires subjects to make straight lines in order to reach four targets separated by 90°.

Individual differences between subjects' learning capacities also need to be investigated more fully to account for the different learning and execution strategies. In fact, the correlation data in the first study suggests that different strategies lead to different patterns of cerebellar activation. Even though the task was simple and subjects were asked to perform it by putting equal amounts of care to speed and precision, they did not. Future experiments should explore “learning styles” and preferences by differentiating these preferences on the basis of performance profiles. Such insight in the individual approaches to motor learning will help control and limit the noise introduced by inter-subject variability. This line of work will also allow researchers to determine the implication of different neural circuits in the acquisition and maintenance of a skill on the basis of “learning styles”.

Furthermore, should we continue to use small samples of subjects in imaging studies and consequently incorporate the noise brought in by data pre-processing? Or rather, should we favour single subject experiments? Another possibility might be to create groups of subjects sharing the same learning capabilities or with similar “learning styles”. What these questions bring about is the need to re-examine the goals we set out to achieve through modern neuroimaging experiments. Before trying to label brain regions as playing specific roles in the motor learning process, we should work to identify the variables that create confounds in the paradigms, to propose and agree on the operational definitions to distinguish between tasks and learning phases, as well as to standardise data analyses procedures and keep up with the high rate of development of imaging technologies. Future dissection of factors that affect experimental tasks will undoubtedly lead to more consistent and reliable data and also lead to a better understanding of the cognitive processes that underlie motor learning and execution. Certainly, the models presently used to conceptualise and understand motor skill learning should, and will, evolve to include more hypotheses that take into account recent physiological data (e.g. hypocampal circuits), which will inevitably lead to clearer interpretations of brain imaging data.

The incredible diversity of skills we have learned since birth and continue to exhibit in everyday life represent a fascinating facet of human behaviour. In fact, I would argue that these skills allow us to live our lives to the extent we do. It is therefore easy to believe that a better understanding of the cognitive and neurological systems that underlie their learning and execution would lead us to make incredible breakthroughs in the treatment of patients suffering from degenerative brain diseases.

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