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Fronto-striatal circuits in mirror reading: An event-related fMRI study of procedural learning in healthy subjects

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PREFACE

Prior to neuroimaging, the only way that we could learn about the human brain was by cataloguing the set of impairments that a group of patients would exhibit when they suffered damage to a given brain region. A surprising amount of progress was made using this method, but it was hampered by several limitations. Most forms of brain damage involve large areas, very likely including regions in addition to the small part of the brain the researcher is interested in. There is also the common problem of brain plasticity - the ability of the central nervous system to re-wire itself and co-opt intact regions with a similar function to take on a larger role.

Functional magnetic resonance imaging (fMRI) is completely non-invasive. This technique relies on the magnetic properties of the nuclear constituents of our blood. When parts of our brain are more active, in order to gain more energy, they draw oxygen from the blood supply, which in turn changes the magnetic characteristics of the blood. The fMRI scanner can then detect this minute magnetic difference. FMRI, a more recent scanning technique than positron emission tomography (PET), is predominantly used at present, due to its non-invasive nature, superior picture resolution (a few millimeters cubed per pixel, normally) and ability to take very fast images of the whole brain (in the order of a few seconds per image).

To navigate our complex world, our brains have evolved a sophisticated ability to quickly learn rules and procedures. This kind of learning is referred as to procedural learning. Studies have revealed that frontal lobe structures (including the prefrontal cortex) as well as subcortical nuclei of the basal ganglia are involved in such learning. Common theories and studies suggest that when we learn new procedures or rules, the prefrontal cortex is the first involved. Then, as our behaviors become familiar and habitual, the more "primitive" subcortical basal ganglia take over so that the now-familiar routines can be run off automatically and occupy less of our cortical processing ability.

Neural correlates of learning have been observed in both brain regions, but whether or not these regions have unique functions is unclear, as they have typically been studied separately using different tasks. Here we try to show that during mirror reading learning in humans, neural activity in these areas changes at different stages of naïve reading and automatization: the prefrontal cortex and the striatum (an input structure of the basal ganglia) showed initial involvement, compared with a single involvement of the prefrontal cortex, which was still activated in the late stage.

ABBREVIATIONS

BA	Brodmann area
BOLD	Blood Oxygen Level Dependent
DLPFC	Dorsolateral prefrontal cortex
FMRI	functional magnetic resonance imaging
FPC	Frontopolar cortex
H	Hemisphere
HD	Huntington's disease
ISI	Interstimulus interval
MR	Mirror reading
NR	Normal reading
TR	Relaxation time
PET	Positron emission tomography
PD	Parkinson's disease
PFC	Prefrontal cortex
PL	Procedural learning
SMA	Supplementary motor region
SPM	Statistical parametric mapping
VLPFC	Ventrolateral prefrontal cortex
vPM	Ventrolateral premotor area
WM	Working memory

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THESIS SUMMARY

Previous neuroimaging studies of normal subjects and studies on patients with focal lesions implicate cortico-subcortical regions to be activated in skill learning, yet the precise role of anatomical distinct networks and the dynamic over time during procedural memory tasks still remains to be unclear. Understanding the neural systems and mechanisms underlying cognitive skill acquisition, i.e. learning to read mirror-reversed, provides not only a foundation for investigation of procedural learning *per se* but also for investigation of language and visuospatial processing pathways in the brain. We studied changes in brain activity related to visuospatial procedural learning in a mirror-reading (MR) task using event-related functional magnetic resonance imaging (fMRI). Eight healthy subjects were investigated during an early (naïve) and a late (after the procedure was well-learned) stage of skill learning. Between the two scan sessions subjects performed training in mirror reading twice a day over the period of almost 3 weeks. We were addressing following question: How are cortical and subcortical components of fronto-striatal pathways implicated in initial and late learning stages during mirror reading? The condition X session interaction contrast for MR compared to normal reading (NR) during the initial learning stage was associated with a broad activation in frontal, temporal, parietal, occipital and striatal activation. Well-learned MR revealed frontal and parietal brain activation during the second scan session, but no striatal activity occurred. In particular, over-learned MR exhibited increased activation in the left middle and superior frontal cortex (DLPFC), in the left medial frontal cortex (VLPFC), right cingulum (Posterior cingulate cortex), the right precuneus and activation in left inferior and superior parietal cortex. Changes in brain activity related to initial procedural learning exhibited thus the significance of striatofrontal loops whereas the extensive practice of the MR task resulted in less activity in these regions and a shift to more posterior cortical areas. The results suggest the requirement of recruitment of a fronto-parietal network for automatic mirror reading. As for learning this procedure, our results support the evidence that fronto-striatal loops seem to be involved in this very early phase of procedural learning, acting as an effective network for acquisition of mirror reading. According to our data and previous studies of skill learning, we postulate that there is no learning-specific distinct neural network associated with the processing of mirror-reversed words before and after extensive training. We rather postulate a common network in cognitive skill acquisition with a critical role in the prefrontal cortex and the caudate nucleus.

Chapter 1: General introduction

1. Introduction

1.1 Learning and memory: declarative versus non-declarative

The ability of humans and animals to learn from experience is recognized as being supported by multiple memory systems with different functional characteristics and neural bases (Cohen and Eichenbaum, 1993; Squire, 1992). A fundamental distinction in memory is between the declarative and non-declarative memory systems. Non-declarative memory functions include procedural learning (skill learning), repetition priming (item-specific learning) and classical conditioning. It can be contrasted with declarative learning of facts or events (Cohen and Squire, 1980) (see Figure 1).

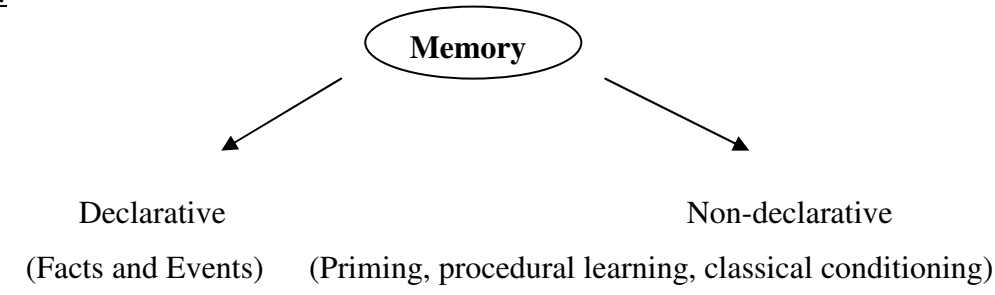
Studies of memory organization in animals and humans have led to a consensus that memory is not a unique faculty, but rather supported by multiple brain systems that differ in terms of types of the memory they mediate. This hypothesis on multiple memory systems was derived from evidence of a pattern of impaired and spared learning abilities following damage to the mammalian hippocampal system, and several dual-memory theories outlining the psychological operating characteristics of hippocampus-dependent and non-hippocampus-dependent memory have been proposed (Cohen and Squire, 1980). Therefore, according to one hypothesis, the hippocampus is an anatomical part of a memory system supporting the declarative memory, characterized by flexible accessible, relational memory for past events and facts (Cohen and Eichenbaum, 1993). In contrary, memories underlying other learned behaviors (e.g. acquisition of stimulus-response habits, procedural learning, and some forms of Pavlovian conditioning) do not seem to rely crucially upon the hippocampus and other structures of the medial temporal lobe, and are termed non-declarative or procedural (Cohen and Eichenbaum, 1993).

Procedural learning (PL), which is investigated in this study, is essential in human and animal life for acquiring a behavioural repertoire. Procedural learning is the acquisition of a procedure with practice. It refers to improvement in performance on a task that results from learning the response demands of the task. PL refers to learning that is governed by

rules or procedures, and can be divided, for example, into perceptual-motor skills or perceptual (non-motor) cognitive skills. Furthermore, procedural memory can be gained without conscious awareness of the rules being learned, whereas declarative memory is characterized by conscious awareness of the facts or events being learned. Declarative memory is acquired in an explicit manner that can be recalled if required, whereas procedural memory is mainly implicit (i.e., is acquired unconsciously by the subject and the knowledge is accessible only through performance). However, when subjects perform a particular learning and memory task, both explicit and implicit learning may be enacted. For example, even though the initial acquisition is implicit, repeatedly practicing a visuomotor task usually results in the development of explicit knowledge of the task (Soliveri et al., 1997).

Hence, PL is thought to reflect learning by doing: experience-based modification of the neural systems used to perform either perceptual-motor tasks (Karni et al., 1995; Willingham et al., 2002; Doyon et al., 2002) or perceptual non-motor tasks (Cohen and Squire, 1980). However, dissociations in the learning of different skills bear the view that procedural learning is in itself a heterogeneous phenomenon (Harington et al., 1990). Examples of different cognitive procedural tasks are, to mention some of them, the serial reaction time paradigm (SRTP; Nissen and Bullemer, 1987), the mirror reading task (Cohen and Squire, 1980) and the Tower of Hanoi task (Cohen and Eichenbaum, 1993). In this study the mirror reading task seemed to be particular suited for the restricting conditions of the scanning machine.

Figure 1:



(Adapted from Squire and Zola-Morgan, 1991)

1.1.1 The ACT model

There are a number of neuropsychological models on skill acquisition and research on the cognitive mechanisms that underlie procedural learning has largely been limited to normal subjects.

According to one model, the Adaptive Control of Thoughts (ACT) production model of skill acquisition (Anderson, 1982, 1987), cognitive procedural learning is inherent in three stages through the generation, combination and improvement of so-called condition-action pairs, referred to as productions. Firstly, a "declarative stage" of learning involves the interpretation of task-relevant facts and knowledge. At this stage, non-specific problem solving strategies ("weak methods") are applied. Information about the task and the underlying problem is represented in working memory and processed in multiple successive steps. Secondly, a "knowledge compilation stage", that involves two processes: composition, i.e., unification of successive productions to faster macroproductions and proceduralization, i.e., translation of non-specific productions that eliminate the need to hold explicit information in working memory. Finally, the third, "procedural stage", is reached through continuous practice and is thought to lead to a refinement, tuning and acceleration of established productions by means of strengthening, generalization and discrimination processes and by an increase of domain-specific working memory capacities.

Practice is important for the acquisition of a new skill and even after practice, information processing still takes place. The term "consolidation" describes the skill improvements that occur between practice sessions. Eysenck and Frith (1977) mentioned that for procedural memories, which relate to the acquisition of a new skill, consolidation could describe the following behavioral phenomena. They state an "off-line" improvement of a skill, which occurs without physical practice and is often dependent on sleep. For instance, overnight improvements of 15-20 % were shown in a perceptual discrimination task (Karni et al., 1994). Skills can be acquired unintentionally (implicit learning), and in this situation, off-line learning seems to be non sleep-dependent (Robertson et al., 2004).

1.2 Procedural Learning: studies in humans

In skill-learning tasks, subjects perform a challenging task on repeated trials in one or more sessions. The indirect measure of learning is the improvement in speed and accuracy achieved by a subject during trials and sessions.
Learning to read mirror-reversed text is a perceptual skill that has been well studied in patients. In a landmark study, Cohen and Squire (1980) found that amnesic patients can learn to read mirror-transformed words, but were worse than controls on repeated words. Amnesic patients gain skill in reading such a text at a normal rate, despite poor declarative memory for the particular words read or even the episodes in which they gained their skill. Thus, as mentioned in the previous chapter, lesion studies in patients with global amnesia who exhibit completely intact skill learning have suggested that non-declarative (procedural) memory is independent of diencephalic structures and of the medial temporal lobe (Cohen and Squire, 1980; Deweer et al., 1993; Hopkins et al., 2004) and therefore distinct from declarative memory (Squire, 1992). Recent findings of Cavaco and colleagues (Cavaco et al., 2004) indicate that preserved learning of complex perceptual-motor skills in patients with amnesia is a robust phenomenon, and that it can be demonstrated across a variety of conditions and perceptual-motor demands.

Conversely, impaired skill learning occurs in patients with Parkinson's disease (Heindel et al., 1989, Doyon et al., 1997; Pascual-Leone et al., 1993). In some studies, procedural learning has been shown to be intact in PD patients, for example, in a task of target tracking (Bondi et al., 1991) and in three studies that applied mirror reading (Bondi et al., 1991; Harrington et al., 1990, Schmidtke et al., 2002).

However, observation of other studies reported impaired procedural learning in PD patients (Saint-Cyr et al., 1988; Wallesch et al., 1990; Koenig et al., 1999). Memory impairments have been reported in PD patients in both explicit and implicit memory, for example in explicit memory for visuo-spatial location of pictures (Pillon et al., 1996). Especially sensorimotor skill learning is often impaired in patients with basal ganglia diseases and its associated structures (Gabrieli et al., 1997; Heindel et al., 1989). Procedural learning deficits, for example, are shown as well in Huntington's disease (Knopman and Nissen, 1991, Butters et al., 1985). Impaired procedural learning is observed in schizophrenic patients (Kumari et al., 2002) and in patients with damage to in

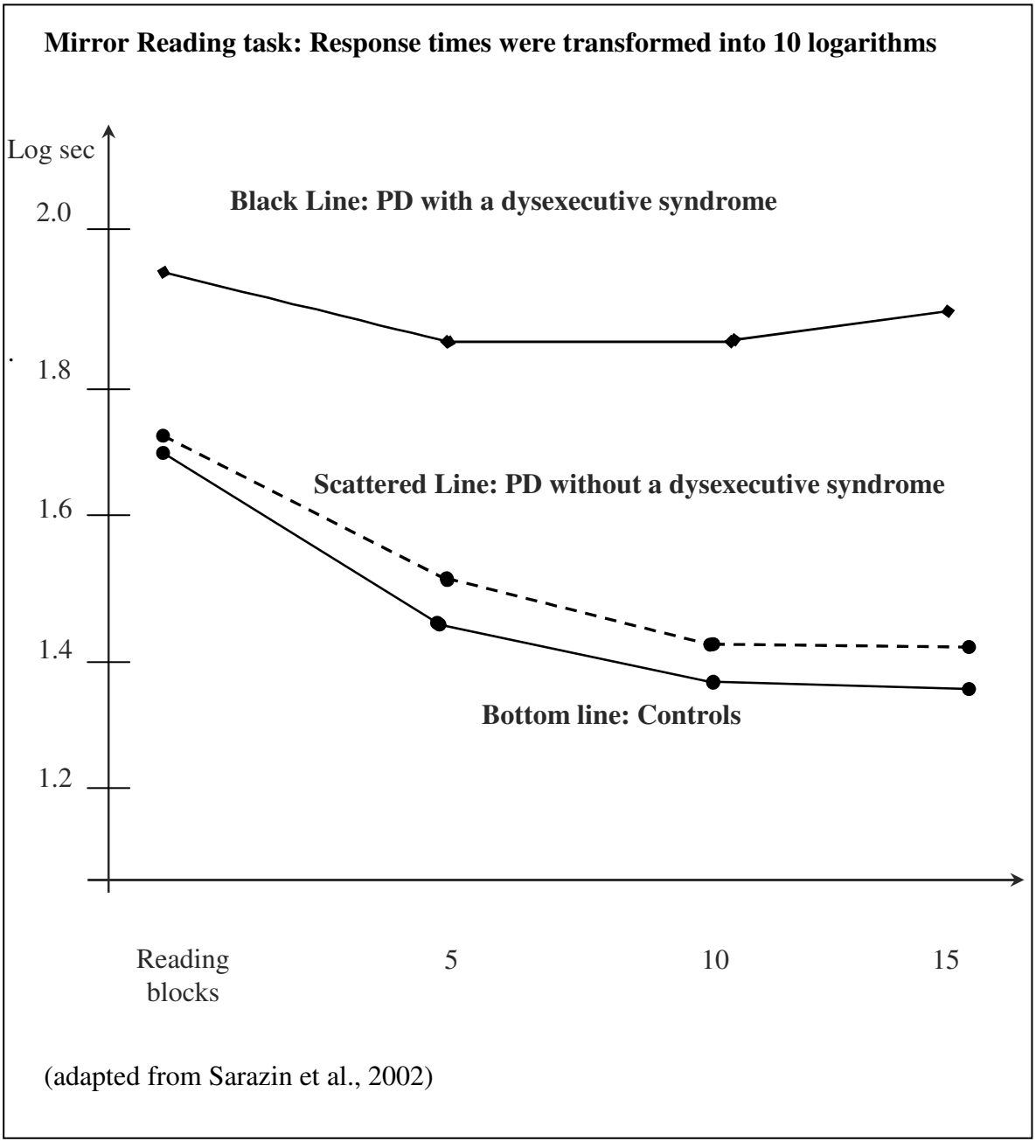
the cerebellum (Doyon et al., 1997), in autism (Mostofsky et al., 2000) and the prefrontal cortex (Jackson et al., 1995; Pascual-Leone et al., 1995), suggesting strongly the implication of these anatomical structures for this task. Marsh and colleagues (2005) described PL deficits a probabilistic weather prediction task in patients with Gilles de la Tourette disease.

Hence, studies in patients with Parkinson's disease (PD) suggest that the characteristic motor symptoms of the disorder are frequently accompanied by impairments in cognition that are most profound in tasks of executive function. Neuropsychological deficits are not an inevitable consequence of this disease, yet the reasons underlying cognitive heterogeneity in PD are not well understood.

To date, discrepancies appear in the interpretation of impairment in mirror reading learning in patients with PD. Learning impairment in these patients (Harrington et al., 1990) has been interpreted as a direct consequence of striatal dysfunction as it is correlated with the degree of motor deficits. However, a recent neuropsychological study of PD patients showed that the prefrontal cortex was also critically involved in mirror reading since Sarazin and colleagues (Sarazin et al., 2002) have shown that only those PD patients with a dysexecutive syndrome were unable to learn mirror reading, suggesting its critical role in mirror reading. In this study the existence of a significant correlation between mirror reading parameters and scores in tests of executive functions (Wisconsin Card Sorting Test, California Verbal Learning Test, Trail Making Test, verbal fluency and Stroop Test) and of frontal related memory component (free recall in California Verbal Learning Test scores) suggested the involvement of frontal lobe function in acquisition of a new cognitive procedure. "Frontal" PD patients were significantly impaired, as compared to normal controls, either in terms of initial reading speed or in terms of enhancement with practice, while PD patients without dysexecutive symptoms (but with motor deficits similar to those of frontal patients) were able to learn the new procedure at a similar rate to normal controls (Figure 2):

Figure 2:

Performance of PD patients and controls at mirror reading shown for the whole group of PD patients with dysexecutive syndrome (top line) and the PD patients without a dysexecutive syndrome and controls (bottom lines). While PD patients as a group exhibited substantial procedural learning, analyses of subgroups with respect to frontal dysfunction allowed a distinction to be drawn between frontal PD patients, whose learning was severely impaired, and non-frontal PD patients, whose learning did not differ from controls.



This data confirmed previous data, which suggested that the intra-individual variability in PD patients in acquiring a cognitive skill was presumably reflecting their inability to maintain a new reading strategy and therefore could be related to frontal lobe dysfunction. This data is in agreement with another study (Koenig et al., 1999) showing that PD patients failed to learn either an inverted reading task or a dot counting task in which subjects were asked to process a horizontal series of black and white dots from left to right. While these two tasks likely involve frontal lobe function, executive functions were not explored in this study and neither in others previous studies that showed impaired skill learning in PD patients (Ronacci et al., 1996; Yamadori et al., 1996).

A study on 22 patients with prefrontal lesions investigated by a serial-reaction-time task, suggested that the frontal lobes might be an essential component of the neural network responsible for procedural acquisition (Beldarrain et al., 1999). They reported that patients with poorer working memory and verbal sequence learning were more impaired in visuomotor sequence learning and suggested that prefrontal cortex may act as an integrator of the contribution of the cerebellum and the basal ganglia to the learning task by inducing the appropriate changes in the cortical outputs. Lewis and colleagues (Lewis et al., 2003) used event-related functional magnetic resonance imaging (fMRI) to compare groups of cognitively impaired and unimpaired PD patients, matched on all other clinical measures. FMRI revealed significant signal intensity reductions during a working-memory paradigm in specific striatal and frontal lobe sites in patients with cognitive impairment compared with those patients who were cognitively not unimpaired. These results demonstrate that cognitive deficits in PD are accompanied by neural changes that are related to, but are distinct from, those changes that account for motor deficits in those patients. Furthermore, they suggest that fMRI may provide a valuable tool for identifying patients with cognitive deficits.

The following chapter shortly introduces into current theories on the brain structures investigated in this study.

1.3 The anatomy of the prefrontal cortex

The prefrontal cortex is the association cortex of the frontal lobe. The prefrontal cortex is the neocortical region that is most elaborate in primates, animals known for their diverse and flexible behavioral repertoire. Imaging studies indicate that, in humans, prefrontal areas do not attain full maturity until adolescence (Paus et al., 2005). The prefrontal cortex (PFC) is a collection of interconnected neocortical areas that sends and receives projections from virtually all cortical sensory systems, motor systems, and many subcortical areas. The frontal lobes are segregated from more posterior regions in the brain by the central sulcus. The PFC is lying anterior to the motor and premotor cortices in the frontal lobes. The inferior frontal cortex, the so-called 'ventrolateral' PFC (VLPFC) in humans comprises Brodmann Areas 44 (pars opercularis), 45 (pars triangularis) and 47/12 (pars orbitalis), the middle frontal gyrus, the "dorsolateral" PFC (DLPFC), involves BA 46, 9 and 9/46. (See figure 3).

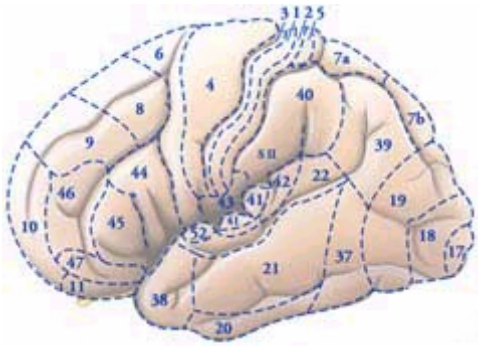


Figure 3: Picture of the lateral surface of the human brain with corresponding Brodmann areas (taken from Hasboun, 1998, with permission from the author).

1.3.1 Anatomical subdivisions within the prefrontal cortex

At the beginning of the twentieth century, Brodmann carried out many studies, using architectonic markers, to differentiate regions in the neocortex (Brodmann, 1905; Brodmann, 1909). As part of these studies, Brodmann anatomically subdivided the PFC in the monkey (Brodmann, 1905), and in the human (Brodmann, 1909). These so-called "Brodmann areas" have been highly influential ever since, although a later development

in histological staining has led to an extensive reorganization of this scheme recently by Pandya and colleagues (Petrides and Pandya, 1999; Pandya and Yeterian, 1990).
Of particular note to this thesis is the lateral surface of the PFC, posterior to the frontal polar regions. It broadly comprises the ventrolateral region, involving Brodmann areas (BA) 45 and 47, as well as the dorsolateral region, involving BA 46, 9 and 9/46.

1.3.2 Extrinsic and intrinsic prefrontal cortex connections

The lateral PFC has the greatest level of connectivity with sensory areas, because this region receives visual, auditory and somatosensory information from the occipital, parietal and temporal cortices (for review see, Pandya and Yeterian, 1984; Pandya and Yeterian, 1990; Miller and Cohen, 2001). The PFC does not seem to have direct motor connections with primary motor cortex, however the DLPFC (particularly involving BA 46), seems to have direct connections with an extensive array of secondary motor regions, including the supplementary motor area (SMA), the pre-supplementary motor area (pre-SMA), the cingulate, premotor cortex, cerebellum, superior colliculus and the frontal eye fields (Goldman and Nauta 1976; Bates and Goldman-Rakic, 1993).

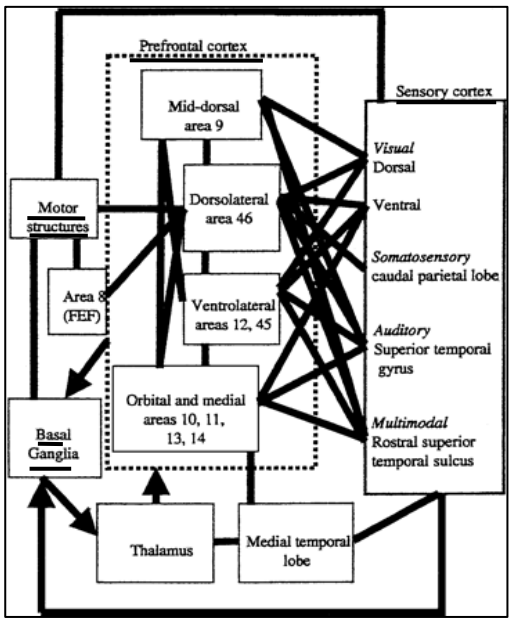


Figure 4: Schematic diagram showing some of the numerous intrinsic and extrinsic connections of the PFC. Connections that are not reciprocal are indicated by arrows (taken from Miller and Cohen, 2001).

1.4 Theories about prefrontal cortex function

There are a number of competing theories on prefrontal cortex functions in the current literature. One of the key functions of the PFC is described in Baddeley's working memory model (Baddeley 1986). Especially the lateral PFC is supposed to play a crucial function in central executive and episodic buffer. While the central executive is critical for attentional control and the manipulation of information, the episodic buffer is thought to integrate information from multiple sources. Specific theories attempting to fractionate the lateral PFC according to domain (for details, see Goldman-Rakic, 1996), or process (for details see Petrides, 1995; Petrides, 1998) have been discussed and are described in the following chapters.

1.4.1 The domain-specific model of the lateral prefrontal cortex

The domain-specific model of the lateral prefrontal cortex discussed here is partly based on an influential model describing the parallel processing of the visual system (Mishkin and Ungerleider, 1982; Milner and Goodale, 1993). This model states that from very early on, two pathways emerge in a so-called "stream" (immediately after the retina), segregated by function: one is a "ventral stream", carrying object-centred visual information ventrally to temporal lobe structures. The second stream contains locational information, which is primarily processed in dorsal brain regions, particularly within the parietal cortex (Mishkin and Ungerleider, 1982; Milner and Goodale, 1993). Goldman-Rakic has extended this model further, suggesting that the endpoints of the parallel stream lie within the lateral prefrontal cortex (Goldman-Rakic, 1996). Anatomical studies have shown that projections from areas in the dorsal stream terminate mainly in and around the Brodman area 46 of dorsolateral prefrontal cortex (Ungerleider and Desimone, 1986). Specifically, the VLPFC is said to be involved in object-based working memory processing, while it is claimed that the DLPFC is involved in spatial-based working memory processing. Evidence to support such a model largely comes from monkey electrophysiology. For instance, Wilson et al. (1993) presented two types of delayed response trials, either based on location or pattern, while recording either in the inferior convexity (VLPFC) or the principle sulcus (DLPFC). They found that the VLPFC fired

selectively during the delay for the patterns, while the DLPFC fired selectively during the delay for the locations. Although this domain specific theory has enjoyed considerable recognition over the last decade, this theory is still under debate and there is increasing evidence to suggest both that such a theory could not extend to humans, and that the picture even in monkeys is not as clear-cut. For instance, Rao and colleague (Rao et al., 1997) demonstrated that both monkey DLPFC and VLPFC neurons could code for location, object, or a combination of both. In addition, another group (D'Esposito et al., 1998) showed in a review of 24 human working memory neuroimaging papers that there was no division whatsoever within the lateral PFC, according to whether the working memory task was spatial or not.

1.4.2 The 2-stage model of the lateral prefrontal cortex

In distinction to the domain specific theory, Petrides described a so-called 2-stage model of the lateral prefrontal cortex (Petrides and Pandya 1994; Petrides, 1995). The author postulates a model for the lateral PFC based on process, rather than content. According to this hypothesis, the VLPFC would subserve the expression within memory of various first-order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long-term memory while the DLPFC is involved in second order working memory processes, where multiple sources of information needed to be monitored or manipulated on the basis of the requirements of the task or the subject's current plans (Petrides, 1995). This model was initially proposed based on monkey lesion studies. For instance, Petrides (1995) found that monkeys with DLPFC lesions were impaired when they had to monitor which of three stimuli they had previously selected, although they were not impaired when they had to choose which of the three stimuli had been previously presented to them. Far more support for this model has come from human neuroimaging. Most tasks presented in the scanner that involve some form of monitoring or manipulation activate the DLPFC, while most tasks involving lower level working memory demands, requiring maintenance of information only, activate the VLPFC. Owen and colleagues have shown by PET that while a standard working memory task, such as the spatial span task, only activates the VLPFC, tasks involving a manipulation component, such as a searching task or a 2-back task (Owen, Herrod et al., 1999) activate the DLPFC. However, the 2-stage model of the lateral PFC suffers from various

problems. Due to the under-specified definitions of the two processes, it is unclear whether such a model can be proven. In addition, it has never been clarified how the two processing "domains" interact.

Another, complementary view of PFC function is that it integrates events over time (Fuster, 2001). Meta-analysis of neuroimaging results suggested a localization of function to a network of PFC regions. It showed that, regardless of the particular contrast of cognitive tasks, there is regularity in (bilateral) activation of the dorsolateral prefrontal cortex (DLPFC), inferior frontal cortex (IFC) and dorsal anterior cingulate cortex (ACC), but not in other frontal regions (Duncan et al., 2000). This could show another sort of specialization of the PFC: a specific frontal network consistently recruited for solution of diverse cognitive problems.

There is, in general, theoretical controversy over whether subregions of PFC are functionally differentiated. One influential view is that different areas within the PFC perform the same operation, for example, working memory but for different sensory inputs (Goldman-Rakic, 1987). While the domain-specific theory has not found supporting evidence in human neuroimaging studies, the 2-stage processing model has lacked specificity. A variant of the 'working memory' hypothesis is one, which regards the PFC as providing top-down bias of posterior cortical and subcortical 'modules' (O'Reilly et al., 2002).

1.4.3 PFC and top-down control of behaviour

Research work that is especially important for the underlying study, has emphasised the role of the frontal lobes in maintaining task-based information and in strategic processes. The function of the prefrontal cortex (PFC) is broadly one of 'executive control', for example the scheduling and optimizing of supplementary processes implemented by posterior cortical and subcortical regions (Miller and Cohen, 2001). For that reason, the PFC acts like a gatekeeper and depending on the context; different incoming information would get directed towards different outcomes (Miller and Cohen, 2001). A well-known and important paradigm for studying executive control has been the Wisconsin Card Sorting Test (WCST). Subjects sort a series of cards on different dimensions such as

colour, number and shape. Once the subject has established the currently appropriate rule (e.g. 'sort successive cards by colour'), the experimenter gives negative feedback, and the subject is required to change classification to another dimension. Patients with frontal cortical damage are notoriously bad at the change stage (Demakis et al., 2003) and this is explained by 'perseveration' of the previously appropriate rule or a failure to inhibit a learned strategy. For example, researchers demonstrated that damage to right inferior frontal cortex crucially affects performance in response inhibition and task-set switching (Monsell 2003), apparently by disrupting inhibition.

More generally, Duncan and Owen (Duncan and Owen, 2000) carried out a Meta-analysis of neuroimaging studies containing contrasts involving harder compared with easier versions of the same task in a wide array of cognitive demands. Such processes included perception, working memory, novelty and response conflict. The results indicated that whatever the task involved, three regions would commonly be activated. As well as the anterior cingulate, both the VPFC and DLPFC would almost always increase in activation in response to more difficult tasks

1.4.4 VLPFC and DLPFC in rule learning

In a recent review Bunge (2004) described how interactions between VLPFC and temporal cortex could be required for rule retrieval in primates and how brain-imaging findings in humans suggest that rule knowledge is stored in the posterior middle temporal gyrus. In her view, dorsolateral PFC appears to be more closely related to rule-based response selection than to rule retrieval. But it is still a matter of debate how PFC, basal ganglia, temporal, parietal, and motor cortices interact to produce rule-guided behaviour. Figure 5 depicts that the brain regions that might probably contribute to rule use. According to Bunge, within this hypothetical framework, different sets of possible actions associated with objects or visual symbols are learned through interactions between anterior VLPFC and post middle temporal gyrus (MTG). These associations are then stored long term in post MTG and retrieved with the assistance of anterior VLPFC. According to the author, well-learned rules can be retrieved automatically through bottom-up activation of post MTG, in the absence of interactions with VLPFC. The prefrontal cortex (PFC) elaborates on rule meanings and/or participates in task management through its interactions with VLPFC. The author suggested that once

relevant rules have been retrieved, these are then transformed into relevant response contingencies, that can be maintained on line over a delay through interactions between posterior VLPFC, ventrolateral premotor area (vPM), parietal cortex and pre-SMA. Subjects can mentally rehearse response contingencies using a phonological code (P) and can also prepare to respond with one or more effectors, by maintaining relevant high-level action representations (A). In this figure, posterior VLPFC, vPM, parietal cortex, and pre-SMA are depicted as contributing to phonological and/or action code representation. These regions might interact with dPM, SMA and other motor structures to activate for example, relevant motor representations so that subjects can take action. DLPFC receives information about the currently relevant rule from VLPFC and interacts with the regions that represent action/motor codes. These inputs from DLPFC enhance the activation of currently relevant response representations, ensuring that the correct response is selected when competing responses have been activated or when a strongly prepotent response must be overridden.

How these prefrontal brain areas are connected to subcortical areas is depicted in the following chapter.

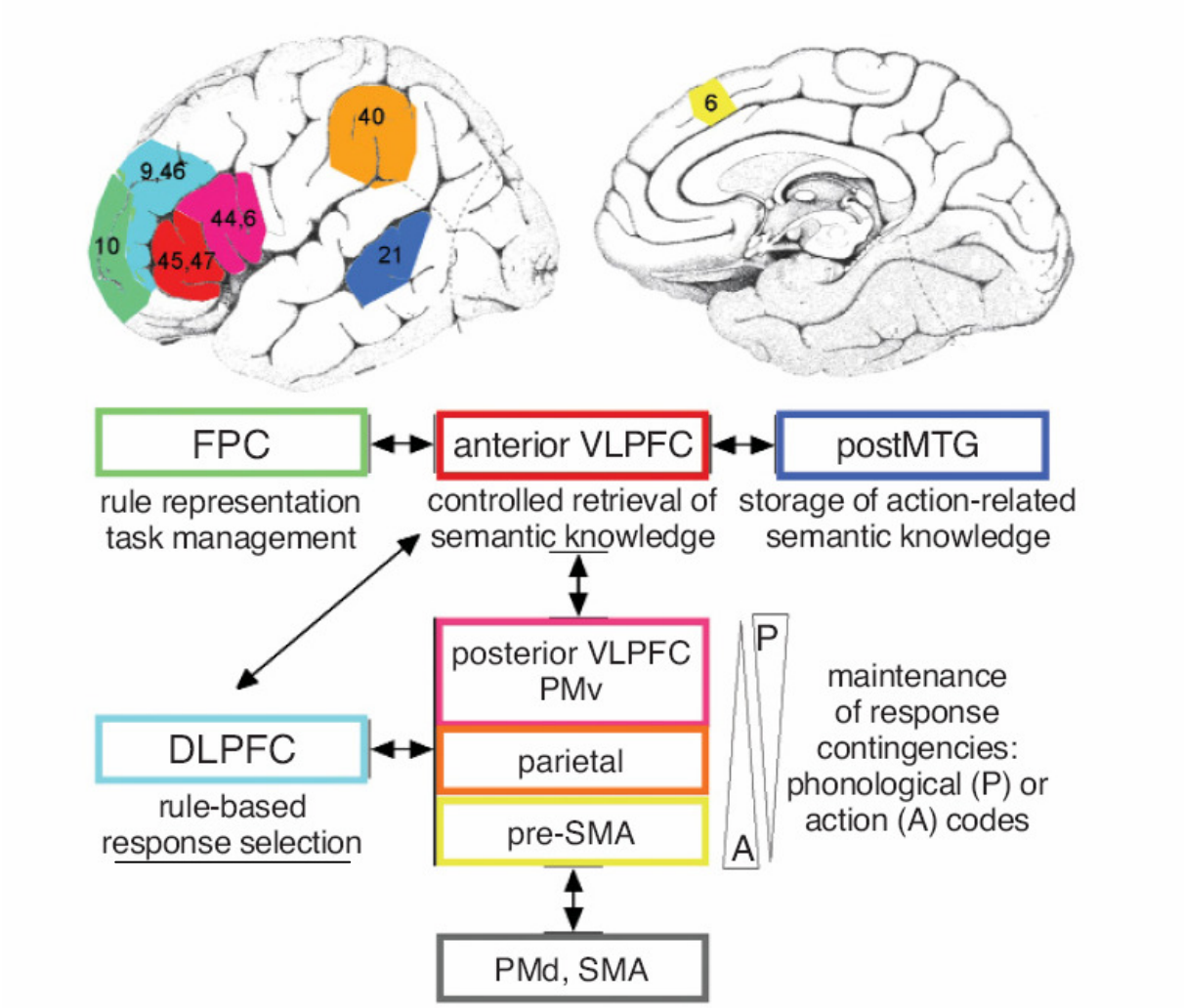


Figure 5: Brain regions that might probably contribute to rule use (adapted from Bunge, SA., 2004)

1.5 The system of the basal ganglia and basal ganglia-thalamocortical loops

The notions about the structural and functional relationship between the cerebral cortex and the basal ganglia (BG) have undergone major changes. It has long been assumed that the BG deal exclusively with extrapyramidal motor functions (e.g. Marsden, 1982), but in the recent past it has become widely accepted that these structures are involved in cognitive and motivational as well as affective aspects of behavior (Dubois et al., 1995).

The principal components of the basal ganglia (BG) are the striatum, the pallidum, the substantia nigra and the subthalamic nucleus (Duus, 1990). Since the cortex imposes a functional organization upon the basal ganglia, studies of the processing of cortical information through the basal ganglia gives us important clues. Yet, the anatomical

substrate of information processing at basal ganglia level is still poorly defined. It has been proposed (Alexander et al., 1986) that the basal ganglia participate in five parallel segregated circuits with the cerebral cortex.

These are the motor loop, an oculomotor loop, and three complex loops within the BG. These series of discrete, parallel fronto-subcortical circuits have been demonstrated in primates to link specific frontal lobe areas to areas within the basal ganglia (BG) and the thalamus (Alexander et al., 1986). Anatomically, the striatum is closely connected to the prefrontal cortex (DeLong et al. 1983, Alexander et al. 1986, Alexander and Crutcher, 1990). Their association is based on partially closed cortico-striato-pallido-nigro-thalamo-cortical loop systems (Fig. 6). The caudate nucleus serves as a relay for two of these complex loops, namely the:

1) The Dorsolateral prefrontal loop, which includes the prefrontal Brodmann areas (BA) 9 and 10, parts of the premotor cortex and parietal BA 7,which projects primarily to the dorsolateral head of the caudate nucleus.

2) The Lateral orbito-frontal loop, which includes the inferior parts of prefrontal BA 10 and 11 and parts of the temporal neocortex.

3) The oculomotor loop originates in the frontal eye fields (Brodmann's area 8) as well as prefrontal and posterior parietal cortex and connects sequentially the central body of the caudate nucleus, the globus pallidus, the thalamus and the frontal eye fields.

4) The anterior cingulate loop includes BA 24, temporal limbic areas and the ventral striatum.

5) The motor loop originates from neurons in the SMA, premotor cortex, motor cortex and somatosensory cortex and these areas project to the putamen (for review, see Alexander and Crutcher, 1990; Saint-Cyr and Taylor, 1993; Cummings, 1993).

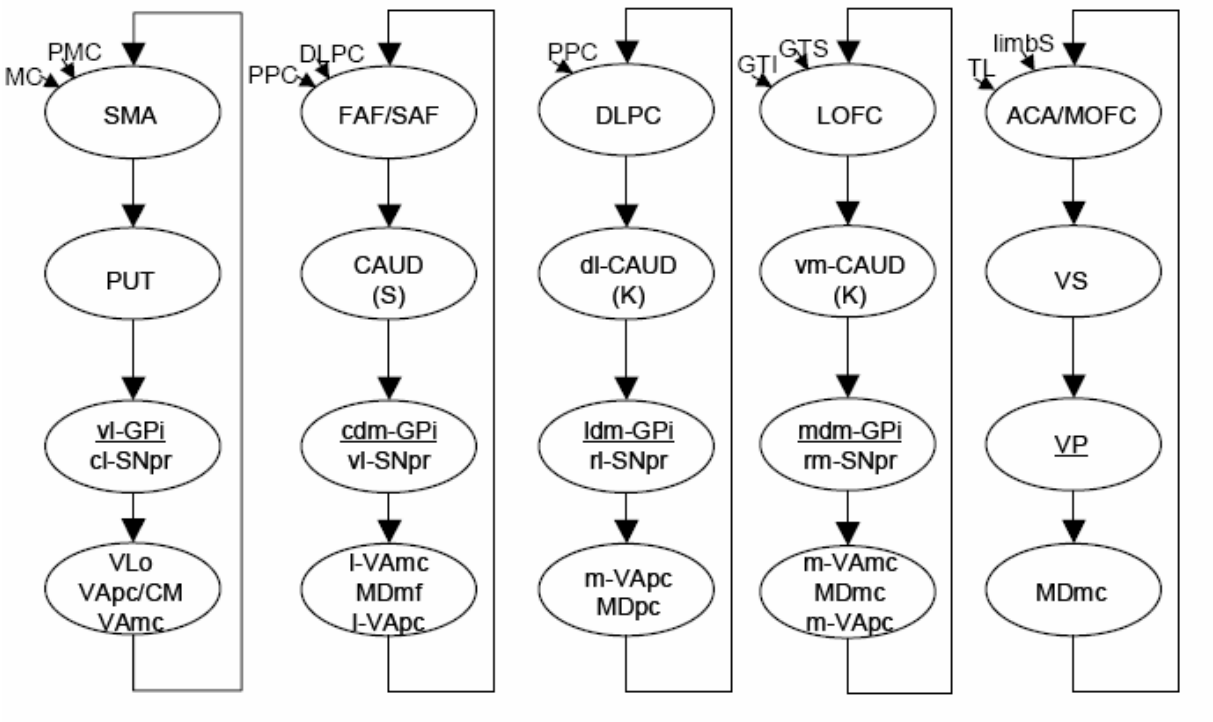


Figure 6: Schematic depiction of the 5 loops (adapted from Alexander et al., 1990, 1986): Motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, anterior cingulate, ACA = anterior cingulate area, CAUD = caudate nucleus, S = tail, K = head, cdm = caudo-dorsomedial, CM = centromedian nucleus, FAF = frontal eye field, GTI = inferior temporal gyrus, GTS = superior temporal gyrus, LOFC = lateral orbitofrontal cortex, MC = motor cortex, MDmc = medial dorsal part magnocellular nucleus, MOFC = medioorbitofrontal cortex, SMA= supplementary motor area, PUT = putamen, PMC = premotor cortex, vl = ventrolateral, GPi = globus pallidus internus, cl = caudolateral, SAF = supplementary eye field, SNpr = substantia nigra pars reticulate, VLo = ventral lateral part of the oral nucleus, VAmc= anterior ventral part of the magnocellular nucleus, VApc = ventral anterior part of the parvocellular nucleus, vm = ventromedial, VP = ventral pallidum, VS = ventral striatum

There are two pathways within each circuit: a direct pathway connecting the striatum and the globus pallidus interna; the substantia nigra complex and an indirect pathway linking striatum to globus pallidus externa, then to the subthalamic nucleus and back to the globus pallidus interna and the substantia nigra (Alexander et al., 1990). Both direct and indirect circuits modulate input to the thalamus. Each set of circuits is present in every hemisphere.

The precise role of these loops, connecting the cerebral cortex and in particular the frontal cortex, with the basal ganglia, in particular the striatum, remains to be determined in

humans. It is a matter of discussion whether the circuits are anatomically and functionally fully segregated and act in a parallel manner, or whether they are mutually interconnected and form open systems (Joel, 2001). However, it is probable that they participate in the planning, control and execution of behaviour patterns depending on frontal lobe function (Strick et al., 1995; Middleton and Strick, 2000). Experimental animal data and clinical observations in humans support this hypothesis by showing that striatal dysfunction induces behavioural disorders similar to lesions of frontal cortical regions projecting to the striatum (Dubois et al., 1995; Gabrieli et al., 1996). Clinical syndromes observed with frontal lobe injury are recapitulated with lesions of subcortical member structures of the circuits. Each prefrontal circuit has a signature behavioural syndrome: executive function deficits occur with lesions in the dorsolateral prefrontal circuit, disinhibition with lesions in the orbitofrontal circuit, and apathy with injury to the anterior cingulate circuit. Frontal-subcortical circuits may also mediate depression, mania, borderline personality disorder and obsessive-compulsive disorder. Movement disorders identify involvement of the basal ganglia component of frontal-subcortical circuits. The caudate nucleus degenerates in Huntington's disease (HD), and it suffers dopaminergic denervation in PD. The putamen belongs to the motor loop and is affected by both HD and PD.

1.5.1 The role of the basal ganglia in procedural learning

The BG seem to play a crucial role in implicit learning. Mishkin and colleagues (1984) first proposed that the BG and its corticostriatal inputs subserve what they termed as „habits“. They assumed that the features of habitual behaviour include a stored association between a stimulus and a response, that information is slowly learned, stable over time and unavailable to the mechanisms of consciousness.

Although the mammalian BG have long been implicated in motor behaviour, it is generally recognized that the behavioural functions of this subcortical group of structures are not exclusively motoric in nature (Dubois et al., 1995). Extensive evidence now indicates a role for the BG, in particular the dorsal striatum, with learning and memory. The above-mentioned hypothesis is that this brain region mediates a form of learning in which stimulus-response (S-R) associations or habits are incrementally acquired. Support for this hypothesis is provided by numerous neurobehavioral studies in different

mammalian species, including rats, monkeys and humans (Mishkin et al., 1984, Knowlton et al., 1996). In rats for example, localized brain lesion and pharmacological approaches have been used to examine the role of the basal ganglia in S-R learning (Faure et al., 2005). In humans, a study of patients with neurodegenerative diseases that compromise the basal ganglia, as well as research using brain neuroimaging techniques also provide evidence of a role for the BG in habit learning.

As discussed in the previous chapter the striatum is known to have strong anatomical connections with the frontal cortex, (Alexander et al., 1986, Parent and Hazrati et al., 1995) the deficit of procedural learning found in patients with PD or with other diseases involving the basal ganglia could result from the dysfunction of striatofrontal loops.

However, the data in the literature are controversial. In a critical review, Wise and colleagues (1996) concluded that available data did not convincingly support the hypothesis that the basal ganglia and their cortical inputs underlie automatic stimulus-response behaviour (habits) and other procedural memories.
According to Bondi and Kaszniak (1991) parallel subcortico-cortical networks, described in primates, would mediate performance according to the specific demands of the tasks. Therefore, apparent discrepancies in the literature might result from the specific pattern of involvement of striatal structures and of the procedural task under study.

Furthermore, despite the fact that the medial temporal lobe structures and the basal ganglia are apparently independent in function from each other, as described above, other recent evidence suggests that during learning, basal ganglia and medial temporal lobe memory systems might be activated simultaneously and that in some learning situations competitive interference might exist between these two systems (see Poldrack et al., 2003).

1.6 Changes in neuronal activity during motor and non-motor learning

Changes in activity in the striatum have been observed at different stages of the acquisition process of motor sequence learning. Some studies have reported learning-related increases in activation in numerous cortical and subcortical regions in humans and

primates (Grafton et al., 1998; Hazeltine et al., 1997; Hikosaka et al., 1995; Jueptner et al., 1997; Toni et al., 1998), whereas others have shown no change or decreased activation with practice in some of these same areas (Jenkins et al., 1994; Sakai et al., 1998; Toni and Passingham, 1999). Some investigators have reported striatal activation in the early acquisition phase of motor sequence learning, when subjects have to rely on the use of cognitive strategies and working memory (Jenkins et al. 1994; Jueptner et al., 1997; Toni et al. 1998). The results of other studies have shown that the striatum is significantly more activated when subjects have reached asymptotic performance of the task rather than when they are at the beginning of the acquisition process (Doyon et al., 1997; Grafton et al., 1998; Doyon et al., 2002). In a study where motor skill acquisition was investigated, normal human subjects who learned to perform a pursuit rotor task with their dominant right hand during serial positron emission tomography (PET), Grafton and colleagues (Grafton et al., 1998) found that activation in the parietal lobe progressively increased with learning. Other groups observed greater parietal activation during novel motor sequence learning.

These divergent findings suggest that the striatum may be critical both for the long-term storage of well-learned sequences of movements and for new learning. One model for example, suggests that these discrepancies may be explained in part by the distinct roles of corticostriatal and corticocerebellar systems in different stages of sequence learning and motor adaptation, respectively (Doyon et al., 2003). By this account, corticocerebellar systems are involved primarily in early motor adaptation phases of learning where the adjustment and monitoring of sensory-motor information is most crucial. Once a motor task becomes more practiced, these mechanisms are less active and corticostriatal systems become more active due to their primary role in automatization of sequence learning. Although relatively few studies have investigated neural plasticity over extended periods of practice, motor-sequencing learning sometimes produces a shift in activation from the cerebellum in early stages of learning to the striatum in later stages (Doyon et al., 2002; Penhune and Doyon, 2002); however, this has not always been found (Müller et al., 2002; Sakai et al., 1998; Toni et al., 1998).

Thus, a discrepancy between the results of imaging studies in which subjects learn motor sequences. Some experiments have shown decreases in the activation of some areas as learning increased, whereas others have reported learning-related increases as learning

progressed. Toni and colleagues (Toni et al., 1998) have exploited fMRI to measure changes in blood oxygen level-dependent (BOLD) signal throughout the course of learning. Images were acquired for 40 min while the subjects learned a sequence with eight components by trial and error. Changes of BOLD signal over time were found in prefrontal, premotor, parietal cortex and in neostriatal and cerebellar areas. Single-unit recordings in nonhuman primates during the learning of motor tasks have also clearly shown increased activity early in learning, followed by a decrease as learning progressed. Both learning increase and decrease were observed in this study. The failure to observe striatal, cerebellar or other patterns of learning-related plasticity may also be related to insufficient practice of a task. For example, Karni and colleagues (Karni et al., 1998) showed only subtle changes in motor cortex activity during the first 3 weeks of practicing sequential finger movements, but an expansion of activation was found after 3 additional weeks of practice. These findings suggest that sensorimotor representations of motor sequences evolve more gradually. Wu and colleagues (Wu et al., 2004) used fMRI and a dual task paradigm to investigate the physiology of how movements become automatic. Normal subjects were asked to practice some self-initiated, self-paced, memorized sequential finger movements with different complexities until they could perform the tasks automatically. The fMRI results before and after automaticity was achieved were compared. No additional activity was observed in the automatic condition. There was less activity in bilateral cerebellum, pre-supplementary motor area, cingulate cortex, left caudate nucleus, premotor cortex, parietal cortex, and prefrontal cortex during the automatic stage. These findings suggest that most of the motor network participates in executing automatic movements and that it becomes more efficient as movements become automatic, but there is no additional activity in brain structures required.

Another important hypothesis is that in motor learning, there might probably be a somatotopical distinction within the striatum for new and practiced skills (Doyon et al., 2005). The same authors have recently demonstrated 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 and they also suggested that motor skills are probably stored in the latter territory of the basal ganglia (Lehéricy et al., 2005).
This raises the question, if such a shift within the striatum could occur as well as in non-motor learning.

In non-motor learning, some imaging studies have showed engagement of basal ganglia in a variety of perceptual procedural learning tasks. In mirror-reading, Poldrack and colleagues described their involvement for the first time (Poldrack et al., 2001), but their specific function in mirror reading is not fully understood. Previous neuroimaging studies (Kassubek et al., 2001; Poldrack et al., 1999, Sakai et al. 1998; Poldrack et al., 2001) have investigated the MR task and its acquisition over time. But the amount of time spent on training sessions varied and training in mirror reading reached not always the extent where the skill was completely over-learned, and subject's mirror reading speed had not reached its asymptotic value.

Dogma in the literature about fontal cortex function has it, that the frontal lobes are responsible for daily and long-term decision-making, with the frontal cortex we learn the rules first and then transfers the knowledge to the more primitive, large forebrain region of the basal ganglia. Specifically, some results have led to the suggestion of a sequential relationship, in which the PFC is involved in new learning and the basal ganglia are subsequently involved in consolidating familiar routines into automatic habits (Graybiel, 1998; Packard and Knowlton, 2002).

Another hypothesis, not necessarily incompatible with the one mentioned above, suggests a dominant role for the BG in new learning due to its anatomical architecture and the membrane properties of striatal spiny neurons. Pasupathy and Miller (2005) found that in monkeys, the striatum showed more rapid change in the learning process than in the prefrontal cortex. They found also that as monkeys learn new, simple rules and associations analogous to "stop at red, go at green" the striatum of the BG shows evidence of learning much sooner and faster than the prefrontal cortex. They simultaneously recorded neural activity from the dorsolateral PFC (areas 9 and 46) and the head and body of the caudate nucleus, a part of the striatum that receives direct projections from and indirectly projects to, the PFC in primates. The monkeys learned associations between two visual cues and two saccadic eye movements. The authors suggested that the basal ganglia first identify a rule, and then "train" the prefrontal cortex, which absorbs the lesson more slowly. An interesting point was that the monkey's behavior improved at a slower rate, similar to that of the slower changes in prefrontal cortex. The authors suggested that while the BG "learn" first, their output forces the prefrontal cortex to change, albeit at a slower rate.

Chapter II: general fMRI methodology

2. General methods: neuroimaging analysis

FMRI can only ever reveal *associative* data, i.e. neuroimaging can only demonstrate that a certain brain region is correlated with a certain cognitive process. Only in combination with other data, such as human lesion studies, or animal studies can inferences about involvement be made. In fMRI, blood oxygen levels are measured, which are dependent on neuronal activation. The basic MRI signal comes from the magnetization of water protons and their relaxation time following perturbation within static (eg. 3 Tesla) field.

2.1 The BOLD effect

Concerning functional MRI methods, the ratio of oxygenated to deoxygenated blood is used as an index of neuronal activation and this ratio is detectable due to the fact that oxygenated blood has a different effect on the phasing of protons to deoxygenated blood. Local increases in neural activity are thought to cause an initial deoxygenating of blood, followed by an increase in blood supply which causes a more enduring oxygenation in local blood supplies (Friston, 1997). It is this increase in oxygenated relative to deoxygenated blood that is thought to reflect increases in neural activity. Temporal resolution is determined in large part by the length of time it takes to create one whole functional image, typically two to three seconds, although statistical techniques can increase the resolution to approximately half a second. Spatial resolution is determined by the magnetic field strength of the scanner and is normally in the order of 2-3 mm. Two landmark papers described the work of Kwong and colleagues (1992) and Ogawa (1992), which succeeded in showing that the change in deoxyhaemoglobin in human visual cortex, while the subject viewed a bright light, which was sufficient to cause measurable changes in the gradient-echo MRI images of a slice passing through the calcarine fissure. The technique was finally dubbed “Blood Oxygen Level Dependent Contrast” (BOLD). (For further details and current discussion on the signal measurements and BOLD effect see Logothetis et al., 2001; Logothetis and Pfeuffer, 2004). Thus the way was opened to

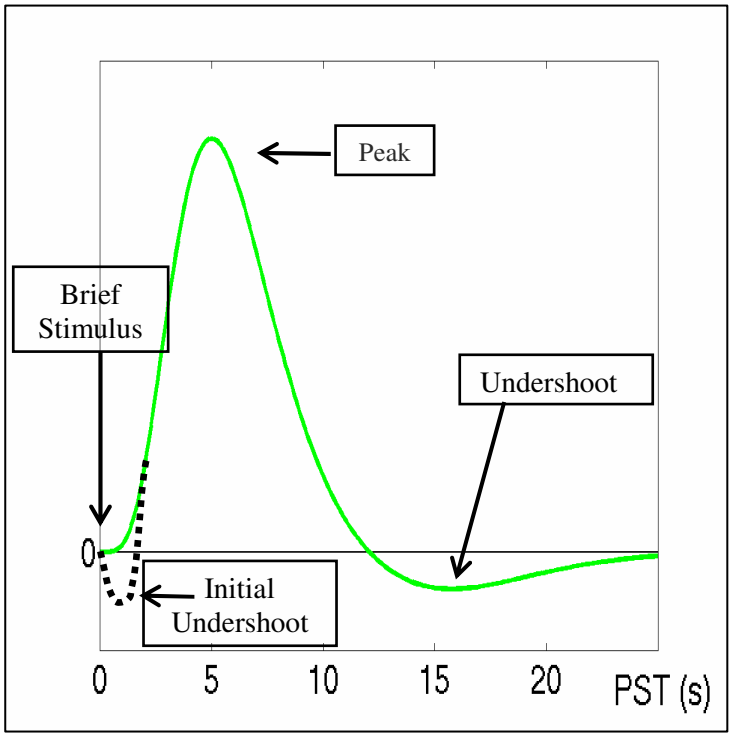
functional mapping studies of the human brain without use of a contrast agent, non radiation dosage and with the high spatial resolution of MRI.

2.2 Characteristics of the hemodynamic response

In order to map brain activity based on the transient fMRI signal, it is mandatory to understand the basic nature of the BOLD-contrast hemodynamic response. The hemodynamic response is a function that depends on the blood oxygenation, the blood flow and on the volume of the venous system (Buxton et al., 1998). A peak of response that corresponds to a maximum of oxygenation is observed 4 to 6 seconds after a stimulus, or brief sensory event. After about 20 seconds the system re-establishes its basic level (Blamire et al., 1992) (see Figure 7). This response is stable and has been observed in all primary (e.g. visual, auditory etc.) brain areas, but there is an inter-individual difference (Aguirre et al., 1998).

Most of the work on imaging relies on the existence of this response, the hemodynamic response function (HRF) and on the mechanism that stands behind it, the neuro-vascular coupling.

Figure 7:



2.3 Design Issues with functional neuroimaging

Common functional imaging designs (Friston, 1997) usually contrast a few conditions of psychological interest with a carefully matched control. Whatever increased activation is observed when the control signal is subtracted from the activation associated with the psychological condition may be taken as activity specific to the cognitive process isolated by that psychological task (Fletcher, Shallice et al., 1998; Owen, Herrod et al., 1999). In this study, the mirror reading task was contrasted with a control task where the visuomotor aspects of the task were the same (reading and pressing a button for response).

2.4 Preprocessing

Neuroimaging pre-processing was undertaken with Statistical parametric mapping (SPM) 96 (provided by the Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk/spm). Analyses and graphical presentations in this thesis were carried out using the SPM 99 software (provided by the Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk/spm) that is a widely used tool for neuroimaging analysis.

The raw data in fMRI can suffer from various problems. For instance, head movement during or between scans can severely reduce the signal when comparisons between scans are made during the analysis. In addition, the shape and size of subject's brains can differ markedly, making direct comparison between subjects in a group analysis difficult. Various mathematical procedures are therefore carried out on the raw data before analysis, in order to minimise such problems.

2.4.1 Slice timing correction

Taking a set of slices creates each fMRI image. These slices are collected in the same order (for instance, from the bottom to the top of the brain) for every single image. Therefore, one part of the brain may always be scanned a second before another. Due to the fact that a single image is taken as a single time point, the hemodynamic response will

be consistently displaced by one second between these two brain regions. In order to correct for this displacement and to make a single image appear properly as a single time point the hemodynamic response at each slice is modified so as to appear from the same time point as, the middle slice.

2.4.2 Image realignment

In fMRI, the subject's head movements in the scanner mean that images are not properly aligned with each other – sometimes to a substantial extent. This stage generates movement parameters for each image so that they are realigned appropriately to a reference image, usually via a mean of all the images in the series (Friston et al., 1995a).

2.4.3 Normalisation

In order to compare different subjects with varying brain sizes and shapes, as well as to be able to extrapolate to different studies, each image needs to be warped so that it closely matches a standard template. This warping process usually involves various linear and non-linear transformations in the three dimensions and three planes of rotation, again via sinc interpolation algorithms (Friston et al., 1995b). The template is normally that of the Montreal Neurological Institute, which is generated from an average of 305 normal brains, although specialised ones do exist for fMRI studies. All templates roughly correspond to the atlas of Talairach and Tournoux (1988), which shows how specific coordinates for activations in the normalised brains correspond to the brain regions.

2.4.4 Smoothing

In order to increase the signal to noise ratio, the intensity values at each voxel are locally averaged, which has the effect of "blurring" the signal. A Gaussian smoothing kernel applied in three dimensions to each image is the most usual method to achieve this.

2.5 The comparison of fixed effect analysis versus random effect analysis

The fixed effect analysis, which was performed in this study after pre-processing images, refers to the intra-individual variability. The number of degrees of freedom for this statistical test depends on the total number of volumes that are acquired for all subjects and is in general very high. Those statistical tests are therefore easily significant, however, not necessarily reflecting population's behavior. There is a high probability of false positives and of type I errors. In contrast, the random effects analysis refers to the variance between individuals; the number of degrees of liberty being therefore dependent on the number of subjects included in the study.
In this study, the difference between the total number of volumes acquired (8928) and the number of subjects included (8), explains the diminution of the degrees of liberty and the decrease of the statistical power for a random effect analysis (an increase of false negatives and type II error).

2.6 Small Volume Correction

Concerning the caudate nucleus, we performed a "small volume correction", where the statistical thresholds for multiple comparisons were corrected. Classically, the variations of the signal in the BG are threefold weaker than those in the cortex. Hence, a correction for multiple comparisons over the entire volume could lead to the risk of high type II error. This analysis is validated on the basis of strong anatomical a priori assumptions concerning the basal ganglia (Worsley et al., 1996). Nevertheless this solution bears some inconveniences, because with the fixed effect analysis conclusion about the population cannot be drawn.

2.7 Analysis of the temporal course of activations

The use of an event-related design allowed the analysing of each event (stimulus) individually. It was then possible to analyse the temporal course of the signal in different regions observed during the group analysis for each type of event. First we extracted the raw signal, which was corrected by the effects of non-interest and was corresponding to

the regional maximal activation cluster in the group analysis. Then, averaging the signal for each type of event, we obtained temporal curves for these voxels. This averaging is done for the whole population permitting one temporal curve for each event type (eg. mirror reading).

2.8 Aim and Hypotheses

Aim of the study:

The functional neuroanatomy of PL has not been fully established using functional resonance magnetic imaging (fMRI).

The primary objective of this study was to provide further evidence on the implication of subcortical areas, namely striatal, as well as in cortical areas; in specific dorsolateral prefrontal cortex in learning to read mirror-reversed words. Secondary, as learning is a function of time, the research question itself leads to the repeated measurements design for investigating initial procedural and final, i.e. automatic, procedure learning. We designed a study to examine learning-specific changes in cortical and subcortical activation over two acquisitions and across two different levels of performance in the response time of healthy subjects.

Hypotheses:

In these conditions, as mentioned above, following hypotheses were in our view equally possible:

1. At the initial stage of mirror reading cognitive constraints that the mirror-reading task should trigger the recruitment of the prefrontal cortex (given the novelty and the strategic aspects of mirror reading) because the incremental proceduralization process probably starts at the very beginning of training.
2. After an extensive training period, implicit proceduralization of the task should recruit subcortical structures, i.e. the basal ganglia and trigger less prefrontal areas.
3. The cognitive constraints of the mirror-reading task should trigger the recruitment of the striato-frontal loop system.

More generally, referring to the above mentioned research findings, we further tried to investigate the striato-frontal loop system in procedural learning, i.e. mirror reading with fMRI, to answer the question of its implication on initial rule learning and automatic behaviour:

1. Are there learning-specific distinct neural networks associated with the processing of mirror-reversed words before and after extensive training?

To address the issue of initial rule learning and implicit proceduralisation:

2. Are they two distinct superimposed processes being under control of different neural structures?

Chapter III: methods

3. Materials and methods

3.1 Participants

Eight right-handed volunteers (mean age: 25.6 years, range: 23-29 years; four men and four women) with no history of neurological or psychiatric disease participated in this study. All subjects were native French speakers, right-handed and had equal educational levels (PhD students from the Pitié-Salpetrière's neuroscience laboratories). All subjects gave written informed consent. The Local Ethics Committee approved the protocol.

3.2 Materials

For the two scanning experiments, a list of 144 French words was drawn from the Brulex database (Content et al., 1990). Words from this list were randomly assigned to each condition within the experiment. Half of the words were presented mirror-reversed or in normal script, respectively. They were all selected according to their frequencies, their degree of difficulty and length. Figure 8 shows an example of a mirror word, which had to be read from right to left:

***Figure 8**: "absolu", example of a mirror-reversed word presented during scan sessions*

Each word was 6-letters long, was presented in lower-case and contained at least one "ambiguous letter" such as 'd', 'b', 'p' or 'q', which turn out to lead easily to confusion if read as a mirror image. For the training sessions, 2058 words were drawn from the same database. During training, each word was presented mirror-reversed, in lower-case and comprised ambiguous letters. Unlike during the scanning sessions, 9 letter long words were chosen in order to yield maximum training benefit for the second scanning session.

3.3 Experimental paradigm and study design

The study design (Figure 9) consisted of two scanning sessions, which were separated by training sessions held outside the scanner. The time-lag between the two scanning sessions was determined by the subject's individual performance during the training sessions, i.e. if response times decreased to 80% corresponding to subject's initial performance during the first training session.

Figure 9:

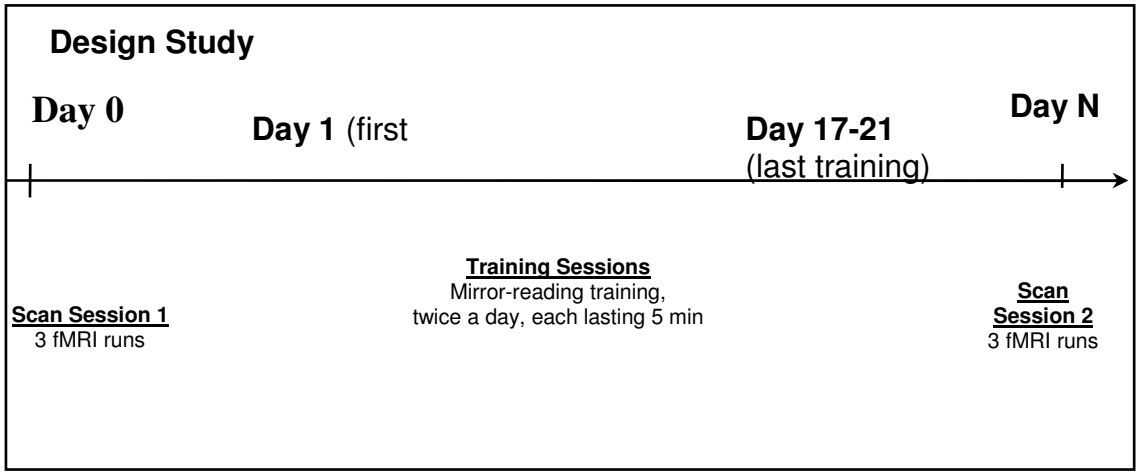
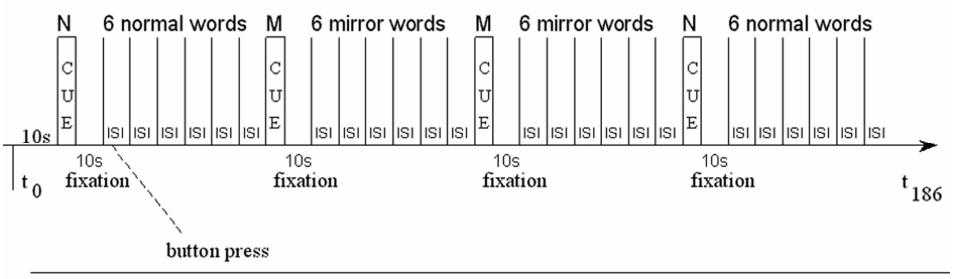


Figure 9: The study design: each scanning session comprised three consecutive scanning runs. One scan session lasted a total of 1395 seconds, during which 558 images were collected. Within each run, two mini-blocs of six consecutive mirror-words and two mini-blocs of six consecutive normally oriented words were randomly displayed on the center of the projection screen. Words were presented for 2.5 seconds. The inter stimulus-interval was variable (10, 12.5, 15, 17.5 or 20 sec) and randomly assigned to each word. After each stimulus presentation, subjects were asked to fixate a central white cross on the screen. Before each mini-bloc, a cue was presented during 2500 milliseconds. The cue consisted of a single word 'normal' or 'mirror' written in red indicating the subject on the forthcoming condition. This cue was followed by a 10 sec lasting fixation period. The task was to read the mirror words from right to left and to read the normally oriented words. Subjects were told to press a response button in their right hand as soon as the word was read, allowing determination of accuracy and response time. Subjects were also asked to withhold the response when they did not succeed in reading a word. There were no repeated items.

A set of demonstration with 5 mirror words, different from those used for the experiment, printed on a white sheet of paper, was used to train the naïve subjects outside the magnet and presented until each subject understood task difficulty. All stimuli were generated by a computer running Expe6 software (Pallier et al., 1997). They were back projected, using a video projector, onto a screen located at the level of the subject's legs. Subjects viewed the screen through a mirror installed 20 cm above their head. A computer interfaced with the response button collected responses. Subject's heads were immobilized with a foam-rubber holder and cushions to reduce motion artifacts. The experimental design is shown in figure 10:



<u>Figure 10:</u> Experimental Paradigm: This figure shows the experimental event-related design used in the present fMRI study. Numbers indicate repetition time (TR = 2.5 sec) after the beginning of the session. After a fixation period of 10 sec, a 3 sec lasting cue, representing either the word "normal" or "mirror"(written in red) appeared on the screen. After each cue, there was a 10 sec fixation period. Following the preceding cue, a series of 6 "normal" or "mirror" words were presented for 2.5 sec at a variable, randomly assigned, interstimulus interval (ISI) of 10 sec, 12.5 sec, 15 sec, 17.5 sec, and 20 sec. When the word was read, the subject had to respond by pressing a button. Each run consisted of four series of 6 words. Sequences were mixed throughout the three scanning runs. N = "normal"; M = "mirror", t = time.

Following the first fMRI session, subjects returned each day to the lab performing twice a day five minutes of mirror reading. In each session subjects were presented a novel 9-letter long mirror reversed words. Unlike the scanning sessions, the word remained on the computer screen until the correct response was given by subjects pressing the mouse button. Subjects were required to read the words aloud. Stimuli were generated and response times were collected by Expe6 software (Pallier et al., 1997) on a PC. Due to the subject's individual performance (subjects performance reflected typical Gaussian normal distribution, with one subject beginning to read 25 words/5 min reaching a plateau at 150 words/5 min and one subjects starting with 80 words/5 min reaching plateau at 220 words/5 min), training lasted from 16 to 21 days before admission to the second scan was permitted.

The scanning procedure and the three runs performed in the second session were identical in design and acquisitions to those performed in the first scanning session. All presented items were novel. All subjects performed a short exercise in reading 6-letter mirror reversed words before the experiment was started. As it was not possible to use the real measures of mirror reading accurately (subject were required to read silently) in the fMRI scanning environment, we asked subjects to omit responding when they were unable to accurately read the word.

3.4 Imaging parameters

Functional imaging for both scanning sessions was performed on a 1.5 Tesla GE SIGNA (General Electric, Milwaukee, Illinois, USA) scanner using T2*-weighted gradient echo, echo-planar imaging sequence, sensitive to Blood Oxygen Level Dependent (BOLD) contrast (repetition time 2.5 sec, echo time 60 ms, flip angle 90°, 16 contiguous axial slices, 3.75 × 3.75 mm^2 in-plane resolution, 5 mm thickness). Functional image runs consisted of 558 sequential acquisitions. The first four images of each functional scanning session were discarded to allow longitudinal magnetization to reach equilibrium.

A set of T1-weighted axial three-dimensional fast SPGR anatomical images (gradient-echo inversion-recovery sequence, echo time 10 ms, flip angle10°, 1.5 mm thickness, in-plane resolution of 0.94 × 0.94 mm^2), were collected to provide detailed anatomic

information. Each entire session, including both structural and functional sequences, lasted between 1 and 1.5 hours.

3.5 Data analysis

All behavioral data was examined in terms of response time (RT). Behavioral data for the eight subjects during the scan acquisition were analyzed using a 2 (sessions) × 2 (conditions) × 3 (repetitions of run) analysis of variance (ANOVA) with repeated measures and no between group factors. Paired comparisons (*t*- test, paired) were used to examine differences between conditions. During training sessions outside the scanner we tested for learning-related differences in behavior by comparing response times during the first and the last individual training unit by applying a paired *t*-test over the first and last training block.

Pre-processing of imaging data was performed using SPM96 (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm) modified for fMRI (Friston et al., 1995b). Images for each subject were first realigned to correct for head motion (Friston et al., 1995a), then normalized into a standard stereotactic space using the MNI templates and smoothed with a Gaussian filter, set at 5 mm full-width at half-maximum, to minimize noise and residual differences in gyral anatomy. Event-related fMRI group analysis was performed with SPM99, using a fixed-effect model.

In this model, data from each subject and each run were processed together using the general linear model with separate functions. Each event type (normal word or mirror reversed word) was modeled by a combination of a standard hemodynamic response function and its time derivative. Four regressors of interest were therefore designed: Mir1 and Nor1 corresponding respectively to mirror reading and normal reading conditions in the first experiment; and Mir2 and Nor2 corresponding respectively to mirror reading and normal reading conditions in the second experiment. Overall signal differences between runs were also modeled. A temporal cut-off of 540 seconds was applied to each run to filter subject-specific low frequency drift related mostly to subject biological rhythms and magnetic field drift. Global changes were removed by proportional scaling. An SPM {F}

map was obtained; reflecting significant activated voxels according to the model used ($p< 0.001$). To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constituted a SPM $\{t\}$ map which was transformed to the unit normal distribution to give a SPM {Z} map.

Comparisons of interest were performed between the two different reading conditions. The mirror-reading task (MR) was contrasted to the normal reading task (NR) for scan sessions one and two, respectively. Contrasting MR to NR should reveal specific activation associated with mirror reading. A threshold of $p<0.05$ corrected for multiple comparisons along with a cluster threshold of at least 5 voxels were used to identify significant voxels. Furthermore, regions were both identified in which activity was either significantly greater (i.e. activation) or significantly less (i.e. deactivation) during the MR condition compared to the NR condition and vice versa. Finally, an analysis across the two sessions, creating a 2 (sessions) × 2 (conditions) interaction contrast. Data were also examined for activation trends at a more liberal threshold of $p<0.001$ not corrected for multiple comparisons.

Results were superimposed on an anatomical "group" image consisting of an average of all the individual anatomical images. Time curves of change of signal activity were calculated for the DLPFC and caudate nucleus, in order to show task specific increase or decrease in signal. Signal intensity was plotted as a function of time in order to illustrate a detailed observation of the hemodynamic course. Concerning the caudate nucleus for the contrast (Mir1 vs Nor1) and ((Mir1-Nor1) vs. (Mir2-Nor2)) we performed a "small volume correction", where the statistical thresholds for multiple comparisons were corrected. This analysis is validated on the basis of strong anatomical a priori assumptions concerning the basal ganglia (Worsley et al., 1996).

CHAPTER IV: results

4. Results of behavioural and imaging data

4.1 Behavioral data

4.1.1 Experiment 1

For each run, averaged response times were 2096 ms (Standard Deviation, SD = ±590 ms), 1846 ms (SD = ±419 ms) and 1968 ms (SD = ±486 ms) for mirror-presented words, and 662 ms (SD = ±224 ms), 640 ms (SD = ±175 ms) and 707 ms (SD = ±244 ms) respectively for normally presented words.

4.1.2 Experiment 2

For each of the three consecutive runs of the second acquisition, averaged response times were 976 ms (SD = ±167 ms), 1064 ms (SD = ±232 ms) and 1049 ms (SD = ±187 ms) for mirror-presented words, and 483 ms (SD = ±68ms), 503 ms (SD = ±85 ms) and 548 ms (SD = ±112 ms) for normally presented words.

Analysis of variance (ANOVA) with repeated measures using 3 within-group factors (type of stimuli, session and repetition) and no between group factors, showed a significant main effect of session *($p=0.004$),* a significant main effect of type of stimuli *($p<0.001$)* along with a significant interaction of session and type of stimuli (*$p<0.001$*) and no effect of repetition *($p=0.078$).* Paired comparisons (*t*- test, paired) were used to examine differences between conditions. MR words were read more slowly than NR words (*$p<0.001$*) in both sessions. A more detailed analysis for reading mirror-reversed words was used by examining each run of the two sessions separately for learning-related RT decreases during scan acquisition. There was no significant RT difference in MR between the first and second run (*$p=0.086$*), the second and third run (*$p=0.088$*) and the first and third run (*$p=0.36$*) run within the first scanning session. Though there was a tendency towards a learning-related decrease in RT seen in the first two runs. There was no significant RT difference in MR between the three runs within the second scanning session (*$p=0.27$; $p=0.69$; $p=0.16$*). As expected, there were no significant RT differences in reading normal words between both sessions (*$p=0.069$*; paired *t*-test over three runs),

but as the significant main effect of session shows, there was a general acceleration in reading words, irrespective of the word type, between the sessions, probably related to the subject's habituation to the scan setting, which lead to the marginally non-significant differences. Comparison of mean response time data from eight subjects during each scanning session and for each of the three runs is plotted as a function of time in figures 11 a and 11 b. There was one subject, who omitted response (missing button press) during the scanning procedure during the first run of the scanning session 1 (for a period of twelve mirror word stimuli) and another subject during the third run of scanning session 1 (for a period of six following mirror word stimuli). Both missing RT were included into statistical analysis as missing values.

Figure 11 a

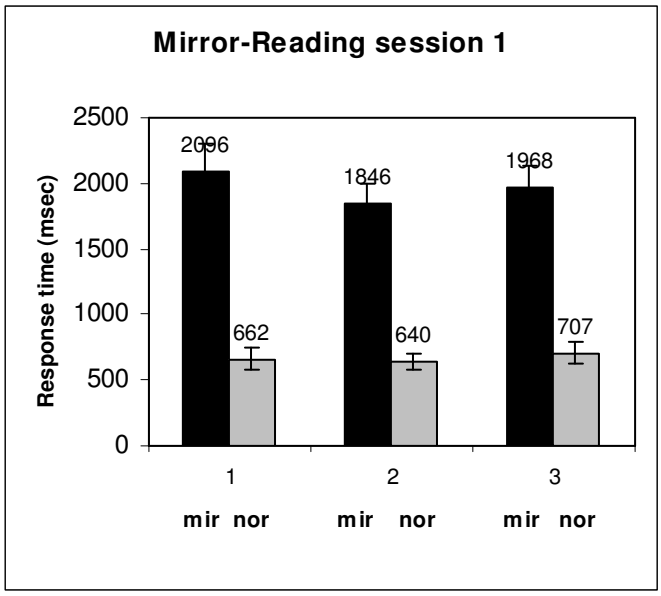


Figure 11 b

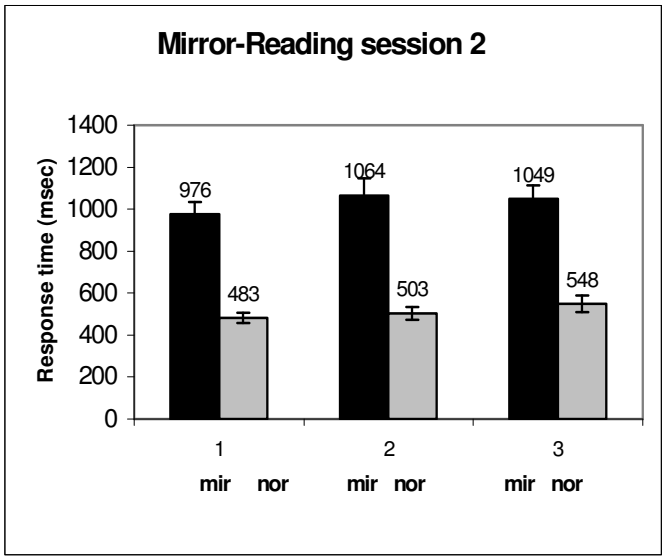


Figure 11 a and 11 b: Behavioral data during scanning experiment 1 and experiment 2. Black bars are response times in milliseconds indicating mean reading times of mirror reading for each run during scanning sessions with the error bars indicating SD. Grey bars are response times in milliseconds indicating mean reading times for normal reading of each run during scanning sessions and error bars indicating SD.

4.1.3 Training Experiment

Training data for all 8 subjects were individually analysed for response time. Subsequently the means and a paired *t*-test over the first and last training block was calculated (see individual and mean learning curves in figures 12 a and 12 b. Reading time significantly decreased over the learning blocks *(p=0.004).*

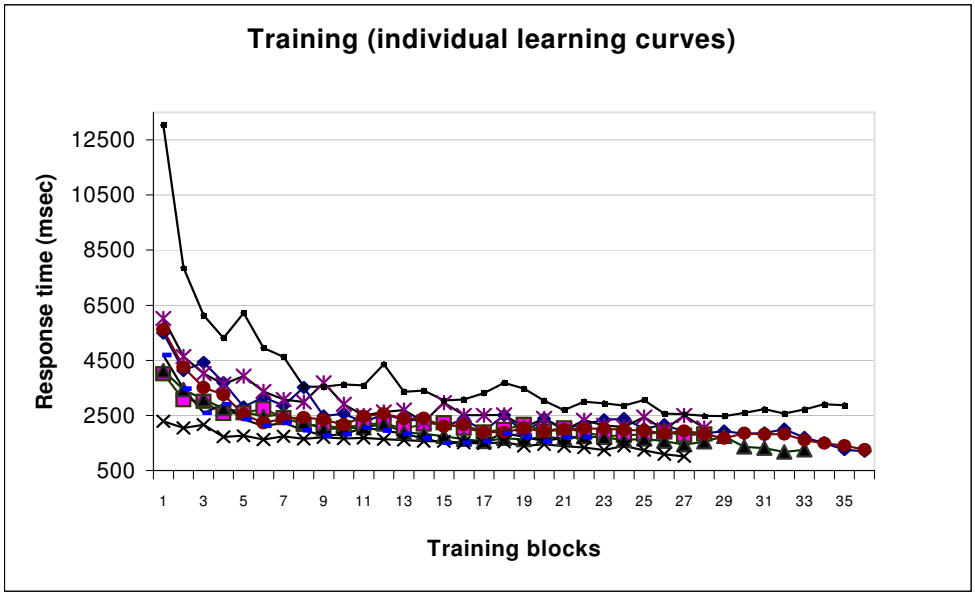


Figure 12 a: Behavioural data during training. Individual learning curves are shown for each of the 8 subjects. Length of training differs individually. Numbers on the x-axis describe training blocks.

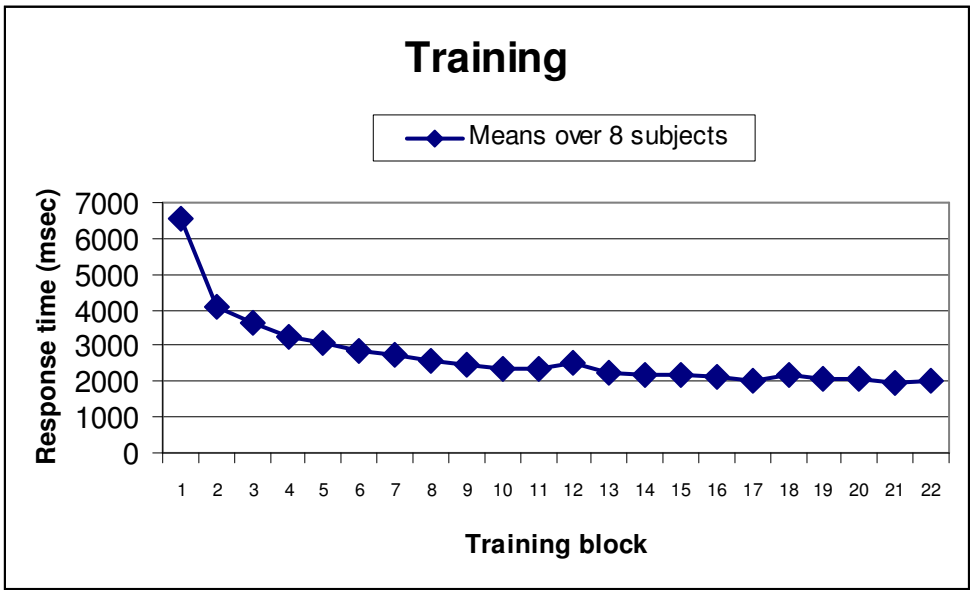


Figure 12 b: Behavioral data during training. Mean response time over 22 training blocks.

4.2 Imaging data: Group analysis

4.2.1 Experiment 1 (scanning session 1):

Mirror Reading compared to Normal Reading (Mir1 vs. Nor1)

Enhanced activation during mirror reading relative to normal reading was detected in multiple brain regions. Voxels exceeding a significant threshold of $P<0.05$ (corrected) overlaid onto standard MRI in Talairach's space are shown in Figure 13 a and 13 b and coordinates are listed in Table 1. In the frontal lobe, the mirror-reading task led to widespread activation along the right and left dorsolateral prefrontal cortex (DLPFC), corresponding to BA 9 and BA 46 (middle frontal gyrus), right and left ventrolateral prefrontal cortex, corresponding to BA 44 and BA 45 (inferior frontal cortex), bilateral pre-supplementary motor area, bilateral middle frontal gyrus (BA 6), the right superior frontal gyrus (BA 6), and the right medial frontal gyrus, corresponding to BA 8. In addition to these frontal regions, the left caudate nucleus (head and tail), bilateral dorsomedial thalamus and left cingulate gyrus (BA 31) were activated. Activation was also observed in the parietal and temporal regions including the right and left cuneus (BA 17), bilateral inferior (supramarginal and angular gyri) and superior parietal lobules (BA 40/7), the right and left fusiform gyrus (FG) corresponding to BA 37 and right middle temporal gyrus (BA 39). Bilateral middle occipital gyri (BA 19) were activated as well as the left hemisphere of the cerebellum. FMRI signal average time-course curves within the left head of the caudate nucleus (small volume correction centred at [-9, -12, 9], with a 8 mm radius) and the left DLPFC region (small volume correction centred at [-48, 42, 18], with a 6 mm radius) were exhibiting maximal task-dependent differences, which revealed different patterns for MR compared to NR (Figure 15). Signal in the caudate nucleus reached its peak 2 TR (= 5 seconds) after stimulus onset (presentation of mirror-reversed word).

Table 1: Activation for mirror-reversed words compared with normal written words. Contrast: Mirror reading I [Mir1] vs. [Nor1]

Anatomical region	H	BA	Talairach coordinates x	y	z	Z scores
Frontal						
DLPFC						
Middle frontal gyrus	R	9	54	18	30	6.27*
	L	9	-42	9	33	5.43*
	L	46	-51	39	21	4.10
	L	46	-48	42	18	4.03
Middle frontal gyrus	R	9	39	48	30	4.06
VLPFC						
Inferior frontal gyrus	R	9/44	48	15	30	7.03*
	L	45	-33	36	3	6.79*
	L	44	-54	9	33	6.35*
Inferior frontal Sulcus	L	45/46	-45	27	21	4.08
Inferior frontal gyrus	R	45	36	33	3	5.13
Premotor						
Middle frontal gyrus	R	6	54	9	45	5.65*
Middle frontal gyrus	L	6	-27	3	57	5.69*
Superior frontal gyrus	R	6	6	15	63	9.85*
Pre-SMA	L	6	-3	18	54	12.09*
Pre-SMA	R	6	3	18	54	10.09*
Medial frontal gyrus	R	8	9	30	42	8.20*
Temporal						
Middle temporal gyrus	R	39	36	-66	27	8.88*
Fusiform gyrus	R	37	51	-51	-6	6.61*
Fusiform gyrus	L	37	-45	-54	-12	6.94*
Parietal						
Superior parietal gyrus	R	7	27	-63	54	7.85*
Superior parietal lobule	L	7	-24	-60	54	9.65*
Inferior parietal gyrus	R	40	36	-48	51	10.68*
Inferior parietal lobule	L	40	-48	-33	42	5.63*
Occipital						
Middle occipital gyrus	R	19	39	-72	18	8.33*
	L	19	-33	-69	24	5.57*
Cuneus	R	17	15	-63	9	6.04*
Cuneus	L	17	-12	-66	9	5.54*
Subcortical						
Thalamus (dm)	L		-3	-12	9	5.81*
Thalamus (dm)	R		6	-6	9	5.39*
Caudate nucleus (head)	L		-12	15	9	5.70*
Caudate nucleus (tail)	L		-9	-12	9	3.17
Cerebellum	L		-24	-63	-12	4.25
Cingulate gyrus	L	31	-9	-69	12	5.43*

Anatomical regions, Brodmann's areas (BA) and stereotactic coordinates of significant cluster maxima in the group analysis. *Significant at voxel-level corrected $P<0.05$. $P<0.001$ uncorrected, extent of at least 5 voxels. SMA = supplementary motor area; (dm) = dorsomedial. H = Hemisphere, R = Right, L = Left, Coordinates are in millimeters, relative to the anterior commissure, corresponding to the Atlas of Talairach and Tournoux (1988)

Figure 13 a and b **Activation during scanning session 1**

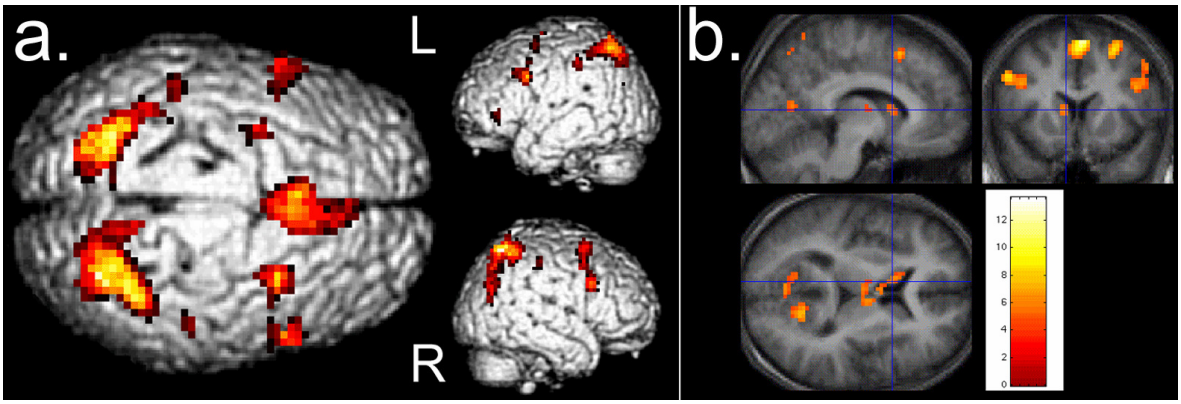


Figure 13 a: Three dimensional surface rendering of an activation map on a standard template brain from fixed-effects analysis for Mir1-Nor1 during scan session 1 and b: projection of activation maps from fixed effects analysis for Mir1-Nor1 on averaged anatomical slices. SPM {t} maps are superimposed upon sagittal (upper left), coronal (upper right) and axial (lower left) sections of a standard normalized brain. Height threshold: $p<0.05$, Extend threshold: 5 voxel

Figure 14 **Activation during scanning session 2**

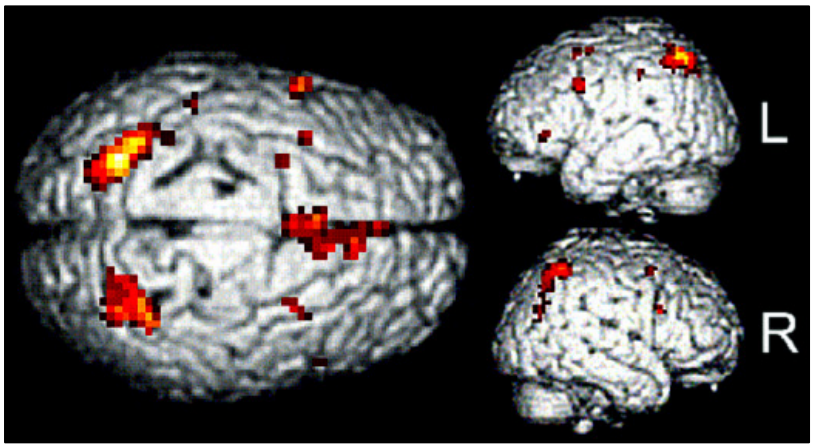


Figure 14: Three-dimensional surface rendering of an activation map on a standard template brain from fixed-effects analysis for Mir2-Nor2 during scan session 2. Height threshold: $p<0.05$, Extend threshold: 5 voxel.

Temporal course of signal change during MR

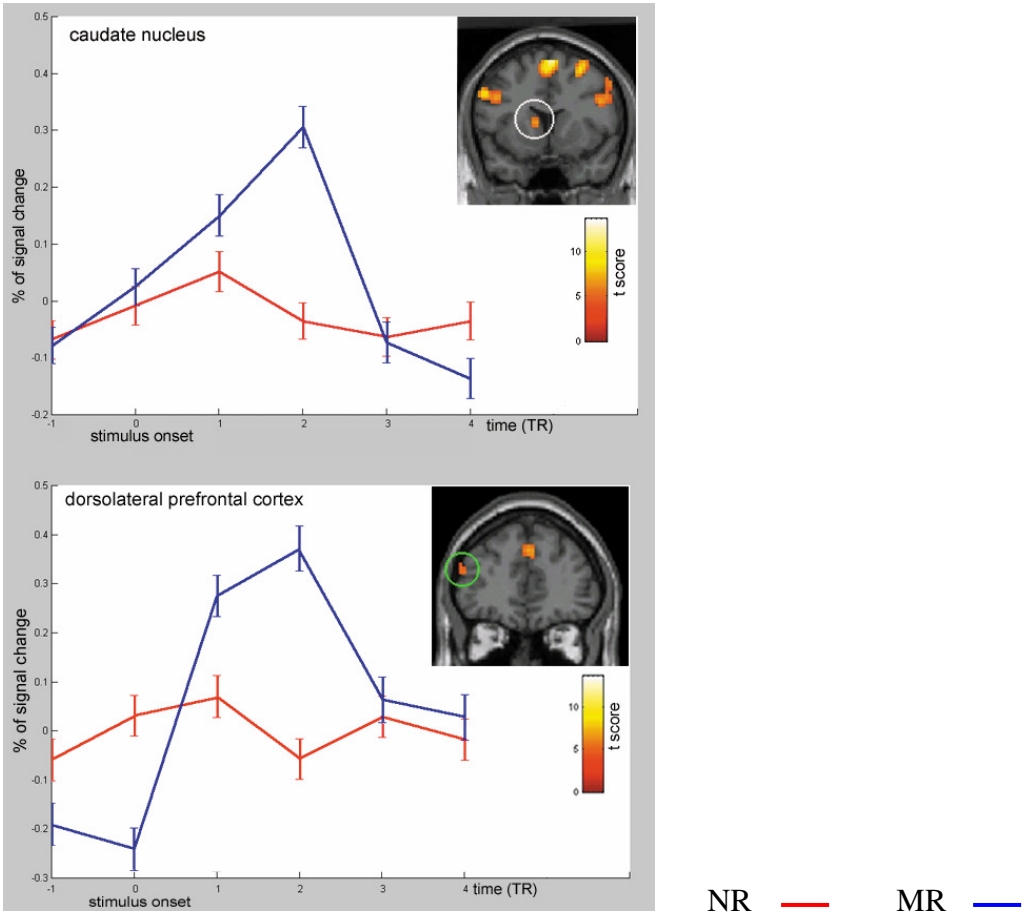


Figure 15: Signal Intensity plotted as a function of time in order to illustrate a detailed observation of the hemodynamic course. fMRI average time-course curves for a region of interest in the left head of the caudate nucleus (centred at [-9, -12, 9], with a 8 mm radius) and the left DLPFC region (centred at [-48, 42, 18], with a 6 mm radius, respectively) exhibiting maximal task-dependent differences. SPM {t} maps corresponding to the group study results during the contrast [Mir1-Nor1] at scan session 1 superimposed on coronal brain slices. Time-scale unit is expressed as TR (repetition time; 2,5 seconds per TR). Blue averaged time-course curves are indicating signal change during mirror reading; thus, exhibiting an increase in signal; red averaged time-course curves are indicating minimal signal change during normal reading in the caudate nucleus and DLPFC.

4.2.2 Experiment 2 (scanning session 2):

Mirror reading compared to normal reading (Mir2 vs. Nor2)

In the second session, enhanced activation during mirror reading relative to normal reading was detected within the frontal lobe bilaterally. Specifically, activation was reported in the left DLPFC (middle frontal gyrus corresponding to BA 9), in the superior frontal gyrus corresponding to BA 10, in the VLPFC bilaterally (right and left inferior frontal gyrus corresponding to BA 44, 47, 45, respectively). In the premotor region, the right and left middle frontal gyrus (BA 6, 8) and the left superior frontal gyrus (BA 6), as well as the SMA were activated. In the parietal lobe, bilateral superior and inferior parietal lobe (BA 7 and 40) activation occurred. Furthermore, significant activation at $p<0.001$, uncorrected for multiple comparisons, occurred bilaterally in the fusiform gyrus (BA 37 left and BA 19 right) as well as in the dorsomedial thalamus and in the right middle temporal gyrus (BA 39). There was activation of the left caudate nucleus and activation of the left cuneus (BA 17). Voxels exceeding a significant threshold of $p<0.05$ (corrected) overlaid onto standard MRI in Talairach's space are listed in Table 2 and shown in Figure 14.

Table 2: Day 2: Activation for mirror-reversed words compared with normal written words. Contrast: Mirror Reading II [Mir2-Nor2]

Talairach coordinates Anatomical region	H	BA	x	y	z	Z scores
Frontal						
DLPFC						
Middle frontal gyrus	L	9	-54	9	36	7.87*
Superior frontal gyrus	L	10	-12	69	12	3.29
VLPFC						
Inferior frontal gyrus	L	45/47	-30	36	0	6.65*
	L	45	-39	30	3	6.32*
	R	44	51	15	24	5.15
	R	46	38	36	3	5.12
Premotor						
Superior frontal gyrus	L	6	-36	9	57	5.60*
Middle frontal gyrus	L	6	-24	3	60	5.86*
Middle frontal gyrus	R	6	33	6	51	6.24*
Middle frontal gyrus	R	8	9	30	45	7.34*
SMA			0	9	63	7.70*
Parietal						
Superior parietal lobe	R	7	27	-66	51	7.96*
Inferior parietal lobe	R	40	36	-51	51	7.01*
Superior parietal lobe	L	7	-24	-63	51	7.48*
Inferior parietal lobe	L	40	-48	-33	42	5.53*
Temporal						
Fusiform gyrus	R	19	48	-48	-12	4.40
Fusiform gyrus	L	37	-42	-60	-12	4.57
Middle temporal gyrus	R	39	39	-69	21	5.86
Occipital						
Occipital gyrus	L	19	-24	-69	27	4.67
Cuneus	L	17	-6	-75	9	3.99
Thalamus	L		9	-12	6	4.48
Thalamus (dm)	L		-6	-12	9	4.85
Caudate nucleus (head)	L		-18	21	3	4.54

Anatomical regions, Brodmann's areas (BA) and stereotactic coordinates of significant cluster maxima in the group analysis. *Significant at voxel-level corrected P<0.05. P<0.001 uncorrected, extent of at least 5 voxels, SMA = supplementary motor area; (dm) = dorsomedial. H = Hemisphere, R = Right, L = Left. Coordinates are in millimeters, relative to the anterior commissure, corresponding to the Atlas of Talairach and Tournoux. (1988)

4.2.3 Comparison of experiment 1 and 2: initial rule learning

Initial mirror reading compared to advanced mirror reading (Mir1- Nor1) vs. (Mir2 - Nor2)

In order to examine changes related to initial procedural learning, activation for mirror reading compared with normal reading was compared across the pre-training and post-training scanning sessions (by testing for a condition × session interaction). A network including frontal, premotor, temporal as well as parietal activation was seen in the cortex (see Talairach coordinates in Table 3 and cortical and subcortical activation depicted in Figures 16 a, b and c. Mirror reading at the initial stage was as well associated with caudate nucleus activation. In the frontal lobe, right VLPFC (inferior frontal gyrus; BA 6/44) was activated. In the premotor region right superior frontal gyrus (BA 6), the left middle frontal gyrus (BA 6), left medial frontal gyrus (BA 6), left precentral gyrus (BA 4) and left paracentral lobule (BA 5) were activated. In the temporal lobe, left middle (BA 39) and superior temporal gyrus corresponding to BA 22 were activated, as well as right middle temporal gyrus (BA 21) and the right angular gyrus (BA 39). Foci of activation within the superior parietal lobule (BA 7) were observed bilaterally. Subcortical activation in the head of caudate nucleus was detected bilaterally. In Figure 17 the time course of signal changes for the right caudate nucleus during mirror reading compared to normal reading is presented showing task specific differences. The right caudate nucleus is exhibiting an increase in signal during initial rule learning and underactivity during overlearned mirror reading. During normal reading, both curves for the two days show negative signal intensity.

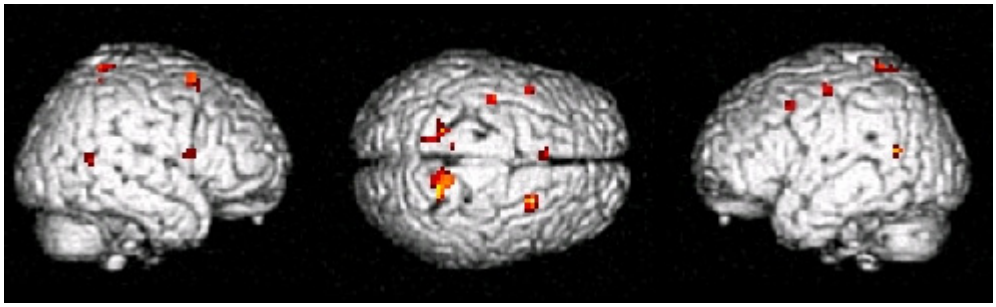
Table 3: Day 1 versus Day 2:

Activation for mirror-reversed words compared with normal written words. Contrast: Initial rule learning [Mir1-Nor1] vs. [Mir2-Nor2]

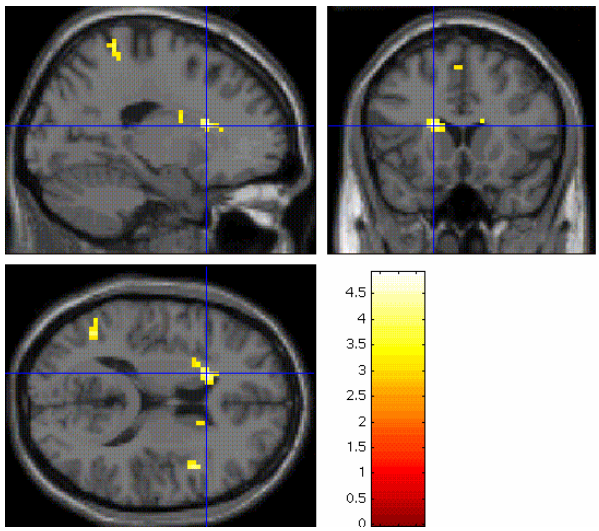
			Talairach coordinates			
Anatomical region	H	BA	x	y	z	Z scores
Frontal						
VLPFC						
Inferior frontal gyrus		R	44/6	45	9	12	4.27
Premotor						
Superior frontal gyrus		R	6	27	12	57	4.30
Medial frontal gyrus		L	6	-3	21	54	3.89
Middle frontal gyrus		L	6	-45	9	45	3.86
Precentral gyrus		L	4	-36	-12	54	3.92
Paracentral Lobule		L	5	-9	-39	63	3.73
Temporal						
Middle temporal gyrus		R	21	45	-54	9	4.33
Middle temporal gyrus		L	39	-45	-60	15	4.13
Superior temporal gyrus		L	22	-54	-57	15	3.38
Angular gyrus		R	39	27	-69	33	3.66
Parietal						
Superior parietal lobule		L	7	-12	-54	66	3.97
Superior parietal lobule		R	7	18	-45	66	4.89
Caudate nucleus		R		15	12	18	3.97
Caudate nucleus (Head)		L		-18	18	15	4.90
Caudate nucleus		L		-15	0	21	4.36

Anatomical regions, Brodmann's areas (BA) and stereotactic coordinates of significant cluster maxima in the group analysis. P<0.001 uncorrected, extent of at least 5 voxels. Coordinates are in milimeters, relative to the anterior commissure, corresponding to the Atlas of Talairach and Tournoux (1988) H = Hemisphere, R = Right, L = Left

16 a **Initial versus late learning stage**



b



c Caudate nucleus activation

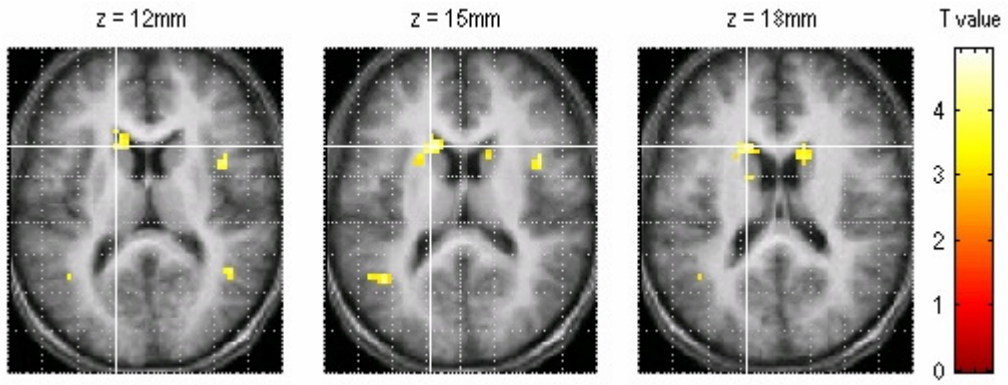


Figure 16 a, b and c

Figure 16: Contrast [(Mir1-Nor1) vs. (Mir2-Nor2)] for the comparison between scan session 1 and scan session 2. Height threshold: p<0.001, Extend threshold: 5 voxel

a: Three-dimensional surface rendering of activation map from fixed-effects analysis b: SPM {t} maps are superimposed upon sagittal (upper left), coronal (upper right) and axial (lower left) sections of a standard normalized brain. Centred on the left caudate nucleus c: Clusters of caudate nucleus activation are shown on different coronal slices at z = 12 mm, z = 15 mm and z = 18 mm.

Temporal course of signal intensity in the caudate nucleus

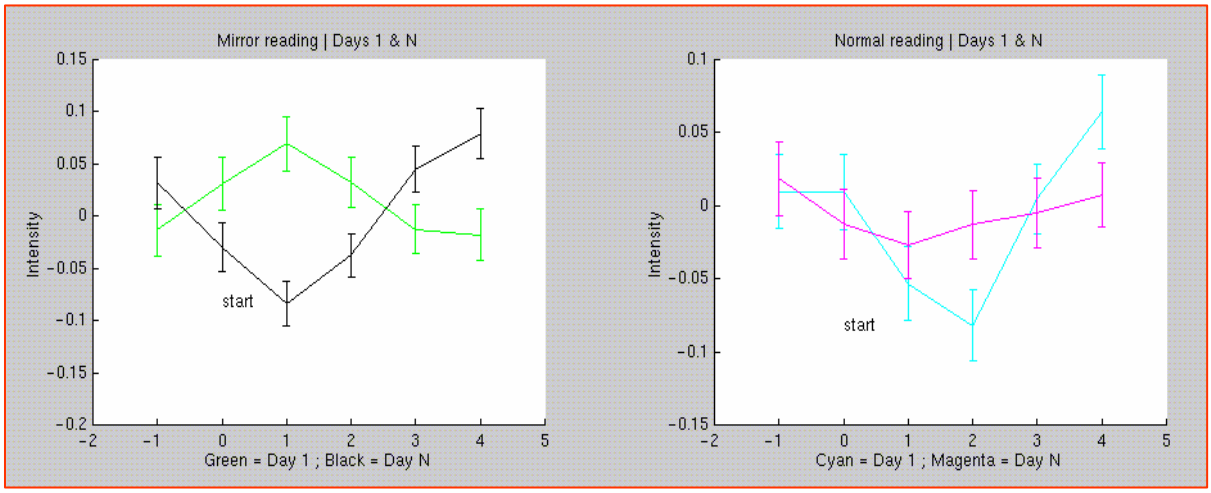


Figure 17: Signal Intensity for the right caudate nucleus plotted as a function of time in order to illustrate a detailed observation of the hemodynamic course. Time-scale unit is expressed as TR (Repetition time; 2,5 seconds per TR). Intensity variation is expressed in %. Hemodynamic response curves are shown for the right caudate nucleus (centred at [15, 12, 18] with a 8 mm radius) during mirror reading (left image) on day 1 compared to the second day (Day N) and during normal reading (right image) on day 1 compared to the second day (Day N). Caudate nucleus is exhibiting an increase in signal during initial rule learning and underactivity during overlearned mirror reading. During normal reading, both curves for the two days show negative signal intensity. There is a peak of signal intensity 1 TR (2,5 sec) after stimulus presentation (mirror-reversed word).

4.2.4 Comparison of experiment 1 and 2: implicit proceduralization (late stage): *Advanced mirror reading compared to initial mirror reading* [*(Mir2 vs. Nor2) vs. (Mir1 vs. Nor1)*]

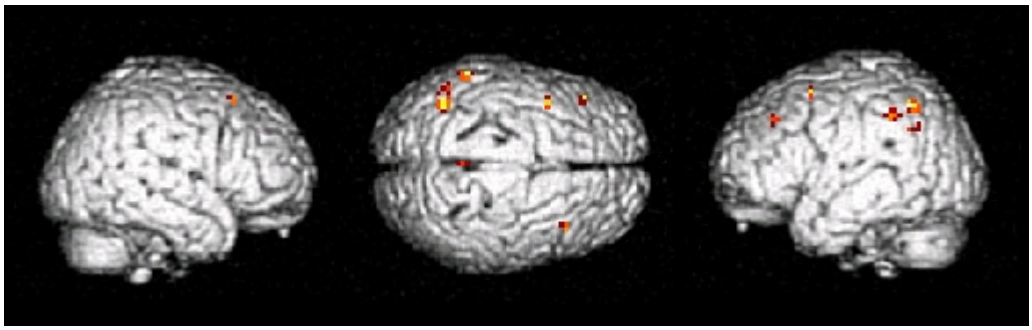
In order to examine changes related to learning and implicit proceduralization, activation for mirror reading compared with normal reading was compared across the pre-training and post-training scanning sessions (by testing for a condition × session interaction). The Talairach coordinates are shown in Table 4 and activations are presented on a surface rendering in Figures 18 a and b. Enhanced activation was found in the left DLPFC (middle frontal sulcus, BA 9/46) and the left superior frontal gyrus (BA 9), as well as in the left VLPFC (medial frontal gyrus; BA 6). Premotor activation occurred in the right middle frontal gyrus (BA 8). There was greater signal activation in the left inferior parietal gyrus (BA 40), in the left superior and inferior parietal lobule (BA 7 and BA 40, respectively) as well as in the paracentral area (BA 5) and there was occipital activation found in the precuneus (BA 7). In the right hemisphere posterior cingulate gyrus was activated (BA 23/31).

Table 4: **Day 1 versus Day 2:** Activation for mirror-reversed words compared with normal written words. Contrast: Learning effect [Mir2-Nor2] vs. [Mir1-Nor1]

			Talairach coordinates			
Anatomical region	H	BA	x	y	z	Z scores
Frontal						
DLPFC						
Middle frontal gyrus/sulcus	L	9/46	-42	33	42	3.89
Superior frontal gyrus	L	9	-6	51	15	3.89
VLPFC						
Medial frontal gyrus	L	6	-39	9	57	3.64
Premotor						
Middle frontal gyrus	R	8	42	21	57	4.60
Parietal						
Paracentral lobule		5	0	-24	45	5.00
Inferior parietal gyrus	L	40	-48	-54	33	3.56
Superior parietal lobule	L	7	-36	-57	48	4.72
Inferior parietal lobule	L	40	-57	-42	42	4.59
Occipital						
Precuneus		7	0	-66	27	3.60
Cingulate Gyrus		23/31	9	-24	33	3.59

Anatomical regions, Brodmann's areas (BA) and stereotactic coordinates of significant cluster maxima in the group analysis P<0.001 uncorrected, extent of at least 5 voxels. Coordinates are in milimeters, relative to the anterior commissure, corresponding to the Atlas of Talairach and Tournoux (1988) H = Hemisphere, R = Right, L = Left.

18 a **Late versus initial learning stage: Automatization**



b

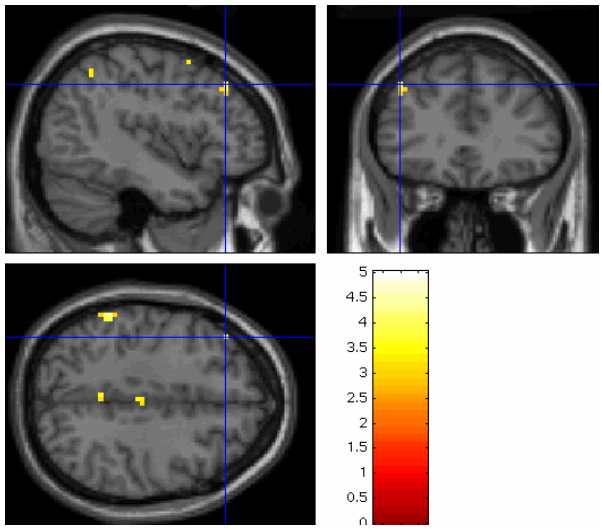


Figure 18 a and b: *Contrast [Mir2-Nor2] versus [Mir1-Nor1] for the comparison between scan session 1 and scan session 2. a Three-dimensional surface rendering of activation map from fixed-effects analysis. b SPM {t} maps are superimposed upon sagittal (upper left), coronal (upper right) and axial (lower left) sections of a standard normalized brain. Centred on the left DLPFC. Height threshold: p<0.001, Extend threshold: 5 voxel.*

CHAPTER 5: Discussion

5. General discussion

By means of neuroimaging techniques, isolating specific neural networks for skill learning still seems difficult to determine. One reason is that the attempt to measure this specific cognitive skill is often related to a restricted task setting and/or its unique experimental paradigm. Higher cognitive capacities such as language, lexical decision, set shift, mental rotation, visuospatial processing, working memory and rule learning intervene in the mirror reading paradigm. For all these processes constituting the "mental state" during the subject's effort to read mirror-reversed words, lack on consensus on what "makes them work" adds to the complexity of studying learning related brain areas and their respective connections.

In this study we examined neural changes related to procedural learning of mirror reading before and after an extensive training period. With this paradigm it was not possible to measure the activation in the sense of a temporal dynamic shift of one brain area activation to another over the two scanning sessions. It gives an insight into activation pattern before and after automatization of the mirror reading skill.

Activation reported for the following contrasts and their possible relation to different cognitive processes are discussed:

1) Mirror reading I (Mir1 vs. Nor1), that activated a broad network of frontal areas including the DLPFC, premotor areas, temporal, parietal, occipital areas and the caudate nucleus.

2) Mirror reading II (Mir2 vs. Nor2), that activated a broad network of frontal including DLFPC, premotor areas, temporal, parietal, occipital areas and the caudate nucleus.

3) Initial procedural learning ((Mir1 vs. Nor1) vs. (Mir2 vs. Nor2)), that activated prefrontal areas without DLFPC activation, premotor cortex, temporal areas bilaterally, parietal cortex areas, bilaterally and caudate nucleus.

4) Implicit proceduralization ((Mir2 vs. Nor2) vs. (Mir1 vs. Nor1)), that was associated with frontal areas including the DLPFC, premotor areas, parietal areas (precuneus) and the posterior cingulum.

Firstly, the results are discussed in relation to other fMRI studies on mirror reading and PL, with an overview of their activation sites.

There are a number of fMRI studies on perceptual-procedural learning, which are all very heterogeneous in their paradigms and experimental settings.
For example, Dong and colleagues (Dong et al., 2000) used fMRI to investigate the neural substrates responsible for Japanese kana mirror reading. They found significant increase in the blood oxygen level-dependent signal during mirror reading relative to normal reading in the bilateral superior occipital gyri, bilateral middle occipital gyri corresponding to BA 18/19, bilateral lingual gyri (BA 19), left inferior occipital gyrus (BA 18), left inferior temporal cortex (BA 37), bilateral fusiform gyri (BA 19), right superior parietal cortex (SPC) (BA 7), left inferior frontal gyrus (BA 44/45) and an inferior part of the left BA 6. In addition to these cortical regions, the right caudate nucleus and right cerebellum were also activated. In particular, they found a significant correlation between the fMRI signal change in the right SPC and the behavioural performance (error index) in this study. This may reflect increased demand on the right SPC for the spatial transformation, which is required for the accurate recognition of mirror-reversed kana items. Japanese kana words, however, are arranged vertically from top to bottom, and not horizontally like in our study and might trigger different brain regions more responsible for spatial transformation.

The two fMRI studies to our knowledge, investigated mirror reading before and after training. Kassubek and colleagues (Kassubek et al., 2001) investigated changes in cortical blood oxygenation contrast and recorded 10 healthy subjects while they alternatively read visually presented single mirror script words and normal script words. Responses in naive subjects were compared to those acquired after training of mirror script reading. They showed that the striate and extrastriate visual areas, associative parietal cortex and the premotor cortex were bilaterally active during normal and mirror script reading. Significantly stronger activation during mirror reading occurred in their study in BA 7, BA 40 (parietal associative cortex) and in BA 6 (corresponding to the frontal eye fields).

The authors recorded simultaneous eye movements, which indicated that activation in BA 6 was related to processing components other than saccade frequency. After training sessions, BA 6 and BA 7 exhibited a decrease of activation during mirror reading that significantly exceeded non-specific changes observed in the normal script control condition. The authors did not investigate subcortical activation. Their findings confirmed their hypothesis of practice-related decrease of activation in task-related cortical areas during nonmotor procedural learning, but did not respond to the question of implication of striato-frontal recruitment in mirror reading.

Poldrack and colleagues (Poldrack et al., 2001) investigated skill learning and repetition priming with the mirror-reading task. Their results confirmed the importance of striatofrontal neural networks for the acquisition of skills and suggested that skill learning and repetition priming could have common substrates within a particular task. Their subjects, too, were scanned before and after five training sessions. It is therefore noteworthy mentioning, that training was less intensive than in our study. Mirror reading compared with reading normal text was associated with extensive activation in occipital, temporal, parietal and frontal regions. Learning to read mirror-reversed (MR) text in this study was associated with increased activation in left inferior temporal, striatal, left inferior prefrontal and right cerebellar regions and with a decreased activity in the left hippocampus and left cerebellum. The second task the authors applied was short-term repetition priming, associated with reduced activity in many of the regions active during mirror reading and extensive item-specific practice (long-term repetition priming) and resulted in a virtual elimination of activity in those regions. The authors suggested that short and long-term repetition priming thus might rely upon common neural mechanisms. Interestingly, in their study the comparison of MR items with other spatially transformed typographies showed that learning-related changes were general to all of the spatial transformations.

5.1 Mirror Reading I and II

When compared to normal reading (NR), mirror reading (MR) in both scanning sessions was associated with activation in a large but specific cortico-subcortical network that can be divided into three different regions:

(1) Retro-rolandic areas implicated in visual processing, particularly in reading;
(2) Prefrontal areas involved in strategic processes and executive functions;
(3) And subcortical structures connected to the DLPFC.

Results of experiment 2 were similar to that of experiment 1. The major activation clusters in the temporal, occipital and subcortical areas were less pronounced in this comparison. In experiment 1 pre-SMA activation was observed, whereas in experiment 2 activation cluster of the SMA was yielded.

5.1.1 Mirror reading I: activation of the occipitotemporal pathway and parietal regions

Both ventral and dorsal visual stream, the ‚What' and ‚Where' systems for visual memory, object recognition, location memory and processing words (Ungerleider et Mishkin, 1982; Ungerleider et al., 1994; Haxby et al., 1991; Nobre et al., 1994) were found to be elicited during MR compared to NR.
The occipitotemporal pathway or “ventral stream” is crucial for the identification of objects. In monkeys, cells within the area of the ventral stream respond to visual features relevant to object identification such as texture or shape (Ungerleider et al., 1998). The activation that was found in temporal and occipital areas during mirror reading which are involved in visual discrimination, may be attributed to an additional processing in the "what" system needed for unusual visual material (i.e., inverted visual word form and inverted letter by letter discrimination).

The “dorsal stream” contains location information, which is primarily processed in dorsal brain regions, particularly within the parietal cortex. Activation was also found bilaterally

in inferior and superior parietal cortex during mirror reading and may be attributed to location memory for mirror shaped words. The posterior parietal cortex (PPC) is considered to maintain spatial information during the delay phase of spatial working memory task (Smith and Jonides, 1988). Furthermore, Chafee and Goldman-Rakic (1998) provided support for a functional interaction of parietal and prefrontal neurons by reporting similarities in their discharge patterns during the delay of a visuo-motor task. Anatomical studies have shown that projections from areas in the dorsal stream terminate mainly in and around BA 46 of dorsolateral prefrontal cortex (Ungerleider and Desimone, 1986). During mirror reading compared to normal reading, activation of a fronto-parietal neuronal network, namely bilateral parietal and bilateral DLPFC activation occurred and could be attributed to the spatial demands of the task.

Specifically, bilateral parietal activation was observed in the superior parietal lobules which may result from additional visuomotor processes triggered by MR: spatial attention for the spatial linkage between stimuli (i.e., letters) and for mental rotation of visual representation needed for ambiguous letter discrimination ('b','d' and 'p','q') and an increased demand on the visuomotor system to read in a spatially unusual sense. Indeed, activation within the same sub-areas of the superior parietal lobule was reported in a study while reading pseudo-words (Mechelli et al., 2000) and when performing mental rotation of words (Jordan and Huntsman, 1990). Mechelli and colleagues (Mechelli et al., 2004) showed as well that learning a second language increases the density of grey matter in the left inferior parietal cortex and that the degree of structural reorganization in this region is modulated by the proficiency attained and the age at acquisition.

The activation that falls into the left fusiform gyrus is likely to be associated with the visual processes recruited for reading. Indeed, studies have emphasized a specialized role of this area for processing written words (Nobre et al., 1994). Cohen and colleagues even suggested that a subpart of the left fusiform gyrus has a specific role in decoding the visual word form (Cohen et al., 2000). In the context of our tasks, such activation may be interpreted as resulting from an additional effort to bridge new grapheme or word-like information to a visual lexicon for known words. It is consistent with prior findings in patients with right occipital lobe lesions, who did not show disturbed performance in mirror reading (Yonelinas et al., 2001) and with a previous fMRI report using a mirror-reading task (Poldrack et al., 1999). In addition to the left fusiform gyrus, activation was

found in the left inferior parietal lobule (supramarginal and angular gyri) and Broca's area. These areas belong to the spread cortical network involved in language processing. In particular, left parietal and Broca's areas have been associated with the maintenance of verbal material and in the subvocal rehearsal in working memory, respectively (Paulesu et al., 1993). Specifically, MR requires probably the activation of the phonological loop of the working memory system at the beginning of the learning phase.

In the mirror reading task there was posterior cingulate gyrus (BA 30/31) activation present. The posterior cingulate gyrus activation may be related to the increase of attention during the MR task (Kim et al., 1999). Mesulam and colleagues (2001) reported that the posterior part of the cingulate gyrus appears to be associated with a cue-induced anticipatory shift from one task to another.

5.1.2 Mirror reading I: activation of the prefrontal cortex

The main difference between MR and NR is that the former involves new stimuli and requires the establishment of new rules (conversion for ambiguous letters 'b', 'd', 'p' and 'q') and thus implies the inhibition of the over-learned procedure from reading left to right. It implicates a subvocal rehearsal (Baddeley and Hitch, 1974) and requires maintenance of letters in memory in order to build the correct word, while the NR directly accesses visual word form lexicon familiar to subjects.

Bilateral DLPFC activation (BA 9/46) has to be related to strategic constraints and the cognitive control involved during MR: inhibition of the over-learned strategy of reading from left to right and mental manipulation within working memory of ambiguous letters to the processes required to set and apply a new rule over time. All these functions are known to involve the anterior and lateral aspects of the prefrontal cortex (Wise et al., 1996; Strange et al., 2001, Wallis et al., 2001). This has as well been demonstrated in a number of lesion studies on frontal patients evidenced from neuropsychological tests (Grafman et al., 1995; Fuster, 1989; Stuss and Benson, 1984; Stuss and Benson, 1986). For example, in a lesion study on patients with frontal lobe damage who performed the Wisconsin Card Sorting test (WCST), patients with superior medial frontal damage, right and left, tended to be the most impaired on all measures. Right and left lateral prefrontal damaged patients were also significantly impaired in this frontal lobe function test (Stuss et al., 2000).

FMRI signal changes within the left DLPFC confirmed that task related differences occur between MR compared to NR (Figure 12). Beside its role in executive function, planning, cognitive control and working memory, the DLPFC might be also specifically required for MR. A critical role of the DLPFC in this specific task is the preparation and selection of responses, as subjects tend to have internal representations of the letters. Within the working memory framework, the DLPFC has been related to response preparation (Pochon et al., 2001) and at the time at which subjects retrieve items and select their response (Rowe et al., 2000). It seems that within working memory tasks maintenance of items is uniquely attributed to the premotor and posterior parietal cortex whereas manipulation of items held in working memory recruit the specific activation of the DLPFC (Rowe et al., 2000; Pochon et al., 2001). This is in line with statements from our subjects who reported outside the scanner that their strategy to read mirror reversed was always associated with "holding" information about the ambiguous letters in mind, in order to achieve the correct meaning of the word. DLFPC involvement in MR is consistent with an impairment of cognitive skill learning following transient magnetic stimulation (TMS) of the dorsolateral cortex in normal subjects (Pascual-Leone et al., 1995). Strafella and colleagues (2001) showed that application of repetitive TMS over the left DLPFC lead to an augmentation of dopamine synthesis in the ipsilateral caudate nucleus. The authors hypothesized that this stimulation of the caudate nucleus would be more due to a direct connection of the DLPFC with the caudate nucleus, than due to an indirect connection through intermediate cortico - substantia nigra pathways. The recent study by Sarazin (2002) strongly pleads in favor of a crucial involvement of DLPFC in the MR task since only PD patients with frontal dysfunction were impaired in the MR learning task. Beldarrain and colleagues (1999) observed impaired procedural learning in patients with frontal lesions.

The mirror-reading task has to be related to an extensive literature on the Stroop task effects because this specific task requires suppression of automatic processes and the incongruent condition of the Stroop Test (Stroop, 1935) is one of the most commonly accepted measures of frontal lobe functioning. Meta-analyses of the Stroop task (Bush et al., 2000) have stressed activation of the dorsal anterior cingulate cortex (ACC), as well as a wide number of areas in the prefrontal cortex (Casey et al., 2000). Especially the medial and ventral aspect of the pre-SMA, a region that is supposed to be implicated in resolving response competition (Ullsperger and von Cramon, 2001) and the posterior

extent of the inferior frontal sulcus are associated with the Stroop task (Milham et al., 2002). Both areas were bilaterally activated during mirror reading, with the pre-SMA showing highest Z-scores among all clusters.

It should be noted that part of the premotor activation (lateral BA 6) that partially overlapped the FEF could be related to visuomotor processing (Georgopoulos and Lurito, 1991; Ungerleider et al., 1998), including saccadic movements (Milea et al., 2005).

5.1.3 Mirror reading I: subcortical activation

In addition to areas related to the reading system, significant striatal activation within the left caudate nucleus was observed when mirror reading was compared to normal reading. This is consistent with prior fMRI studies using MR tasks. Cognitive skill learning assessed by mirror reading has been associated with activation in the head of the caudate (Poldrack et al., 1999) and increases in the left tail of the caudate nucleus during practiced MR (Poldrack and Gabrieli, 2001) and in the left caudate nucleus during early learning phases (Müller et al., 2002). Procedural learning of the mirror reading skill was reported to be impaired in PD patients in studies by Roncacci and Koenig (Koenig et al., 1999; Roncacci et al., 1996). In the study done by Koenig, patients with PD exhibited learning for repeated mirror words, but they did not respond faster with practice for new words in mirror reading, suggesting that the caudate nucleus is needed for learning a new task but not recruited for repetition learning (Koenig et al., 1999). In patients with Huntington chorea, Martone and fellow researchers (Martone et al., 1984) found a mild PL deficit. Hikosaka and colleagues suggested that basal ganglia might be important for attaching motivational value to the learning process, with anterior involvement of the CN during early sequence learning (Hikosaka et al., 1999; Hollerman et al., 2000; Hollerman and Schultz, 1998). A number of imaging studies on other cognitive skill learning tasks also reported basal ganglia involvement (Toni and Passingham, 1999; Sakai et al., 1998, Parsons et al., 2005). Moreover, caudate nucleus has been proposed to be involved in working memory (Owen et al., 1998) and the rostral striatum in reward-association learning and reward expectation (Schultz et al., 2003). The specific striatal areas required for procedural skills may depend in part on the mnemonic demands of the task. One might speculate as well, according to previous studies, that the putamen may be

particularly critical for the learning of perceptual motor skills and the caudate nucleus for the learning of more complex rules (Doyon et al., 2003; Marsh et al., 2005, Sarazin et al., 2002).

Bilateral thalamic activation in this study was seen in the dorsomedial part. These thalamic regions are connected with the dorsolateral prefrontal cortex and caudate nucleus in primates (Middleton and Strick, 2002). This favors our hypothesis for the implication of basal-ganglia-thalamo-cortical-circuits in mirror reading performance.
Imaging studies have suggested that the early stage of motor skill learning is mediated by the cerebellum (Doyon et al., 2003). Furthermore, in previous studies, cerebellar activations together with FEF activation have been related to execution of saccadic eye movement (Rowe et al., 2001). In this experiment the number of saccadic moves were not recorded in the scanner, therefore not controlled, however, cerebellar activation can not uniquely be explained by saccadic movements as there was no cerebellar activation found during the second scan session. A more likely explanation is that this region might be involved in non-motor skill learning as well as in encoding demands of the mirror reading task (Rowe et al., 2001; Chen and Desmond, 2005).

5.2 Mirror Reading II

Experiment 2 engaged a similar set of frontal, premotor, parietal, temporal, occipital and subcortical regions as in experiment 1. However, the major activation clusters in the temporal, occipital and subcortical areas were less pronounced than in this comparison. In experiment 1 pre-SMA activation was observed, whereas in Experiment 2 only a single activation cluster of the SMA was yielded. Furthermore, no cerebellar or cingulate gyrus activation was observed. There was only activation seen in the left head of caudate nucleus.
Moreover, we found that hemodynamic responses in the ventral pathway declined as reading latencies became faster through multiple exposures. This larger reduction in activity with increased familiarity is consistent with the hypothesis put forward by Desimone (Desimone, 1996). Together, mirror reading II engaged a network of brain regions.

5.3 Comparison of Mirror Reading I with II: Initial rule learning

A greater activation was reported in the caudate nucleus during the MR task than in the NR task when the initial stage of PL was compared to the proceduralization stage. Within the frontal lobe, right VLPFC (inferior frontal gyrus) was activated. In the premotor cortex, the right superior frontal gyrus (BA 6), the left middle frontal gyrus (BA 6); as well as the left medial frontal gyrus (BA 6), and left precentral gyrus were activated. Moreover, temporal and parietal lobes activations were observed. The left middle (BA 39) and the left superior temporal gyrus (BA 22) were activated. In the right hemisphere, angular gyrus was activated (BA 39), as well as right middle temporal gyrus, corresponding to the BA 21. Superior parietal lobules (BA 7) were bilaterally activated. Striatal activation occurred in the right and left caudate nucleus.

5.3.1 Implication of fronto-striatal loops in the early stage of PL

The most interesting result was the activation of the caudate nucleus at this very early stage of learning. Animal lesion experiments suggest that the caudate nuclei may play a specific role in cognition. Damage to different regions in the caudate nucleus produces deficits that resemble the effects of damage corresponding to their projected targets within the prefrontal cortex (Divac et al., 1967). In addition, ^{18}F-dopa PET studies in PD patients have shown a correlation between dopaminergic depletion in the caudate nucleus and neuropsychological results (Owen et al., 1998; Dagher et al., 2001; Cools et al., 2002; Mattay et al., 2002). Anatomically, the head of the caudate nucleus is closely connected to the prefrontal cortex (Yeterian and Pandya, 1991; DeLong et al. 1983; Alexander et al. 1986, 1990; Alexander and Crutcher, 1990). Their association is based on partially closed cortico-striato-pallido-nigrothalamo-cortical loop systems (Middleton and Strick, 2002) and was recently partly demonstrated with diffusion tensor imaging axonal tracking (DTI) in humans (Lehéricy et al., 2004). The caudate nucleus serves as a relay for two of the complex loops, namely the dorsolateral prefrontal loop, which includes the prefrontal BA 9 and 10, parts of the premotor cortex and the parietal BA 7, the lateral orbito-frontal loop, which includes the inferior parts of the prefrontal BA 10, BA 11 and parts of the temporal neocortex. The anterior cingulate loop includes BA 24, temporal limbic areas

and the ventral striatum (Alexander and Crutcher 1990; Saint-Cyr et al., 1995; Cummings 1993). It is known that the rostral striatum receives input from the DLPC, the pre-SMA and other frontal association areas (Selemon and Goldman-Rakic 1985*;* Parthasarathy et al., 1992). Our results suggest that the fronto-striatal loop is involved during the early stage of mirror reading in this paradigm and that the striatum is involved in more than simple pair wise associations and that it reflects the capacity to process higher-order knowledge. The striatum may not only be involved in the learning processes in this task through prefrontal cortex-caudate nucleus networks, but also plays a significant role for the selection of appropriate responses, thus contributing to better efficiency and faster response preparation. A recent study (Vakil et al., 2004) done on patients with ischemic infarctions affecting the basal ganglia showed differential effects of right or left involvement in the improvement of procedural learning tasks. Interestingly, patients with right-sided BG infarctations only showed impaired baseline performance in the mirror reading task but did not differ in their learning rate compared to controls.

The caudate nucleus activation is in agreement with previous evidence that diseases of the BG (PD and HD) are associated with impairment in the procedural acquisition of cognitive (Koenig et al., 1999), perceptual (Martone et al., 1984) and/or motor skills (Heindel et al., 1989; Jueptner et al., 1997). The striatum may serve in the formation of stimulus-response (S-R) associations (Mishkin et al., 1984; Graybiel et al., 1998). In visual discrimination learning in monkeys, neurons in the tail of the caudate nucleus show stronger visual responses to novel stimuli than to well learned ones (Brown et al., 1995). However, if the striatum is involved in learning a new procedure, it remains unclear whether it was as well recruited when using the procedure once consolidated. Compared to Poldrack's study using a close MR task paradigm (Poldrack and Gabrieli, 2001), our results seem to appear contradictive. Indeed, they reported learning-related increases in the right caudate nucleus. However, subjects in their study practiced mirror reading outside the scanner during five sessions (a total of 20 training blocks, mean word length 6.5 letters) within two weeks, yielding a RT decline from 2.6 sec to 1.6 sec for new MR words, whereas in our study RT decline was up to 80% for 9-letter long words. We therefore hypothesize that the total automatism and the stabilization of the learned skill has not yet occurred.

5.3.2 Temporal activation

The bilateral temporal areas (middle temporal gyrus and angular gyrus) as well as the left superior temporal gyrus (BA 22) appeared in the early stage of procedural learning. The left superior temporal gyrus is an associative and unimodal auditory area corresponding to lexical processing of spoken words (Booth et al., 2002). In former mirror reading studies divergent interpretations were established according to phonologic and lexical processing areas over the time course of learning to read mirror reversed words. For example, the left temporal cortex exhibited increased activation during novel presentation of MR letters (Poldrack et al., 1998), and, in another study of the same group left temporal cortex was more activated after training of the mirror-reading task (Poldrack and Gabrieli, 2001). This led the authors to the conclusion that the activation of the left inferior temporal region might be related to increased engagement of lexical/phonological processes as learning progresses. Our results support the former hypothesis that these structures, namely left middle and superior temporal cortices, seem to play a role in establishing novel representations of MR letters during the initial stage of mirror reading learning.

5.3.3 Parietal activation

In this study the superior parietal lobule was more activated during initial rule learning. As previously discussed, this parietal area has been described during tasks involving spatial rotation of word or non-word reading (Mechelli et al., 2000; Jordan et al., 1990). In another fMRI study on Japanese kana mirror reading (Dong et al., 2000) a robust activation of the right superior parietal was also shown. In particular, the authors found a significant correlation between the fMRI signal change in the right superior parietal cortex (SPC) and the behavioural performance (error index) of the task. This may reflect increased demand on the right SPC for the spatial transformation. The parietal cortex has also been specifically implicated in procedural sequence learning, in a study of stroke patients who failed to learn a sequence by following implicit instructions, even after extensive practice (Boyd and Winstein, 2001). It is therefore likely that the additional activation found in the superior parietal lobule depicts the higher demand on visuospatial-related processes required during the early stage of mirror reading.

5.4 Comparison of mirror reading I with II: implicit proceduralization

Significant increases in activation were found in the left middle, left superior frontal gyri (DLPFC), the left medial frontal gyrus (VLPFC), left inferior and superior parietal cortex, the right premotor cortex and the paracentral cortex as well as in the right precuneus and right posterior cingulate gyrus after extended practice in mirror reading. As shown in the results section, significant shortening of responses compared with the first scanning session throughout the three successive runs of the second scanning session were observed, suggesting that training lead to a detectable learning of the mirror reading procedure.

5.4.1 Implication of fronto-striatal loops in the late stage of PL

In contrast to our initial hypothesis there was no significant activation of the basal ganglia after the automatization of the mirror reading task. On one hand, these results contrast those found in other motor and perceptual learning studies (Grafton, et al., 1992; Poldrack et al., 2001; Doyon et al., 2003). Other authors reported increased striatal activation during late stages of learning a cognitive skill (Poldrack et al., 2001; Poldrack et al., 1999; Peigneux et al., 2000). However, results from Miyachi and colleagues (Miyachi et al., 1997) may partially explain such discrepancies. In their study, they examined how procedural learning (sequential button pressing task) triggered neurons discharge within the basal ganglia in primates. They compared the neuronal activity while learning new sequences while executing over learned sequences. They found that more than 25% of neurons in the BG recorded were activated preferentially for new sequences ("new-preferring neurons") and less than 25% coded for over-learned sequences ("learned-preferring neurons"). Almost the half of all neurons were activated non-selectively. It is worth noting that the "new-preferring neurons" were located preferentially in the associative division of the striatum, i.e. the caudate nucleus and anterior putamen (Miyachi et al., 1997; Gerardin et al., 2004), whereas "the learned-preferring neurons" were mostly located in the sensorimotor subdivision of the striatum, i.e. the posterior putamen (Miyachi et al., 1997; Gerardin et al., 2004). The activation found within the CN during the early stage of procedural learning is in line with this study, in which the

monkey's associative division of basal ganglia contributes preferentially to the early stage of procedural learning. However, our study failed to describe significant activation of the sensorimotor division of the basal ganglia after mirror-reading skill acquisition. A hypothesis that may explain this difference would be the nature of the PL task. The posterior putamen contribution for sequential finger movements has largely been described in monkeys (Taniwaki et al., 2003) and in humans (Gerardin et al., 2003; Lehéricy et al., 2004). However, its contribution for automatic reading and for over-learned mirror reading remains to be determined.

Our results are consistent with other imaging studies showing greater striatal activity during novel tasks (Berns et al., 1997; Jueptner et al., 1997; Müller et al., 2002). CN activation during the early learning stage of mirror reading may suggest that subjects have to rely more on the use of cognitive strategies and working memory (Toni et al., 1998; Jenkins et al., 1994, Jueptner et al., 1997).

Reading mirror-reversed words after proceduralization also led to the activation of the left DLPFC. Our hypothesis was that given the novelty and the strategic aspects of mirror reading, DLPFC activity would rather decrease after extended practice and subject's behavioral results showed a clear asymptotic level of performance in mirror reading after training time. Studies on motor sequence learning have reported reduced frontal activation in well learned as compared with newly-learned sequences and under settings of reduced attention following the achievement of advanced levels of performance (Jenkins et al., 1994; Jueptner et al., 1997; Poldrack et al., 2001). Inversely, Berns and colleagues (1997) showed the right DLPFC increased in an implicit learning task during the late stage of a sequence acquisition. They suggest that the DLPFC is implicated in the active maintenance of task-relevant information (Goldman-Rakic, 1987) and in the maintenance of context information for cognitive control (Cohen et al., 1996). Conversely to a number of PL tasks, during the MR task subjects must always overcome the strongly reinforced habit of normal reading. Differences in response time between normal and mirror reading at the end of the training period and during the second scanning (normal = 510 ms and mirror = 1030 ms) reflects that both processes are not equally "wired" within the brain. More than 20 years of training for normal reading and a three weeks training for mirror reading is naturally responsible for such a contrast. Therefore, considering that

both normal and mirror-reading use the same visual material, we postulate that even after proceduralization of the task, normal reading is still interfering with the mirror reading abilities.

It is also worth noting as well that a lateralization in the left hemisphere occurred in the DLPFC compared to the results of the activation in the first experiment, when naïve mirror reading was compared to normal reading. The laterality of activation in the middle and superior frontal regions (BA 9/46) could suggest an effect of memory retrieval, based on neuroimaging studies showing preferential prefrontal involvement on the left hemisphere during encoding and the right during recall (Nyberg et al., 2000). In an fMRI study of motor sequence acquisition by Müller and colleagues (2002), late learning of this task was as well associated with stronger activation in the left superior frontal cortex (BA 9).

Similar as in the Stroop task, (Pardo et al., 1990; Braver et al., 2003; Botvinick et al., 1999) the additional control and maintenance of specific contextual information is required to perform this "non-natural" task. This additional control is also to be segregated from early executive functions required when subjects are still naive in the first scanning session. Even if inhibition is likely to be required in initial and automatic mirror reading, respectively, the higher order spatial processing such as spatial attention and mental rotation are probably more important for the latter. Whereas during naïve reading, the higher order processing of visual verbal information is also probably triggered. This hypothesis could explain the right frontal and superior parietal activation when testing the early stage of mirror reading and could explain left frontal activation when testing mirror reading proceduralization. The left dorsolateral prefrontal region was associated both in imaging studies (Taylor et al., 1997) and lesion studies (Stuss et al., 2001) within the incongruent condition of the Stroop Test.

Alternatively, this difference between frontal activation may also reflect a difference between strategic encoding functions that happened in the early stage as well as the retrieval of long-term representations or the recall of "wired" strategic processes in the final stage of PL (Miller and Cohen, 2001). It is worth noting that pooling the stimulus in mini-bloc should exclude a main effect of task switching related processes on frontal activation (MacDonald et al., 2000).

Interestingly, in a lesion study with different motor and non-motor procedural learning tasks done by Schmiedke and colleagues (2002) on patients with focal unilateral prefronto-striatal lesion or lesions in the head of the caudate nucleus none of the groups were impaired with procedural learning of Mirror Reading. Deficits in motor learning were only observed in patients with whom the motor loop was affected. These results suggest that the dorsolateral prefronto-striatal loop is involved in the establishment of cognitive processing routines, but not mandatory for normal cognitive PL. However, the patient's performance in other PL tasks, Mental Rotation, was markedly impaired, though both tasks involving fast, multi-item, visually guided processing that requires visual working memory and mental transformation of symbols. The authors suggested that mirror reading might predominantly depend on specialized object recognition and object transformation networks that are localized in posterior, temporo-parietal-occipital areas. This is consistent with activations of the precuneus, posterior cingulate gyrus and posterior parietal activity in our study.

Recently, Pasupathy and Miller (2005) found that in monkeys, the striatum showed more rapid change in the learning process than in the prefrontal cortex. They found that as monkeys learn new, simple rules, associations analogous to "stop at red, go at green", the striatum of the basal ganglia shows evidence of learning much sooner and faster than the prefrontal cortex. They simultaneously recorded neural activity from the dorsolateral PFC (areas 9 and 46), the head and body of the caudate nucleus, a part of the striatum that receives direct projections from, and indirectly projects to the PFC in primates. The monkeys learned associations between two visual cues and two saccadic eye movements. The authors suggested that the basal ganglia first identify a rule and then "train" the prefrontal cortex, which absorbs the lesson more slowly. An interesting point is that the monkey's behavior improved at a slow rate, similar to that of the slower changes in the prefrontal cortex. The authors suggested that while the basal ganglia "learn" first, their output forces the prefrontal cortex to change, albeit at a slower rate.

Our study contrasts with the view that basal ganglia or cortico-striatal activity should increase with practice (Doyon et al., 2003) due to its role in automatization of performance. One difficulty with this model is that automatic behaviour could be

indicated by reducing rather than increasing brain activation, because fewer of the cognitive resources might be engaged (Wu et al., 2004). Wu and colleagues reported that before and after training, activity was observed in a distributed network of cortical and subcortical regions involved in the learning and execution of finger movements. There was less activity however in the left caudate nucleus and other related region, suggesting that automatic performance was enabled by a functionally more efficient motor network. A comparable conclusion was also reached on the basis of a study that compared the performance of professional pianists with that of musically naïve subjects with over-practiced tasks requiring bimanual playing scales (Haslinger et al., 2004). The authors concluded that the non-musicians showed stronger increase in cerebellar hemispheres and the right basal ganglia, suggesting that automatic behaviors are associated with a mere increase in efficiency of the same cortical and subcortical brain areas, recruited as well in the early learning phase. Taken together, the results of this study are consistent with studies that reported a decrease in activation and a switch to associative brain regions, which are described in the next chapter.

5.4.2 Premotor and parietal activation

There was bilateral premotor cortex activation found in this study. In a study done by Kassubek and colleagues (2001) a decrease of activation in bilateral premotor areas (BA 6) and parietal area (BA 7) was exhibited after training of mirror reading task. They suggested that a decrease in activity in non-motor skill learning is due to habituation effects in cortical areas that are involved during naïve performance. Our data suggest the premotor cortex to be involved in execution of a trained skill. Left premotor cortex (BA 6) has been associated with planning of motor movements (Deiber et al., 1996). Important results are also presented in a study on a motor sequence-learning task by Doyon and colleagues (2002). In a serial reaction time task they demonstrated cerebellar, premotor, parietal and cingulate activation in the early phase of learning. This same cortical and cerebellar activation however decreased as movement execution became ‘automatic’, by contrast a new distributed neural network, namely striatal, ventrolateral prefrontal cortex, SMA, precuneus and inferior parietal cortex activation appeared. Similarly to their study

we also found premotor and precuneus activation, but as well a strong unilateral left hemispheric activation in parietal cortex and association areas.

In another study on mirror reading learning, Poldrack and colleagues (1999) found a learning related decrease in activation for the parietal cortex. The parietal lobes have long been thought to play an important role in visuospatial analysis and attention in general. A recent repetitive transcranial magnetic stimulation (rTMS) study investigating temporal dynamics of parieto-frontal network in subjects performing a spatial WM task suggested the posterior parietal cortex to be activated when spatial information has to be maintained. Another function that was attributed to the left parietal cortex was motor attention (Rushworth et al., 2001). There is unanimous consensus that in human subjects, the right hemisphere plays the pre-eminent role in controlling visuospatial attention (De Renzi, 1982; Mesulam, 1981; Critchley, 1953). Because the parietal cortex has also been linked to phonological storage, we postulate that the activation may reflect the development of a stronger representation of the phonological store over practice. Chen and Desmond (2005a) and Desmond (2001) found evidence for the parietal cortex showing load dependent increases in activation during verbal working memory but not during an articulatory control task that requires no phonological storage. There is a strong functional connection in the fronto-parietal network reported in previous neurophysiological and fMRI studies (Courtney et al., 1998; Leung et al., 2002; Sakai et al., 2002) providing that the posterior parietal cortex and DLPFC mediate spatial working memory (WM) tasks. This could also be a possible explanation for the additional DLPFC activation in late mirror reading.

Conclusion

The pattern of brain activation in this event-related fMRI study has to be analyzed as a function of behavioral performance in mirror-reading (MR) procedure. In this respect, the decrement of response times during training and in comparison to the first scanning session, can be considered as an index of learning and automatization of the MR procedure. In some studies, practice effects have been shown to increase (Grafton et al., 1992; Iacoboni et al., 1996; Karni et al., 1995) or decrease (Andreasen et al., 1995 a, b; Garavan et al., 2000; Haier et al., 1992) task-related functional activity. It is important to note that a general decrease in activation in some of the areas originally involved during naïve performance of the task has also been observed in other studies of cognitive skill learning (Andreasen et al., 1995a, Fletcher et al., 1999).

Practice has also been observed to alter the functional neuroanatomy of a particular task (Petersen et al., 1998; Petersson et al., 1999; Sakai et al., 1998; Shadmehr and Holcomb, 1997). Those studies showed a shift in cerebral structures recruited over the course of learning. A consensus has not yet been reached as to the underlying neural mechanisms responsible for these changes. However, theories based on increased neural efficiency (Andreasen et al., 1995 a, b) and functional neuroanatomical re-organization (Petersen et al., 1998) have been proposed. Alternatively, there could be decreased demand or effort involved in adapting to the mirror reading task.

Regardless of the neural mechanisms, the consequences of practice-related changes in network function may be detectable with neuroimaging. This is in concert with many fMRI studies that demonstrate reduced BOLD effect after repeated scan sessions (Buckner et al., 1995; Reber et al., 1998).

The lack of a shift to new areas over the course of learning suggests that the decline in activation seen in some areas (i.e. striatal) might be associated with an increased neural efficiency rather than a change in the cognitive processes used for procedural learning. In accordance with the conclusions drawn by Jansma and colleagues (2001), this could indicate that both early and late phases of learning investigated in the present experiment have the same functional anatomic substrate, but differ in efficiency.

Due to a lack of statistical power and the small sample size, no second-level *t*-tests within the fMRI analysis, treating each subject as a random variable, were performed. Thus, the results do not allow generalization of the population by accounting for inter-subject variance and study population was too small to make population based interferences, but this study gives further proof of implication in striato-frontal involvement in procedural learning during the mirror reading task. However, the results suggest the requirement of recruitment of a fronto-parietal network for automatic mirror reading. As for learning this procedure our results support the evidence that fronto-striatal loops seem to be involved in this very early phase of procedural learning, acting as an effective network for acquisition of mirror reading. According to our data and previous studies of skill learning we postulate that there is no learning-specific distinct neural network associated with the processing of mirror-reversed words before and after extensive training. We rather postulate a common network in cognitive skill acquisition with a critical role of the prefrontal cortex and the caudate nucleus. Together, the observations assembled by this experiment support the participation of a fronto-striatal network in cognitive skill learning.

Finally, to better understand the real dynamic plasticity occurring during learning and automatization of a skill; it is necessary to use functional and effective connectivity analyses, which define the temporal correlation between the time courses of activation of several regions and the influence of one neuronal population over another. To further clarify the neural systems that underlie procedural learning in humans, fMRI studies with patients suffering from disorders which involve basal ganglia (i.e. striatal) impairment, such as HD, PD and Gilles de la Tourette syndrome, are necessary.

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Annex

Background of the fMRI analysis: The general linear model

SPM ("Statistical Parametric Mapping") is a massively univariate approach, meaning that a statistic (e.g., T-value) is calculated for every voxel using the "General Linear Model".
In fMRI, the most common way of analysing functional data is based on this mathematical model, the General Linear Model (GLM). In fMRI, with continuous scanning normally carried out, the signal can clearly overlap between images. Therefore fMRI analyses in addition take into account details of the time-series. In GLM, the statistical test is carried out between the actual data and a predicted model. If the fit between the predicted and actual data is good, then the conclusion is that there is a relationship between the actual data (voxel intensity values) and task-related factors (for example, such as mental rotation processes).
Consider a primitive case where there is one independent variable (say mirror reading), then the model can be expressed as a linear relationship:

$Y(j) = \Sigma \beta_i X(j) + c + E(j)$

where Y is the dependent variable (i.e. the intensity for a given voxel),
j refers to a given scan,
$\Sigma \beta_i$ is the parameter estimate of X (or the gradient of the line, if the equation were represented graphically),
X is the independent variable (e.g. mirror reading),
c is the constant (or intercept on the graph),
and E is the error term.
If there is a good fit between the psychological factor and voxel values, then the gradient of the line (i.e $\Sigma \beta_i$.) would be significantly greater than zero.
This can be statistically tested by calculating a t-statistic, which is:
Gradient of the slope ($\Sigma \beta_i$) / standard error of the slope.

Hence, a high gradient (or $\Sigma \beta_i$) compared to a low standard error would produce a significant association between voxel activation and some psychological factor. The model can be extended to more than one independent variable easily. For instance, for two independent variables – (executive function and mirror reading), the formula would be:

$Y_{(j)} = \Sigma\ ß_i\ x1_{(j)} + \Sigma\ ß_i\ 2\ x2_{(j)} + c + E_{(j)}$

Where $\Sigma\ ß_i$ x1 refer to executive function, for instance, and $\Sigma\ ß_i$ 2 x2 refer to memory load. For executive function, one would expect $\Sigma\ ß_i$ 1 to be high compared to the standard error of the slope, while $\Sigma\ ß_i$ 2 would not be significantly different from zero. Meanwhile, one would expect x2 to be high relative to the standard error for mirror reading, but x1 not to be different from zero. Such contrasts can be made more explicitly, with t-scores for one independent variable subtracted from another on a voxel-by voxel basis. After the subtraction, whatever t-scores at any voxel survive the threshold used those are taken to be significantly more active for one variable compared to another.