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Role of the basal ganglia in conditional associative learning : a multidisciplinary approach

Fadila Hadj-Bouziane

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**'Role of the basal ganglia in
conditional associative learning :
a multidisciplinary approach'**

**'Rôle des ganglions de la base dans l'apprentissage associatif conditionnel :
une approche multidisciplinaire'**

Fadila HADJ-BOUZIANE

Directeurs de thèse :

Dr. Driss BOUSSAOUD - Dr. Martine MEUNIER

JURY :

**Pr. Marc Jeannerod, Président
Pr. Bioulac, rapporteur
Dr. Apicella, rapporteur
Pr. Dubois, examinateur
Dr. Burnod, examinateur
Dr. Driss Boussaoud**

Rôle des ganglions de la base dans l'apprentissage associatif conditionnel : une approche multidisciplinaire

RESUME en français

Avec l'expérience, nous acquérons une panoplie de règles, associations arbitraires entre des stimuli externes et des actes moteurs, qui nous permettent d'adapter notre comportement à l'environnement (apprentissage associatif conditionnel). Ce type d'apprentissage met en jeu les boucles reliant les ganglions de la base (GGB) et le cortex frontal. Ce travail visait à préciser le rôle des GGB dans l'apprentissage de règles visuo-motrices conditionnelles en utilisant plusieurs approches : 1) l'enregistrement de l'activité des neurones du striatum chez le singe éveillé, 2) l'étude chez des patients atteints de la maladie de Parkinson (une pathologie neurodégénérative touchant les GGB) et 3) la neuroimagerie fonctionnelle chez l'homme sain. Les résultats des trois expériences convergent pour indiquer que les GGB sont impliqués à la fois dans l'acquisition et la rétention des associations visuo-motrices.

Role of basal ganglia in conditional associative learning : a multidisciplinary approach

RESUME en anglais

The arbitrary mapping of sensory information onto action forms an important element of the intelligent behavior of primates (also called conditional associative learning). The cortico-basal ganglia-thalamo-cortical loops are thought to play a key role in such behavior. The present research was undertaken to investigate the role of the basal ganglia (BG) in conditional visuo-motor associative learning using three complementary approaches: 1) single-unit recordings in awake monkeys, 2) behavioral testing in patients suffering from Parkinson's disease (a neurodegenerative disease affecting the BG), and 3) functional neuroimaging in healthy subjects. The results of all three studies converge to indicate that the BG are involved in both the acquisition and the retention phases of visuo-motor associations.

DISCIPLINE : Neurosciences

MOTS-CLES

Ganglions de la base, striatum, système fronto-striatal, apprentissage visuo-motor conditionnel, neurophysiologie, singe, neuropsychologie, Maladie de Parkinson, IRMf, approche multidisciplinaire

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OVERVIEW

In the typical course of daily events, we make a variety of body movements on the basis of what we sense in our environment. Often, we gaze at an object present in our peripersonal space (e.g. a cup of coffee), attend to its features and place, reach toward it, and grasp it. Such movements were termed by Wise and colleagues (1996) *standard sensorimotor mapping* in that the movement is mapped accurately onto the target of action. The brain uses the location of the object to guide the hand through space, and the shape, size and texture of the object to form the appropriate grasp (Jeannerod, 1997). This type of visuomotor transformations relies on direct, cortico-cortical connections linking the occipito-parietal visual pathway (dorsal visual stream), which processes visuospatial information, to the frontal motor and premotor regions, which control the selection, planning and execution of voluntary movements (Figure O1)

However, mammals in general, and primates in particular, perform far more than simple standard movements. Through evolution, the brain has developed a tremendous capacity to link sensory information to motor responses through purely arbitrary rules. In humans, this *non-standard* mapping (Wise et al., 1996) is present in numerous everyday activities. Abilities such as car driving and phone handling depend on it, as do many language-related skills. We have all learned to stop at a red traffic light and to go at a green one, or to wait for a specific tone before dialing a phone number and to hang up when hearing a busy signal. Likewise, reading is based on learned relationships between the visual form of letters and the movements necessary to pronounce them. Arbitrary sensorimotor associations are also of highly adaptive value for nonhuman primates living in their natural habitat. For example, African vervet monkeys learn through experience to select an escape response according to the specific sound of their conspecifics' alarm calls. Schematically, one sound instructs to stand up, peer into the surrounding grass and watch for a snake, another, to flee into trees away from a leopard, and still another, to run into bushes to hide from an eagle (Cheney & Seyfarth, 1990).

Understanding how arbitrary sensorimotor associations are learned, and how they are retrieved and used when the context requires them, has been one of the challenging issues for cognitive neuroscience. Experimental tasks have therefore been designed in order to assess this type of associations in laboratory situations. Generally, these experimental tasks use two or more stimuli taken from the same category (colors, tones, pictures, positions etc.) and an

equivalent number of motor responses, also from the same class (hand postures, lever displacements, etc.). Subjects, whether human or nonhuman primates, are required to learn and then execute arbitrary rules such as 'if green go right, if red go left'. Hence, these tasks are often referred to as 'conditional' associative tasks. A noteworthy particularity of conditional tasks is that all stimuli being equally associated with reward (or success), correct responses cannot be driven by simple stimulus-reward associations (i.e. approach the rewarded item or class of items, and avoid the non-rewarded one). Instead, subjects must link a stimulus with a response which in turn leads to reward. In their vast majority, experimental studies have focused on how visual stimuli are mapped onto motor responses, in part because the brain organization of vision is better known than that of other sensory modalities. A few experiments on auditory-motor associations suggest, however, that results obtained for vision could apply to other modalities as well.

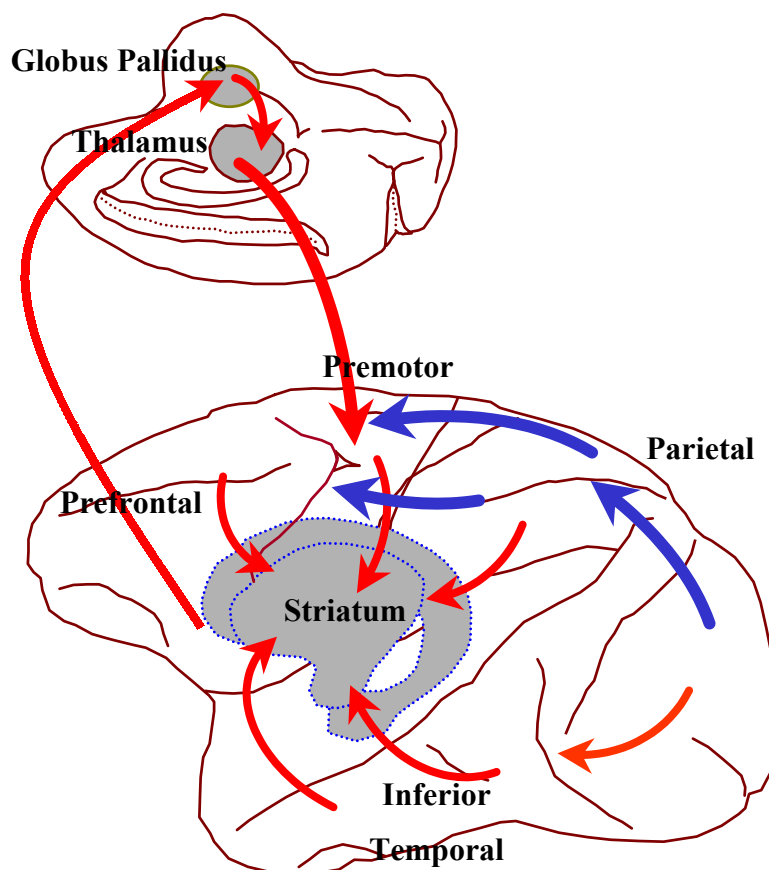


Figure 01. Schematic representation of the cerebral substrates of standard (blue) and non-standard (red) sensorimotor mapping. The former relies on the dual parieto-premotor pathway controlling reaching and grasping, whereas the latter involves a more complex network centered on the loop linking the premotor cortex to the striatum.

Over the last two decades, investigation of the neural bases of conditional visuomotor associations has relied on a combination of four main approaches, human neuropsychology in brain-damaged patients, experimental lesions in monkeys, imaging studies in healthy human subjects, and electrophysiological recordings in intact, awake monkeys. Valuable insights have been gained that indicate that non-standard mapping involves a complex brain network through which the posterior sensory cortices (in particular the dorsal and ventral visual streams), but also the prefrontal cortex, the hippocampal region, and possibly the cerebellum, interact with the loop linking the lateral premotor cortex to the basal ganglia, via the thalamus (Figure O1). Much remains to be done, however, to fully understand the specific contribution of each of this network components to the complex processes underlying arbitrary sensorimotor associations.

Four years ago, at the time the present project was initiated, available data provided strong evidence that the dorsal portion of the lateral premotor cortex (PMd), a region well-known for its role in motor preparation, plays an important role in arbitrary visuomotor associations. Briefly, damage to PMd in humans (Halsband & Freund, 1990) and monkeys (e.g. Halsband & Passingham, 1985) had been found to profoundly disrupt both the acquisition of new associations and the execution of well-learned ones. In addition, single-cell recordings had not only revealed neural properties in PMd cells likely to reflect the selection of action in response to sensory cues in over-trained monkeys (Boussaoud & Wise, 1993a,b), but had also demonstrated the existence, within PMd, of a learning-related plasticity in animals engaged in the acquisition of novel associations (Mitz et al., 1991). By contrast, knowledge regarding the role of the basal ganglia, and in particular, of its main input structure, the striatum, which is intimately linked with PMd, was scarce. A few neuropsychological studies of patients suffering from Parkinson's disease, one of the main pathologies affecting the basal ganglia, had provided contradictory findings as to whether or not these patients remained able to learn conditional associative tasks (e.g. Gotham et al., 1988; Pillon et al., 1998), and, among them, only one had specifically addressed the issue of sensorimotor (as opposed to sensory-sensory) arbitrary associations (Canavan et al., 1989a). Lesion studies in monkeys had provided only indirect evidence of a basal ganglia involvement by demonstrating an impairment following damage to the thalamic relays that convey information from the basal ganglia to the frontal cortex (Canavan et al., 1989b). Likewise, few electrophysiological data were available. Some, recorded in well-trained animals, strongly suggested that the striatum does possess the neural properties necessary to store

arbitrary sensorimotor associations, but little was known on how these properties emerge during learning (Boussaoud & Kermadi, 1997).

In this context, the present research was undertaken in order to specifically test the hypothesis of a pivotal role of the basal ganglia in the learning of new conditional visuomotor associations. In order to obtain converging evidence, the original plan was to combine the four approaches hitherto used in the field by combining: 1) electrophysiological recordings in the monkey striatum during learning of a visuomotor conditional task, 2) reversible inactivation of different striatal subregions in the same animals, 3) a neuropsychological evaluation of the ability of patients with Parkinson's disease to learn such a task, and 4) a brain imaging study of the neuronal correlates of this type of learning in the normal human subject. The single-cell recordings were intended to demonstrate the existence of a learning-related plasticity within the striatum, and compare it to that described in PMd. The monkey and human lesion studies were aimed at providing further evidence that the basal ganglia are indeed necessary for normal learning. Finally, the imaging technique was seen as a unique tool to investigate different stages of learning, and evaluate how these two parameters affect activation in the basal ganglia and their anatomical connections, in particular in the frontal lobe. In all experiments, the subjects (monkeys, Parkinson's patients and healthy human subjects) had to learn the same type of arbitrary associations, or rules, between visual cues and either hand or finger movements.

Because the reversible inactivation study has not yet been completed, the present report will focus on three experiments. In the first experiment, we recorded single unit activity in the striatum while monkeys either executed familiar associations (acquired prior to the recordings), or learned novel ones. The results identified strong learning-related changes of neuronal activity in the striatum, which were either transient (i.e. selectively occurring during early learning stages), or relatively long lasting (i.e. persisting through both early and late stages of learning). These results demonstrate for the first time that the learning-related changes that have been described earlier in PMd are also present in the striatum.

In the second experiment, advanced Parkinson's patients were tested on a series of tasks to determine the possible source of their difficulties in learning conditional associations. Their performance was assessed both with (ON) and without (OFF) dopaminergic treatment, and was compared to the performance of normal controls. We found that a subgroup of PD patients had marked difficulties to learn conditional associations in the OFF condition. This deficit was associated to poor use of a compensatory strategy (termed 'motor strategy').

In the third experiment, we investigated the brain network underlying conditional associative learning using functional MRI. Learning-related activation was studied by contrasting the pattern of activation observed during the early phase of learning new associations (EARLY) to that observed either during the final stage of learning (LATE) or during execution of well-mastered associations (FAMILIAR). Both contrasts revealed brain activation in a network including the premotor regions, medially (anterior cingulate cortex and the presupplementary motor area) and laterally (PMd), as well as the dorsolateral (Brodmann's areas 9/46 - 10) and ventrolateral (Brodmann's areas 47/44) prefrontal cortex, the parietal cortex (intraparietal sulcus, precuneus), the right inferior temporal gyrus, and the cerebellum. Interestingly, subcortical regions, and more precisely, the striatum and mediodorsal thalamic nucleus, were found to be equally active during EARLY and FAMILIAR stages, but less importantly recruited during the LATE stage.

Taken together, the findings of these experiments not only confirm a role of the basal ganglia in the learning and use of arbitrary rules, but also improve our understanding of the dynamics of activity changes in the striatum and the precise source of the deficits related to dopamine depletion in Parkinson's patients. In the following chapters, an Introduction on the anatomy and function of the basal ganglia will be presented, before describing data from each of the three experiments. The overall contribution of this research to current understanding of the basal ganglia involvement in nonstandard mapping will then be discussed in a final General Discussion section.

A - Introduction

SECTION 1 - BASAL GANGLIA ANATOMY

The basal ganglia (BG) are the largest subcortical nuclei in the human brain. They form a functional system consisting of several structures. The naming of the BG has led to some confusion over the years as to which structures should be included within this description. Now, it is generally admitted, albeit not unanimously, that the BG include the caudate nucleus and the putamen (which are collectively referred to as the striatum), the globus pallidus, the substantia nigra and the subthalamic nucleus. These nuclei are heavily interconnected. Specifically, they are organized in functional loops, the cortico-basal ganglia-thalamo-cortical loops. Dysfunction of the BG, and of the functional loops they are involved in, leads to major motor disorders such as Parkinson's disease (characterized by hypokinesia) and Huntington's disease (characterized by hyperkinesia). There is, however, growing evidence that the BG are not important solely for the preparation, initiation and execution of complex automatic and voluntary movements, but contribute as well to non-motor, cognitive and motivational functions.

I. THE BASAL GANGLIA CONCEPT : HISTORICAL EVOLUTION

The first clear identification of the 'basal ganglia' was published by the English anatomist Thomas Willis in 1664, in his basic foundational text on the anatomy of the central nervous system, *Cerebri Anatomie*, written in Latin (Figure A1, cf. Parent, 1986). The term 'basal ganglia' was not yet introduced. These subcortical structures were then denominated as the '*corpus striatum*', and included the caudate nucleus, the putamen and the globus pallidus. Two characteristics drew attention to them. First, their central position in the brain suggested that they should play an important role. Second, massive ascending fibers projecting to them and descending fibers emerging from them raised the possibility that the BG might both receive all sensory modalities and initiate all motor acts.

By the 18th century, subsequent research shed light on the cerebral cortex, leaving the corpus striatum in the dark. Indeed, the attractiveness of the histological organization of the cortex, and the possibility of localizing higher mental functions drew many neurologists of both the 18th and 19th centuries to cortical research.

In 1876, the British neurologist David Ferrier introduced the English term basal ganglia, as an adaptation of the German term 'Stommganglion' previously proposed by Forel

in 1872. During the 20th century, for the majority of the neuroanatomists, the term basal ganglia (also called basal nuclei) referred to the corpus striatum of Willis.

At the beginning of the 20th century, these structures began to gain importance once again with the discovery that their lesions often result in disorders of motor functions in humans (Wilson, 1914, [see page 16](#)). There were serious attempts to provide detailed comparative descriptions of the corpus striatum (Wilson, 1914; Cajal, 1911; Vogt & Vogt, 1920). Vogt & Vogt (1920) published descriptions of the connections between the thalamus and corpus striatum. This accumulation of data was accompanied by controversies regarding the list of structures composing the BG, apart from the corpus striatum of Willis. This lack of consensus explains the famous sentence of Thomas Thach: *'the basal ganglia are no longer mysterious now they are just confusing'*. Parts of the thalamus, the amygdala, and the claustrum, have all in turn been viewed as part of the BG, before the currently predominant view including the substantia nigra and the subthalamic nucleus emerged.

Over the 2nd half of the 20th century, the corpus striatum came progressively to be viewed as the major component of the "extrapyramidal motor system" (Parent, 1986), a system responsible for coordinating and integrating various aspects of motor behavior or body movements. Its "motor" role has been extensively studied. More recently, it has been implicated in various cognitive functions.



Figure A1 : Thomas Willis portrait. Thomas Willis (1621-1675) published the first description of the basal ganglia

(From American Academy of Neurology Rare Neurological Book Collection, Becker Library, Washington University, St Louis, MO, USA)

The exact nature and function of the large mass of basal grey matter known as the corpus striatum have hitherto constituted, it is no exaggeration to say, one of the unsolved problems of neurology. Not that the corpus striatum has failed to attract the attention of anatomist, physiologist, and clinician; on the contrary, since the day of Willis, it has received its full share of investigation along all the familiar lines. The disturbing element in the matter of research into its function has been the conflicting nature of the results obtained. Anyone who will take the trouble to read the curiously philosophical text-books of half a century ago would imagine, it is true, that the corpus striatum, was an organ as high in the cerebral hierarchy as the cortex itself, endowed with motor functions as elaborated and as detailed. But a change took place when neurologists realized that many of the functions assigned to it were the property of all adjacent corticospinal paths, and almost at once it seems to fall from its high estate and depreciate in physiological significance. Under these circumstances the question of its function became an enigma, and, as a consequence, there was eventually assigned to it a varied assortment of motor, sensory, vasomotor, physical, and reflex functions, no one of which, it is safe to say, has ever rested on unequivocal evidence

S.A.K Wilson pp. 428

(An experimental research into the anatomy and physiology of the corpus striatum. Brain 36: 427-492; 1914)

II. THE BASAL GANGLIA COMPONENTS (FIGURE A2)

From a functional and clinical point of view, the BG include the striatum (caudate and putamen) and the globus pallidus, together with two brain stem nuclei, the substantia nigra and the subthalamic nucleus (Carpenter, 1981), which are derivatives of the diencephalon and mesencephalon, respectively. Despite their phylogenitically and ontogenetically distinct origins, these brain stem nuclei are parts of the functional system that arise from the cortex, pass through the striatum, the pallidum and substantia nigra, the thalamus, and project back to the frontal cortex. The striatum constitutes the input stage of the BG. It receives information from virtually all cortical areas as well as from several subcortical areas, including most of the neuromodulatory systems. In this section, a description of the BG will be provided with special emphasis on the striatum.

1. The striatum

The term ‘striatum’ was first introduced by Vogt & Vogt in 1920 to refer to the telencephalic ensemble formed by the caudate nucleus and the putamen. It consists of the largest component of the BG and is considered to represent the first stage of neural computation in the BG.

The caudate nucleus is a large C-shaped structure located medial to the internal capsule. The term derived from a Latin word that means ‘having a tail’. It has an enlarged rostral component (head) that bulges into the lateral wall of the frontal horn of the lateral ventricle. The body in turn becomes further attenuated to form the tail which terminates at the amygdaloid nuclei. The body follows the lateral wall of the lateral ventricle. The tail occupies a position in the roof of the inferior (temporal) horn of the lateral ventricle. In essence, the caudate nucleus follows the curvature of the lateral ventricle.

The putamen is a shell-shaped structure situated medial to the cortex of the insula and surrounded laterally by the external capsule, medially by the lateral medullary lamina of the globus pallidus, and dorsally by the white matter of the corona radiata.

In primates, the putamen and caudate nucleus are incompletely separated by the internal capsule. The two nuclei form a homogenous component, sharing anatomical and cytological similarities (DeLong & Georgopoulos, 1981). They are continuous at the base of the hemisphere around the anterior limb of the internal capsule and are linked by scattered cells that bridge across the anterior limb of the internal capsule. The head of the caudate

nucleus and the putamen are connected by thin bridges of grey matter (pontes grisei caudatolenticularis). The name striatum or striate body is derived from the striated (striped) appearance of the internal capsule as it passes through these nuclei. In rodents, the two structures are not separated by the internal capsule, and are therefore often referred to as the caudate-putamen.

a. Anatomical subdivisions

The striatum is functionally divided into the dorsal and the ventral striatum. The dorsal striatum includes most of the caudate nucleus and the putamen while the ventral striatum comprises the medial and ventral parts of the caudate/putamen, the adjacent nucleus accumbens, and the striatal part of the olfactory tubercle. Allo- and periallocortical areas project principally to the ventral striatum, and neocortical areas project mainly to the dorsal striatum (e.g Lynd-Balta & Haber, 1994). It is on the basis of this regional organization that the dichotomy into limbic- vs. nonlimbic-related striatal regions has been introduced (Heimer & Wilson, 1975). Across this thesis, most of the work presented or cited will be related to the dorsal striatum.

b. Cytology

Unlike cortical cells, striatal cells are densely packed and do not exhibit any dominant configurations or laminations (Jones, 1984). However, as all other major central nervous system nuclei, the striatum is composed of both projection neurons and local interneurons corresponding to Golgi type I and type II cells, respectively, as first identified and denominated by DiFiglia et al. (1976). Still, contrary to most brain structures, the projection neurons greatly outnumber interneurons in the striatum. The ratio of projection neurons *versus* interneurons is approximately 9:1 in rodents, whereas it is 3:1 in primates (Graveland & DiFiglia, 1985).

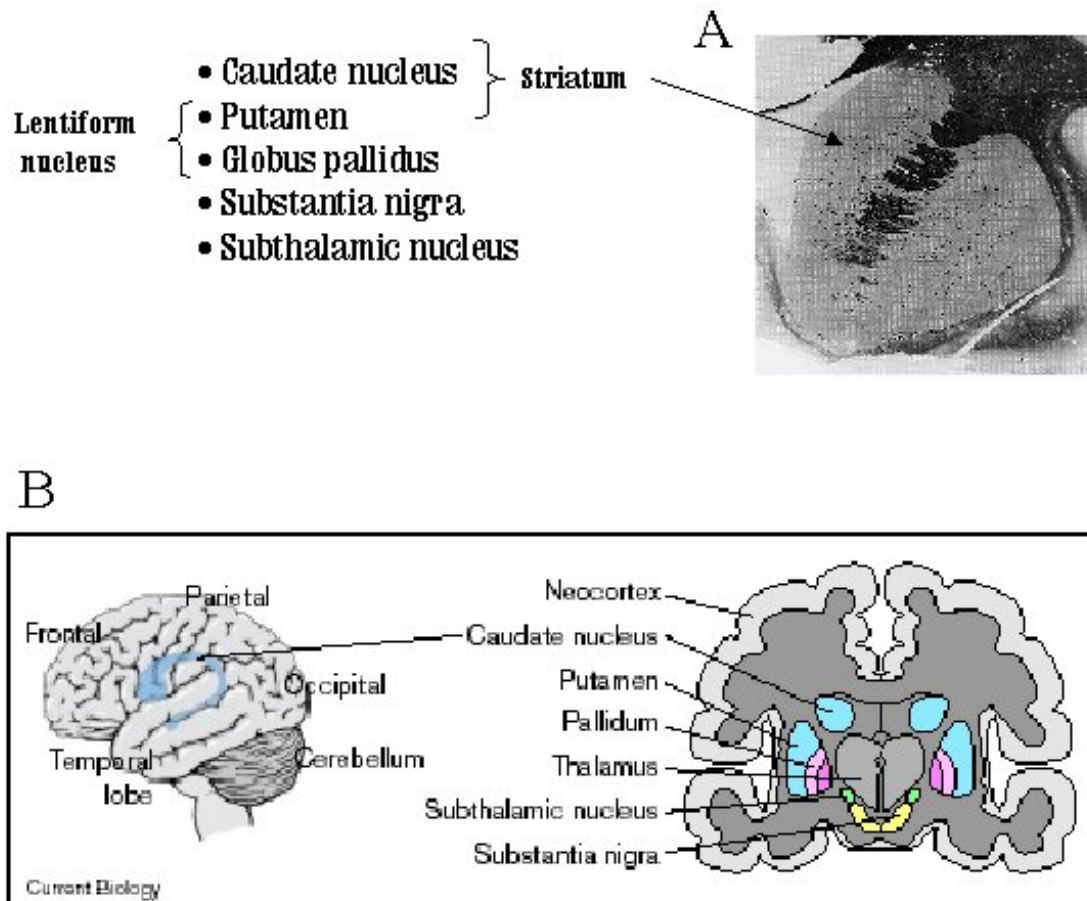


Figure A2 : Functionally defined basal ganglia components. A. Photomicrograph of the striatum. The putamen and the caudate nucleus are incompletely separated by the internal capsule (From *Gray 's Anatomy, 38th ED, Churchill Livingstone*). B. Schematic representation of the BG components. *Left*, the caudate nucleus, characterized by its C-shape form, is represented in see-through on a lateral view of a human brain. *Right*, The BG components are represented on a coronal view (from *Graybiel, 2000*)

□ *Projection neurons: the medium spiny neurons*

The striatum is primarily composed of projection neurons, originally described by Ramon y Cajal in 1911 (Graybiel et al, 1979, Kemp & Powell, 1971). They have a medium sized cell body (12-20 μm in diameter), which gives rise to 3-5 smooth primary dendritic branches, densely covered in spines (Kemp and Powell 1971; DiFiglia et al. 1976). Due to these morphological characteristics, the projection neurons have thus been termed "medium spiny" neurons. Furthermore, the axons of these neurons emit several collaterals, which arborize profusely and contact other spiny neurons (Kawaguchi et al., 1990). An example of these neurons is shown in [Figure A3](#). Striatal projection neurons utilize GABA as their primary neurotransmitter (Smith et al. 1987). They also express a number of neuroactive peptides, such as substance P, enkephalin, dynorphin and neurotensin (Bolam et al., 1983). Not all of these peptides are found in every spiny neuron. The expression of these peptides seems to be related to the target nuclei of the spiny cell.

Neostriatal spiny neurons exhibit spontaneous fluctuations in membrane voltage which consist of transitions between two preferred potentials (Wilson & Groves, 1981), a relatively depolarized level referred to as the Up state (-55 mV) and a more polarized condition termed the Down state (-77 mV; see Wilson, 1993 for review). Action potentials are only generated from the Up state. The spiny cells are thus electrically quiescent in the absence of any extrinsic influence and require massive, relatively synchronous excitatory inputs to produce state transitions and spike triggering. As a consequence, they exhibit low firing rates (< 0.01 - 0.5 Hz), and short duration extracellular action potential waveforms (Alexander & DeLong, 1985). The main striatal inputs, the cortical inputs, are glutamatergic, and the projection neurons have both non-NMDA and NMDA receptors (Kita, 1996). The striatum also receives dopaminergic inputs, and the projection neurons thus express dopaminergic receptors. There are two subtypes of DA receptors in the striatum. D1 receptors have an excitatory effect, and D2 receptors have an inhibitory effect (DiChiara, 1994).

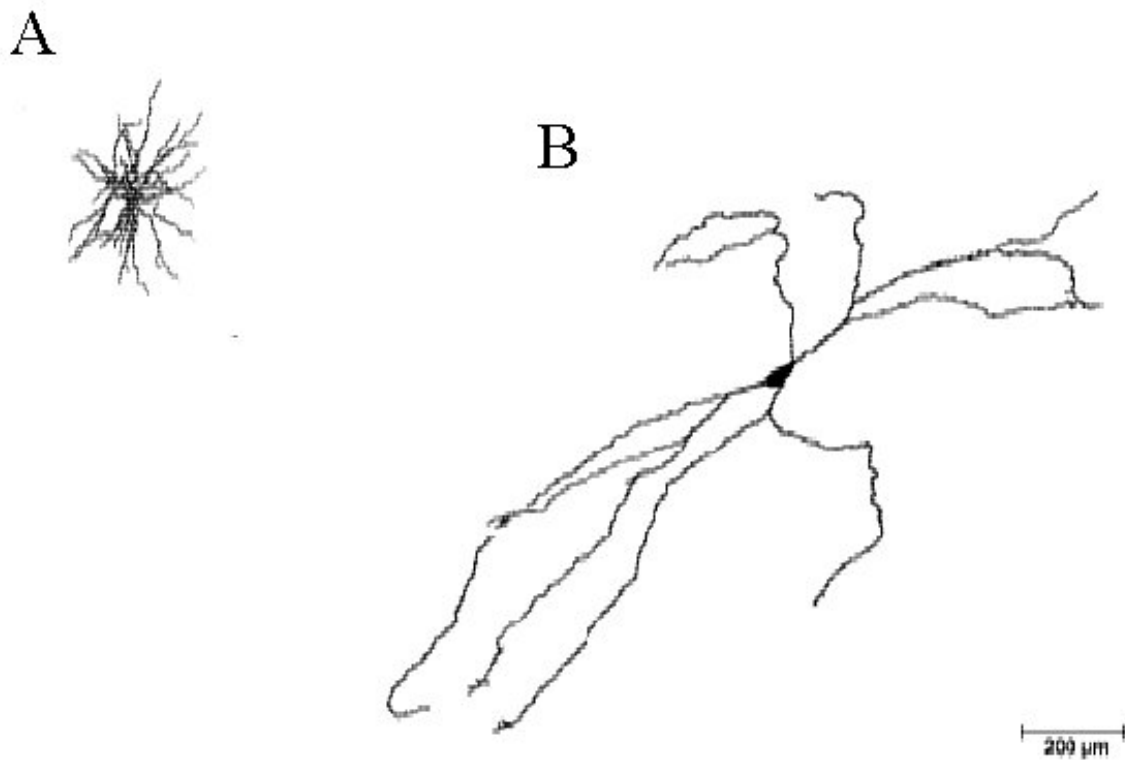


Figure A3 : Morphology of a projection neuron of the striatum (A) and a neuron from the GPe (B), after reconstruction from serial and camera lucida drawing.

Note the importance of the collaterals which arborize profusely from the striatal projection neurons and the long dendrites of the GPe neurons that can extend up to 1mm in length (*Adapted from Parent & Hazrati, 1995*).

□ *Interneurons*

Two broad categories of interneurons have been identified based on their cell diameters: the giant aspiny interneurons and the medium aspiny interneurons (see Kawaguchi et al., 1995). The giant aspiny neurons contain choline acetyltransferase (Bolam et al. 1984; Phelps et al. 1985; Graybiel et al. 1986; DiFiglia, 1987). The medium aspiny neurons include the parvalbumin-containing GABAergic aspiny cells (Gerfen et al. 1985; Kita et al. 1990). Other subcategories have also been described such as the somatostatin/NOS (nitric oxide synthase) containing GABAergic aspiny cells (for a review, see Kawaguchi et al., 1995). For the purpose of this review, there will be only a brief description of the two principal subcategories of interneurons, namely the cholinergic-, and the parvalbumin-containing neurons.

The giant aspiny cholinergic interneurons are the best known interneurons. Ramon y Cajal first considered them to be projection neurons. These cells possess large spherical, oval or elongated cell bodies (approximately 20-35 μm in diameter in rat and primate) from which 2-5 smooth or sparsely spiny dendrites radiate (Bolam et al. 1984; Phelps et al. 1985; DiFiglia 1987). They are identifiable by their content in choline acetyltransferase, the most faithful marker of cholinergic neurons (DiFiglia, 1987; Phelps et al, 1985). These neurons are supposed to correspond to the physiologically defined tonically active neurons (TANs), so called because they fire tonically yet irregularly at 2-10 Hz (Kimura et al., 1984; Bolam et al., 1984, for a review, see Apicella, 2002). Their resting potential is relatively close to the spike threshold. Pharmacological blockade of spontaneous excitatory, inhibitory and neuromodulatory synaptic inputs to cholinergic interneurons did not influence spontaneous firing in vitro, demonstrating that these cells are tonically active in the absence of any input (Bennett and Wilson, 1999).

The parvalbumin-containing GABAergic aspiny cells (fast-spiking cells) exhibit spherical cell bodies (14-15 μm) and have axons with very dense collateral arborizations (Kita et al., 1990). They display immunoreactivity to GABA and/or its synthesizing enzyme glutamic acid decarboxylase (GAD) and also to parvalbumin, a calcium-fixating protein. This class of interneurons, embedded with gap-junctions, fire phasically at high frequency in response to cortical stimulation (Kita et al., 1990).

To summarize, the striatum contains two broad categories of neurons: the projection neurons and the interneurons. The principal and more numerous cells are the spiny

projection neurons. Like pyramidal cells in the cortex, they receive most of the inputs to the striatum and send almost all the efferent fibers. Hence, they provide synaptic input to other BG nuclei and, through local axon collaterals, contact interneurons and other spiny cells. The interneurons, despite their relatively small number compared to the projection neurons, have been shown to exert a powerful control on the activity of projection neurons in the striatum. Nonetheless, like projection neurons, interneurons receive direct inputs from cortical and other afferents to the striatum. Although there are numerous morphologically distinct classes of striatal cells, typically only two types of neurons are reported in unit recording studies. The first class refers to the projection neurons, which exhibit phasic increases in firing in response to cortical stimulation (Phasically Active Neurons, PANs). The second class corresponds to the cholinergic interneurons (Tonically Active Neurons, TANs).

c. Functional domains : matrix/striosome compartments

Neurochemical evidence has allowed to subdivide the striatum into two broad compartments, the striosomes (also called patches) and the matrix (Gaybiel & Ragsdale, 1978; Graybiel, 1995). These compartments were defined by the intensity of histochemical staining for acetylcholinesterase in cats and primates (Gaybiel & Ragsdale, 1978), and by heterogeneous distribution of μ opiate receptors in rodents (Herkenham & Pert, 1981). This compartmentalization is present both in the dorsal and ventral striatum, with the exception of the shell region of the nucleus accumbens (Voorn et al., 1989).

The striosomes, which occupy only about 15% of the striatum (Johnson et al., 1990), are rich in μ opiate receptors, neurotensin and AMPA receptors. They constitute a set of discrete modules with clearly defined boundaries. They are surrounded by a large matrix, which is rich in AChE, somatostatin and calbindin. Striosome-like domains have been identified in the matrix (Graybiel et al., 1994; 1995), and have been termed 'matrisomes'. Individual cortical cells projecting to the matrix often form several small discrete arborizations of approximately the same size as those in the striosomes (Kincaid et al., 1998). This particular architecture provides the striatum with a discrete modular organization in a way that is analogous to the columnar structure of the cortex. Spiny neurons strictly obey the striatal compartment boundaries, with cells in the striosomes keeping their dendritic fields restricted to the striosomes and cells in the matrix having their dendritic fields contained within the matrix. The TANs are largely confined to the borders of the striosomes and the matrix. Given this preferential localization, these interneurons are believed to mediate

interactions between striatal projections of both compartments (Aosaki et al., 1995; Kawaguchi et al., 1995). These interneurons have been suggested to be recipients of direct cortical, thalamic as well as dopaminergic inputs (Wilson et al. 1990) and have been implicated in striatal plasticity .

In summary, the striatum is a heterogeneous structure, exhibiting different levels of anatomical and neurochemical organization.

2. The Globus pallidus (GP)

The globus pallidus is a wedge-shaped structure located between the putamen and the posterior limb of the internal capsule. It is situated medial to the putamen and is separated from it by a thin lamina of myelinated fibers, the lateral medullary lamina. A similar lamina, the medial medullary lamina, divides the GP into a lateral (or external) segment and a medial (or internal) segment. Thus, the GP is crossed by numerous myelinated fibers which explain its characteristic appearance in stained sections and from which derives its name ‘pale body’. The term ‘lenticular or lentiform’ nucleus is sometimes applied to the putamen and globus pallidus together because of their combined lens-shaped aspect in brain sections.

The globus pallidus is divided into three functional domains: the internal (GPi), the external (GPe) globus pallidus and the ventral pallidum (VP, the more anterior part of the GP, located under the anterior commissure). Although these domains are traversed by fibers, their neuronal populations are extremely similar, and for the most part morphologically indistinguishable (Carpenter, 1981). In humans, the GPe constitutes 70% of the total volume of the globus pallidus (Thorner et al., 1975). In non primates, the GPe and GPi usually have a larger separation and are referred to as the pallidum and entopeduncular nucleus, respectively.

There is a variety of neuronal types in the globus pallidus, but all are GABAergic neurons. The majority of them has a large ovoid body (20-60 μm in their long axis), with four to five long, thick and relatively smooth dendrites (Francois et al., 1984). The large dendrites can extend up to 1mm in length as illustrated in [Figure A3](#). In rodents, it has been shown that the dendrites form a discoidal dendritic field and are disposed perpendicularly to striatal afferent axons (i.e. parallel to the lateral medullary lamina separating the globus pallidus from

the putamen). This positions the dendritic fields so as to intercept maximal numbers of striatal afferents (Park *et al.* 1982). GP cells are 100 times less numerous than spiny striatal neurons, which suggests a numerical convergence of striatal projections neurons on pallidal cells.

3. The substantia nigra (locus niger)

The substantia nigra is the largest single mesencephalic nucleus. It lies in the ventral tegmentum of the mesencephalon, forming an elongated nucleus that runs throughout the midbrain (Figure A2). It is divided into two components that have different connections and distinct neurotransmitters, a more ventral part with low cell density, the substantia nigra pars reticulata (SNr), and a dorsal part with high cell density, the substantia nigra pars compacta (SNc). The latter is composed of large neurons exhibiting a characteristic black pigmentation; hence the origin of the structure's name ("black substance or locus niger"). Neurons of the SNc use dopamine as a neurotransmitter and project primarily to the striatum. Neurons in the SNr project principally to the thalamus (ventral anterior, ventral lateral and mediodorsal nuclei) but also to brainstem nuclei (superior colliculus, pedunculopontine nucleus) and use GABA as neurotransmitter. These neurons fire regularly and continuously at a very high rate (up to 100 Hz at rest; Chevalier & Deniau, 1990).

4. The Subthalamic nucleus (Luys Body)

The subthalamic nucleus is a biconvex structure located on the medial side of the internal capsule (Figure A2). It was discovered in 1865 by the French doctor Jules Bernard Luys, and was later named Luys body by August Forel, in recognition of its discoverer. Luys not only discovered the subthalamic nucleus, but he was also the first to think of this structure as being intimately linked to the BG. Among the BG neurons, the subthalamic neurons represent the only excitatory ones, using glutamate as their neurotransmitter.

In summary, the BG are the largest subcortical nuclei in the human brain. They form a functional system consisting of several structures: the striatum, composed of the caudate nucleus and the putamen, the globus pallidus (internal, external, and ventral segments), the substantia nigra (pars compacta and pars reticulata) and the subthalamic nucleus. From the morphological characteristics of the different components of the BG, two important features should be outlined. First, as illustrated for the PANs striatal neurons and GP neurons (Figure

A3), the BG neurons exhibit large dendritic fields and important axonal collaterals. Second, there is a dramatic decrease of cerebral tissue volume from the cerebral cortex to the striatum as well as within the BG structures. Yelnik and co-workers (2002) have made a computer-aided, three dimensional cartography of the BG (cf Figure A4). They found that the volume of the striatum is 12 times larger than that of the GPe, 20 times larger than that of the GPi and SNr, and 60 times larger than that of the STN. It has been proposed an estimated convergence of about 30:1 (rat) to 80:1 (monkey) for striatal projections onto their target neurons. Anatomically, the striatopallidal system is thus characterized by a considerable volumic, numeric, as well as geometric convergence. These features obviously denote an important and

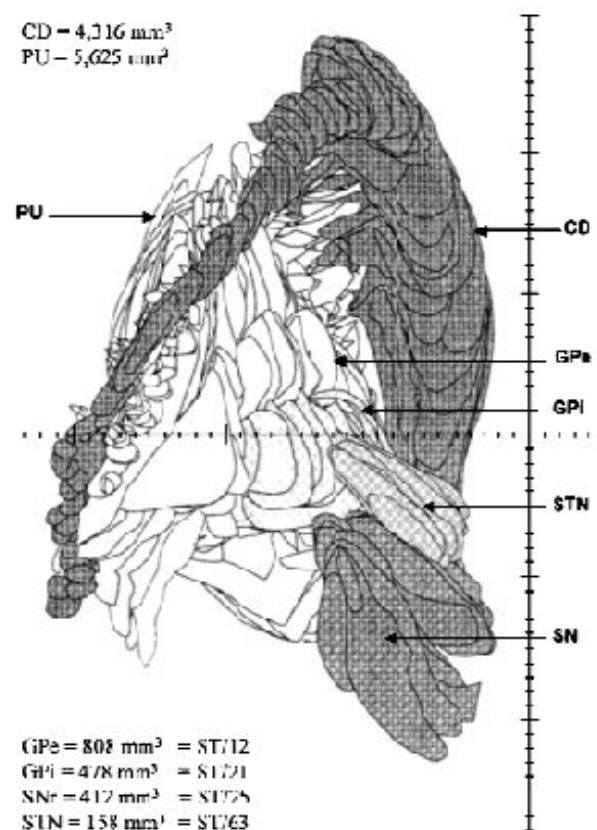


Figure A4 : Volumetric convergence as represented in a posterior view of the BG in humans. Yelnick and colleagues have developed a computer-aided, three dimensional cartography of the basal ganglia to represent the degree of convergence throughout the different components (top) and have estimated the volume of the GPe, GPi, SNr and STN as a function of the volume of the striatum (bottom)
 ST, striatum; GPe, GPi, Globus pallidus, external and internal segments, respectively; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; CD, Caudate Nucleus; PU, Putamen (from Yelnik, 2002).

complicated pattern of connectivity between these different nuclei.

III. INPUTS TO THE BASAL GANGLIA AND 'THE BASAL GANGLIA LOOPS'

The BG are classically viewed as part of neural circuits that arise from the cortex, pass through the striatum, the pallidum and substantia nigra, the thalamus, and project back to the cortex, especially the frontal cortex (Figure A5). The striatum constitutes the input stage of the BG. The GPi and SNr constitute the principal output stages of the BG. The striatum receives projections from almost all cortical areas, as well as from subcortical areas, including most neuromodulatory systems. Among these afferent inputs, the projections arising from the cortex are by far the most prominent, and originate mainly from the ipsilateral cortex. Depending on the striatal target, they arise from neurons located in either supragranular and infragranular cortical layers (Gerfen, 1990). These cortical projections are of particular interest as they seem to impose upon the striatum a pattern of functional organization that is maintained throughout the BG, i.e. what is known as the BG loops or the cortico-basal ganglia-thalamo-frontocortical circuits. In addition to their close relationship with the frontal cortex, the BG nuclei send outputs to brainstem nuclei involved in motor control, including the superior colliculus, which controls axial orientation and saccadic eye movements.

1. The cortico-striatal projections : a funneling or a parallel processing?

The existence of a corticostriatal projection had been a somewhat contentious issue until convincingly shown by Glees (1944). Subsequently, several models have been proposed, suggesting either convergence or segregation of the information processing throughout the BG. I will review some of these models below.

a. Kemp & Powell's proposal

Early investigations with the Glees (Glees, 1944) and Nauta lesion-based techniques (e.g. Nauta & Mehler, 1966) have shown the presence of cortico-striatal fibers arising from the entire extent of the neocortex. Although Cajal (Cajal, 1911) considered corticostriatal fibers to be collaterals of corticofugal projections destined for lower centers, studies using horseradish peroxidase (HRP) have clearly demonstrated that these fibers, both ipsilateral and controlateral, arise from cell populations distinct from those that form the corticospinal, corticobulbar, corticopontine, corticorubral and corticothalamic systems (Jones et al., 1977a,b). In order to characterize the organization of the cortico-striatal projections, Powell and his co-workers made lesions in virtually every areas of the cortex of 47 rabbits (Carman et al 1963) as well as in monkeys (Kemp & Powell, 1970; 1971), and plotted the ensuing

degeneration on reconstruction of the striatum. The cortico-striatal fibers have been found to constitute a massive, topographically organized projection to the striatum with a relative degree of overlap. A mediolateral and anteroposterior topography was described, with the cortex of the frontal lobe being related to the anterior part of the head of the caudate nucleus and putamen, and the visual cortex at the occipital pole to the posterior part of the striatum. In the frontal lobe, the medial surface projects dorsally in the striatum, the lateral surface laterally and the orbital cortex medially. Thus, according to the view proposed by Kemp and Powell, the cortico-striatal projections followed the '*rule of proximity, each striatal region receiving projections from the nearest overlying cortical area*' (Parent & Hazrati, 1995a).

From these data, Kemp & Powell proposed that the BG serve to integrate diverse inputs from the entire cerebral cortex and to 'funnel' these influences to the BG output and to the primary motor cortex (Allen & Tsukahara, 1974; Evarts & Thach, 1969; Kemp & Powell, 1971; Nauta & Mehler, 1966). According to this view, there is "funneling" from wide-spread cortical territories to narrower target areas in the thalamus. Thus, the BG could provide a route by which '*not only the sensory pathways but also the areas of the association cortex of the frontal and parietotemporal lobes*' could influence the motor cortex, allowing convergence of the information relevant to the initiation and control of movement (Kemp & Powell, 1971). On the basis of these anatomical findings and the motor deficits observed after BG lesions, these structures were thought to project exclusively to motor cortical areas and to participate essentially to motor functions.

b. Alexander, DeLong and Strick's proposal

The funneling model has been challenged by more recent data. First, it has been suggested that cortical projections to the striatum are topographically organized, in such a manner that non-adjacent, but functionally related regions, such as areas in the prefrontal and parietal cortices, project to close or even overlapping striatal sectors (Selemon & Goldman-Rakic, 1985; Flaherty & Graybiel, 1991). Second, the BG were found to send information not only to motor areas, but to various frontal regions as well.

In the early 1980's, DeLong and his coworkers suggested that the topographic mapping of cortical inputs provided functionally differentiated striatal subregions which in turn give rise to topographic, restricted projections to the GPi/SNr and thalamic nuclei, preserving the organization until the frontal cortex. This organization introduced the notion of parallelism (DeLong & Georgopoulos, 1981; DeLong et al, 1983; Kemp & Powell, 1970; 1971). In this view, it was proposed that there are two distinct loops through the BG, a motor

loop which links the sensorimotor and premotor cortex through the putamen, and an 'association or complex' loop passing through the caudate nucleus, which receives inputs from the association areas and return to the prefrontal cortex (DeLong & Georgopoulos, 1981; DeLong et al, 1983). In this model, the loops are relatively segregated and subserve distinct functional roles. The recognition that information originating from different parts of the cortex may remain segregated in parallel pathways that pass through the striatum to the pallidum or substantia nigra challenged the traditional view according to which the striatum serves as a kind of funnel trough which information from the cortex converges onto a limited number of output targets.

In 1986, the same group extended this new idea of segregated loops (Alexander et al., 1986, see [Figure A6](#)) by suggesting the existence of at least five loops, defined by their cortical origin: a motor loop originating in the supplementary motor area, an oculomotor loop originating in the frontal eye field, a dorsolateral prefrontal cortex (DLPF, area 46) originating loop, a lateral orbitofrontal cortex (LOF, area 12) originating loop, and a loop originating in the anterior cingulate and medial orbitofrontal cortices (AC/mOFC, areas 24 and 13) (Alexander et al., 1986). An additional feature of this scheme is that the loops are not only parallel but essentially closed, originating and terminating in the same frontal cortical region. The motor loop has received much attention because of its supposed involvement in movement-related disorders such as those observed in Parkinson's disease.

Considerable anatomical and neurophysiological evidence supports the concept of a parallel BG organization. Hoover and Strick (1993) provided the most convincing evidence in experiments using attenuated herpes virus as a transneuronally transmitted tracer of connectivity. This view posits that the BG are in a position that enables them to influence frontal regions involved not only in motor functions, but also in higher executive functions such as planning, working memory, learning, and attention.

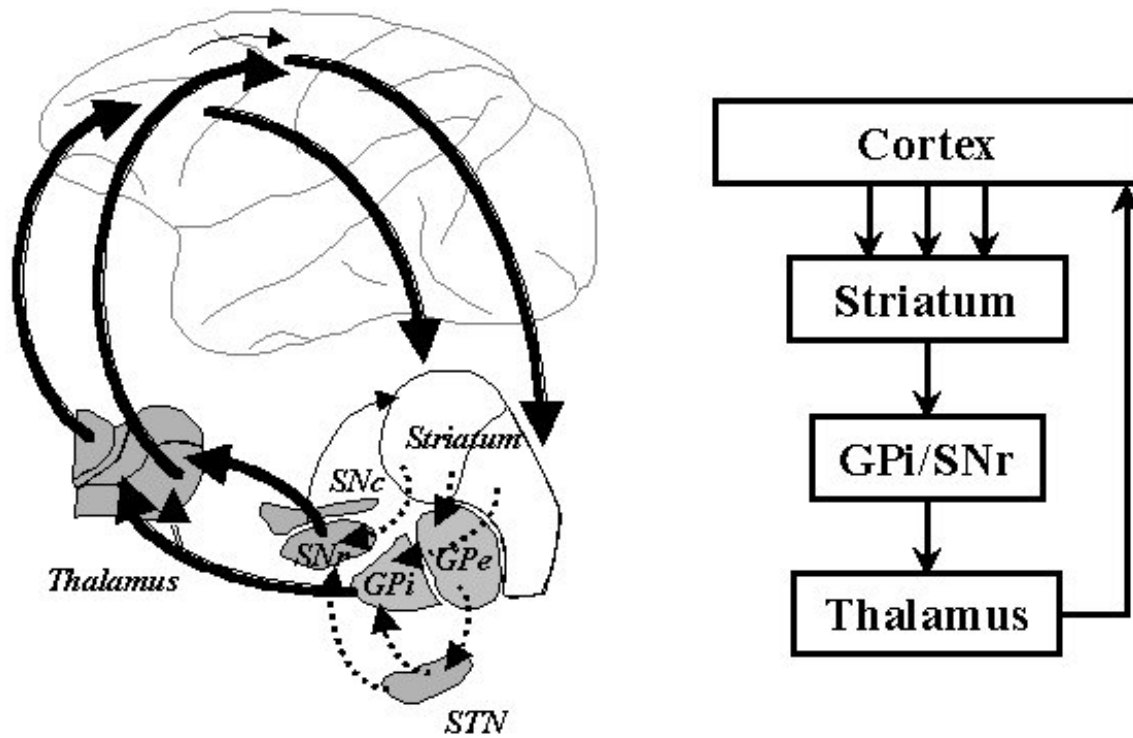


Figure A5. Schematic representation of the basal ganglia loops. Left, Prefrontal and premotor cortico-striato-thalamo-cortical loops. Right, box diagram of processing levels. Abbreviations: SNc and SNr, substantia nigra, pars compacta and pars reticulata, respectively; STN, subthalamic nucleus; GPe and GPi, external and internal globus pallidus segments, respectively.

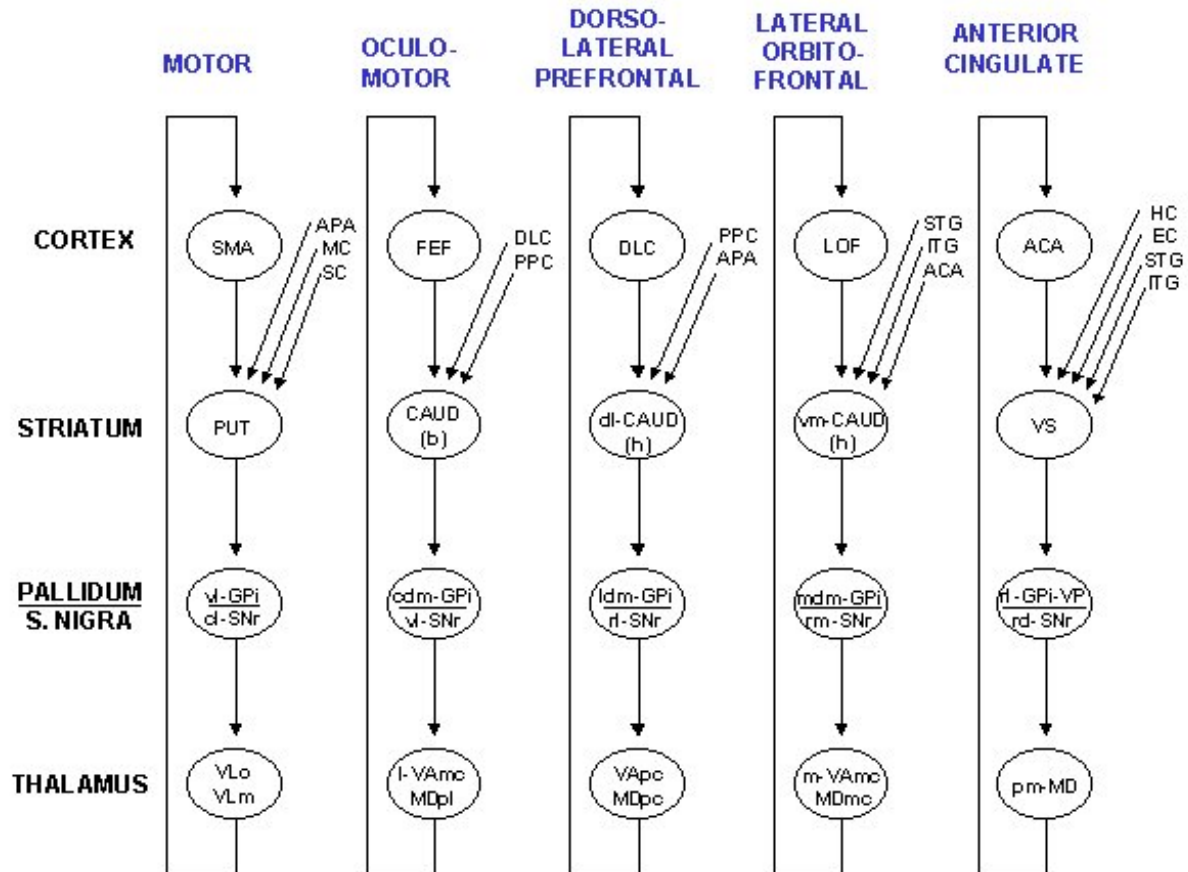


Figure A6 : Alexander et al. (1986) model of cortico-basal ganglia loops : parallel organization of the five basal ganglia-thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra, and thalamus.

Abbreviations : ACA, anterior cingulate area; APA, arcuate premotor area; CAUD, caudate, (b) body (h) head; DLC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FEF, frontal eye field; GPi, internal segment of globus pallidus; HC, hippocampal cortex; ITG, inferior temporal gyrus; LOF, lateral orbitofrontal cortex; MC, motor cortex; MDpl, medialis dorsalis pars paralamellaris; MDmc, medialis dorsalis pars magnocellularis; MDpc, medialis dorsalis pars parvocellularis; PPC, posterior parietal cortex; PUT, putamen; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; STG, superior temporal gyrus; Vamc, ventralis anterior pars magnocellularis; Vapc, ventralis anterior pars parvocellularis; VLm, ventralis lateralis pars medialis; Vlo, ventralis lateralis pars oralis; VP, ventral pallidum; VS, ventral striatum; cl-, caudolateral; cdm-, caudal dorsomedial; dl-, dorsolateral; l-, lateral; ldm-, lateral dorsomedial; m-, medial; mdm-, medial dorsomedial; pm-, posteromedial; rd-, rostradorsal; rl-, rostromedial; rm-, rostromedial; vm-, ventromedial; vl-, ventrolateral (from Alexander et al., 1986).

c. Parent's poposal (Figure A7)

In a similar simplified manner, Parent suggested the subdivision of the striatum into three functional domains: a sensorimotor, an associative and a limbic domain (Parent, 1990; Joel & Weiner; 1994), based on the topographical organization of the corticostriatal projections. In primates, the motor striatum comprises the dorsolateral postcommissural putamen and the dorsolateral region of the caudate nucleus. It is innervated by the primary motor cortex, premotor cortex, supplementary motor and lateral premotor area (Alexander & Crutcher, 1990; Alexander et al., 1990; Parent, 1990; Yeterian & Pandya, 1991; Selemon & Goldman-Rakic, 1985). This domain resembles the motor loop as defined by Alexander et al. (1986). The associative striatum comprises large parts of the putamen, rostral to the anterior commissure, and most of the head, body and tail of the caudate nucleus. It receives inputs from associative areas of the cortex, including areas 8, 9, 10 and 46 of the prefrontal cortex in the primate (Parent, 1990; Yeterian & Pandya, 1991). This domain resembles the striatal target of the oculomotor, the DLPF as well as the LOF loops, as proposed by Alexander and colleagues (1986). The limbic striatum comprises the nucleus accumbens and the most ventral parts of the caudate and putamen. It receives extensive inputs from limbic structures, such as the hippocampus and amygdala, as well as from prefrontal areas subserving limbic and autonomic functions, i.e the orbitofrontal cortex and anterior cingulate areas. This last domain resembles the striatal target of the AC/OFC loop as defined by Alexander and colleagues (1986).

2. The Nigrostriatal projections

The mesencephalic dopaminergic (DA) system is the largest dopaminergic system in the brain. The organization of DA neurons in rats and primates is generally similar. First described in rats using a fluorescence histochemical method (Dahlström & Fuxe, 1964) and subsequently in non-human (Felten et al., 1974) and human primates (Nobin & Björklund, 1973), this mesencephalic DA system is formed by three cell groups: the retrorubral area (RRA, group A8), the substantia nigra (almost exclusively the SNc and to some extent the SNr, group A9) and the ventral tegmental area (VTA, group A10).

The anatomical division of the DA cells is considered to reflect differences in their efferent projections as well as morphological and chemical characteristics. The loosely spaced neurons in the dorsal tiers, i.e the dorsal part of the SNc, the VTA and the RRA, display a strong immunoreactivity for clabindin d-28K and relatively low level of tyrosine hydroxylase

(Gerfen et al., 1985; Haber et al., 1995). The ventral tiers (ventral part of the SNc) includes two parts, a densocellular part, which lies dorsal to the SNr, and columns of dopaminergic neurons that penetrate deeply into the SNr (Joel & Weiner, 2000; Smith & Kieval, 2000). Unlike the dorsal tiers, the ventral tiers does not display immunoreactivity for clabindin d-28K (Gerfen et al., 1985; Haber et al., 1995; Agid et al., 1987; Graybiel et al., 1990; Prensa et al., 1999; 2000; Joel & Weiner, 2000). In rats, the DA neurons from the ventral tiers innervate preferentially the striosomes whereas DA neurons from the dorsal tiers innervate preferentially the matrix (Gerfen et al., 1987). This preferential distribution of the DA projections to specific compartments in the striatum is less clear in the monkey (Graybiel et al., 1987).

Recent reviews have summarized the DA inputs to the striatum according to its functional subdivisions, i.e. the associative, the motor and the limbic subdivisions (Haber & Fudge, 1997; Smith & Kieval, 2000). It seems that the sensorimotor striatum receives its main DA inputs from the cell columns in the ventral part of the SNc in primates. The limbic striatum receives different DA inputs arising from the VTA as well as from the dorsal part of the SNc. Finally, the associative sector of the striatum is innervated by a wide range of DA neurons located in the densocellular part of the ventral SNc. Five types of DA receptors have been described, the D1, D2, D3, D4 and D5. It seems that DA stimulation leads to an activation of the D1 and D5 receptors (previously grouped as D1-like receptors) and an inhibition of D2/D3/D4 receptors (previously grouped as D2-like receptors). Throughout the three sectors of the striatum, spiny neurons contain D1 and D2 receptors. A certain degree of co-localization of these two subtypes of receptors has been reported in the spiny neurons (Aizman et al., 2000). D3 receptors are also found in the limbic striatum. This receptor seems also to co-localize with D1 and D2 receptors. Some interneurons also expressed dopaminergic receptors. For instance, cholinergic interneurons have been found to express D2 and D5 receptors (Lemoine & Bloch, 1990).

Some studies have suggested that SNc and VTA dopamine neurons also innervate, although less massively, the globus pallidus particularly the internal segments, the ventral pallidum and the STN (Lindvall & Kjorkund, 1979; Cossette et al., 1999). Another non negligible source of DA inputs to the BG is the dentritic release of DA in the SNr, where dopaminergic receptors have also been identified (Mrzljak et al., 1996).

Thus, the interactions between the mesencephalic DA nuclei and the BG seem to be more important and more diffuse than previously believed.

3. The Thalamostriatal projections

In addition to the cerebral cortex, the thalamus constitutes another important source of excitatory inputs to the striatum (Parent, 1986; Wilson et al. 1983). The thalamostriatal projections were first demonstrated in humans by Vogt and Vogt in 1941 (Vogt & Vogt, 1941, Parent, 1986). These projections seem to be almost exclusively ipsilateral and they innervate the whole striatum including the nucleus accumbens (Parent, 1986).

The thalamus is composed of several nuclei, including : 1) the intralaminar nuclei, i.e. the centromedian and parafascicular nuclei (CM-PF), 2) the relay nuclei, namely the lateral nuclei subdivided into the ventrolateral (VL), anterolateral (VA) and lateroposterior (LP) nuclei, the mediodorsal (MD) nucleus and the pulvinar, and 3) the midline nuclei.

The most prominent projections to the striatum arise from the intralaminar nuclei (Powell & Cowan, 1954; 1956). Other thalamostriatal projections originate in the midline thalamic nuclei (paraventricular, paratenial, rhomboid and reuniens nuclei), the MD and to a lesser degree in the lateral and posterior thalamic groups (Nauta & Mehler, 1966; Mengual et al., 2000). These thalamostriatal projections are topographically organized. The midline thalamic nuclei, the MD and the PF project preferentially to the associative and limbic territories of the striatum, whereas the rostral intralaminar nuclei, the CM, the ventral nuclei and LP groups project preferentially to the sensorimotor territory of the striatum (Giménez et al., 1995; Nakano et al., 1990).

4. Amygdalostriatal projections

The amygdala is a heterogeneous structure including several nuclei, the basolateral nuclear group (BL), the corticomедial region, and the central nucleus, which are thought to play specific roles in emotional processing (see Rolls, 2000). Because the amygdala has been considered as a component of the limbic system, it has been suggested that its projections to the striatum were mainly directed toward the limbic part of the striatum.

These amygdalo-striatal projections are topographically organized (see for example, Kitai & Kitai, 1990). Electrophysiological studies suggested that these projections are excitatory (Noda et al., 1968). A recent study in non human primates reported that the amygdala projections are preferentially directed toward the shell of the nucleus accumbens (Fudge et al., 2002). The BL seems to be the source of all amygdaloid inputs to the limbic striatum outside the shell. These projections terminate mainly in the striosomes compartments (Ragsdale & Graybiel, 1988). In the shell, projections to the striatum arise from the medial

part of the central amygdaloid complex as well as from the BL. Furthermore, few fibers have been found to arise from the BL and to project to the associative striatum. However, projections from the amygdala to other sectors than the limbic one is still a matter of controversy (Krettek & Price, 1978; Russchen & Price, 1985). A potential confound across studies is the variable definition of the ventral striatum due to its lack of cytoarchitectural boundaries.

5. Other sources of striatal inputs

The neuromediator serotonin (5-HT) is present in relatively high concentrations in the striatum, where it is believed to act as an inhibitory transmitter (Miller et al., 1975; Olpe & Koella, 1977). It arises from the dorsal nucleus of the raphe, also known as the supratrochlear nucleus (Szabo, 1970). Serotonergic fibers are thought to innervate the striatum as well as the substantia nigra and the globus pallidus (for a review, see Halliday et al., 1995). Sparse noradrenalin fibers originating from the locus coeruleus have also been identified in the striatum (Marien et al., 1994).

6. Integration by striatal neurons of different inputs

Excitatory, glutamatergic inputs from the cerebral cortex synapse almost exclusively with the spine heads and distal dendritic areas, whereas inputs from the substantia nigra pars compacta, the thalamus, or other intrinsic striatal neurons contact the proximal dendrites and somata (Kemp & Powell 1970, 1971). The latter inputs are therefore in a crucial position to modulate or inhibit cortical influences. Thus, spiny projection cells are recipients of synaptic inputs from an extremely diverse collection of axons arising from both extrinsic and intrinsic sources as illustrated in [Figure A8](#).

Striatal interneurons, particularly the cholinergic and the somatostatin-containing ones, also receive a very diverse synaptic input. However, one clear anatomical difference between the interneurons, at least the cholinergic and GABAergic cells, and the spiny projection neurons is the spatial distribution of their inputs. As stated above, excitatory inputs are directed to the distal regions of spiny projection cells whereas interneurons receive excitatory inputs on the proximal dendrites and somata. This anatomical arrangement coupled with the profound differences in the electrical properties of interneurons indicates that the regulation of action potential generation in interneurons is likely to differ dramatically from that in spiny cells.

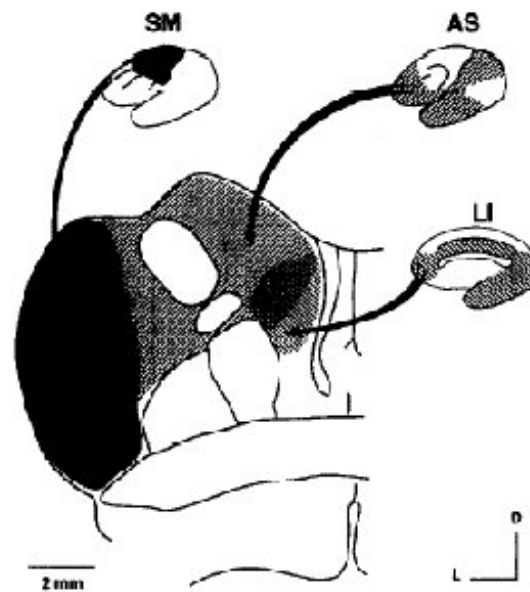


Figure A7 : Functional compartmentalization of the striatum. Based on the topographical organization of the cortico-striatal projections, Parent (1993) proposed the division of the striatum into a sensorimotor domain (SM), an associative domain (AS) and a limbic domain (LI) (from Parent, 1990).

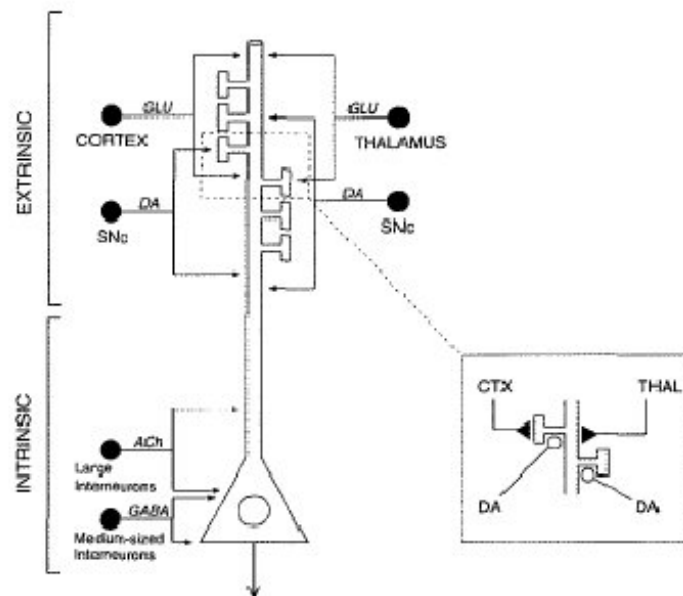


Figure A8 : Integration of multiple informations in the striatum. Note the important degree of convergence into the projection neurons. These neurons are under the influence of intrinsic and extrinsic inputs, at the proximal and distal level, respectively (from Parent & Hazrati, (1995).
Glu, glutamate; DA, Dopamine; ACh, Achetylcholine; CTX, cortex; THAL, Thalamus; SNc, subthalamic nucleus pars compacta

IV. OUTPUT OF THE BASAL GANGLIA AND 'THE BASAL GANGLIA LOOPS'

The GPi and the SNr represent the main output nuclei of the BG. They send their projections to the thalamus, the superior colliculus and to the premotor nuclei of the brainstem.

It has long been suggested that the GPi is innervated by the motor striatum while the SNr is innervated by the associative striatum. But another view, elaborated by Alexander et al (Alexander et al., 1990; Alexander & Crutcher, 1990; Kawaguchi et al., 1990), suggested that each striatal region innervates both GPi and SNr. It seems that the functional segregation of the corticostriatal projections is largely maintained through the circuitry of the BG (Alexander et al., 1986; Parent & Hazrati, 1995a,b) and through the pallidothalamic projection (Sidibé et al., 1997). The ventrolateral two thirds of the GPi, which receive inputs from the sensorimotor striatum, project to the VL and the central part of the CM. The regions of the GPi innervated by the associative and limbic striatum project to the parvocellular VA and the rostral part of PF (Sidibé et al., 1997). The VP, which is mostly innervated by the limbic striatum, projects modestly to the most medial magnocellular part of the mediodorsal nucleus (Haber et al., 1993).

The rostral nuclei of the ventral thalamus (VA, VL, VM) territories innervated by the BG outputs widely overlap with the thalamic territories projecting to the striatum; whereas more restricted areas of overlap are visible in the rostral and caudal intralaminar nuclei (CM-PF), which is the source of the major thalamic input to the striatum (Parent & Hazrati, 1992; 1993). The various thalamic nuclei send in turn projections to the frontal cortex, hence 'closing the loop'. In addition, other BG components send projection to the thalamus. For example, the GPe projects to the reticular thalamic nucleus (Hazrati & Parent, 1991).

Interestingly, it was recently demonstrated that the frontal lobe is not the unique and 'privileged' indirect BG target. Strick and colleagues, using retrograde transneuronal transport of herpes virus type 1, elegantly demonstrated projections to specific areas of the inferotemporal (Middleton & Strick, 1996) and posterior parietal cortices (West, Lynch and Strick, unpublished observations). Moreover, GPi as well as specific territories in the striatum send direct inputs to the pedunculopontine tegmental nucleus (PPN) (Nauta & Melher, 1966; Parent & Hazrati, 1995b). These projections to the PPN have long been ignored in the current model of the BG organization (Parent & Cicchetti, 1998).

V. BASAL GANGLIA INTRINSIC CIRCUITS: THE DIRECT AND INDIRECT PATHWAYS

On the basis of anatomical findings, Albin and co-workers (1989) proposed two segregated feedforward pathways from the striatum to the GPi/SNr¹ (Figure A9). The *direct pathway* is formed by a projection from the striatum to the GPi/SNr, and then to the thalamus. The *indirect pathway* projects to the GPi/SNr complex via the GPe and the STN. Early retrograde labeling investigations have supported the idea of distinct striatofugal projections arising from separate neuronal populations in the striatum (Parent et al., 1984; Selemon & Goldman-Rakic, 1990; Flaherty and Graybiel, 1993). These studies demonstrated that the majority of spiny neurons which project monosynaptically to the output nuclei of the BG, specifically the GPi and SNr, contain substance P and dynorphin and express the D1 dopamine receptor (Gerfen et al. 1990). The neurons projecting to the output structures through the GPe and the STN express enkephalin and D2 dopamine receptors (Gerfen et al. 1990).

Dopamine modulates the activity of striatal neurons that give rise to the direct and indirect pathways, a modulation which depends on the type of receptor involved. D1 receptors have an excitatory effect, whereas D2 receptors have an inhibitory effect (Chiara, 1994). Thus, dopamine allows the direct and indirect pathways to counterbalance each other. Furthermore, the two pathways have antagonistic effects on the output structures: the direct pathway sends an inhibitory output to the GPi/SNr, whereas the indirect pathway results in excitatory effects, eventually promoting activation of the frontal cortex and action.

The main strength of this model (i.e. imbalance between the activity in the direct and indirect pathways) lies in its capacity to account for pathophysiological mechanisms of both hypokinetic and hyperkinetic movement disorders (DeLong, 1990, Albin et al., 1989). Converging evidence suggests that in Parkinson's disease, the loss of neurons in the nigrostriatal dopamine-containing pathway leads to an activation of striatal outputs to the GPe, and to an inhibition of striatal projections to the GPi and the SNr (see Albin et al., 1989). The model predicts that inhibition of the GPe neurons release the STN from its tonic inhibition by the GPe. Increased activity in the STN, the only region of the BG to contain

¹ In 1966, Nauta & Mehler already provided evidence of separate projections of the internal and external segments of the globus pallidus to the thalamus/midbrain and subthalamic nucleus, respectively. The pattern of organization described in the paper is not significantly different from that identified in much more recent studies with more sensitive techniques.

VI. INFORMATION PROCESSING IN THE BASAL GANGLIA: A RE-EVALUATION OF THE CLASSICAL MODEL

The BG models have gained considerable clinical relevance because of their importance in guiding drug development and new surgical approaches. With time, however, the shortcomings of these models have become apparent, necessitating revision and updating.

1. The striatum and the GPi/SNr complex: input and output structures, respectively?

Like the striatum, the STN also receives direct excitatory inputs from motor, premotor and prefrontal areas of the cortex (Hartmann-von Monakow et al., 1978; Nambu et al., 1996, Maurice et al., 1998). In primates, the projections arising from the primary motor cortex are the most important. Some cortical neurons innervate both the STN and the striatum, particularly in the prefrontal cortex (see Parent & Hazrati, 1995b). These direct cortical inputs to the STN innervate the entire STN with a mediolateral topography (Afsharpour 1985; Cameras et al 1990, Parent & Hazrati, 1995b). Therefore, the STN can also be considered as an input structure through which cortical information is transferred to output nuclei of the BG (Kitai & Deniau, 1981; see for review, Joel & Weiner, 1997, Smith et al., 1998).

Although the GPi/SNr complex represents the major output structure of the BG, direct projection from the GPe to the thalamus as well as to the PPN has been also described (Nauta & Melher, 1966; Parent & Hazrati, 1995a,b).

2. Direct/indirect model?

Although many data corroborate the Albin-Delong model, some recent findings seem incompatible with this current dual model of the BG. Indeed, neurons in the BG show extensive collateral connectivity (Parent et al., 2000). The results of the single-cell labeling studies (see also Parent et al., 1995) have revealed an abundance of striatal projection neurons with highly collateralized axons that provide branches to two or three of the striatal recipient structures. Such a high degree of axonal collateralization allows striatal neurons to send efferent copies of the same information to virtually all striatal targets and additional internal and external projections (Bolam et al., 2000).

Furthermore, D1 and D2 receptors co-localize on striatal neurons (Aizman et al., 2000), which suggest that all striatal neurons that project to the GPi could also project to the GPe (Wu et al., 2000). Wu and his co-workers (2000), and Parent & Parent (2002) showed that virtually all striatofugal axons send collaterals to the GPe and none project exclusively to GPi/SNr. They divided striatal spiny neurons into three subtypes, based on anatomical data. Type I medium spiny neurons that project solely to the GPe. Type II medium spiny neurons project to both the GPe and SNr. Type III medium spiny neurons project to the GPe, GPi and SNr (Wu et al., 2000). Thus as concluded by Parent & Hazrati (1995b) the '*GPe cannot be considered as a simple relay structure in the indirect pathway, instead, it appears to be a major integrative structure that can affect virtually all components of the basal ganglia*'.

Moreover, lesions to the GPi not only ameliorate the hypokinetic clinical characteristics of PD, but also alleviate hyperkinetic disturbances, and lesions of the thalamus do not lead to PD-like motor symptoms (Obeso et al., 2000), as opposed to what can be predicted by the model. Thus, currently accumulating evidence is challenging the classical Albin-DeLong model.

3. Information processing in the basal ganglia: feedforward/feedback - parallelism/convergence?

Despite the above considerations, the striatum could still be viewed as an important recipient structure. The current debates concern principally the information processing through the BG. Indeed, until recently the Albin-DeLong model has been widely accepted. According to this view, information processing in the BG followed essentially a feedforward route. However, considerable internal BG feedback loops have been identified. For example, the GPe is reciprocally connected with the striatum and the STN. The striatum is also reciprocally connected with the SNc and some thalamic nuclei, particularly the CM/PF complex. Furthermore, the dopaminergic inputs arising from the SNc do not only influence the striatum but several other BG components, such as the GPi and the STN. Another important connection has long been ignored in the current model of the BG organization, the connection with the PPN (for a review, see Winn et al., 1997). This brainstem structure, containing cholinergic and non cholinergic neurons, receives direct input from striatum. This structure is reciprocally connected with the SN, GP and the STN, and is directly involved in the basal-ganglia-mediated control of behavior (Nauta & Melher, 1966; Winn et al., 1997). For instance, it has been suggested that the striatum could desinhibit the control of descending PPN influences on medullary and spinal targets.

Concerning the debate on parallel versus convergent processes through the BG, it is important to realize that the proponents of these opposing views use different levels of analysis. Most arguments favoring convergence focus on the structure of the dendritic fields of the neurons in the BG nuclei, i.e. the convergence within the recipient structure of inputs arising from different parts of the projecting structures (see § 1, Basal ganglia component, for the numeric and volumic convergence). In contrast, the concept of parallel segregated organization was established on the basis of the topographical organization of the projections with the different basal ganglia thalamocortical circuits. Synaptic convergence within the BG nuclei is not incompatible with the evidence that the striatal efferent projections are topographically organized. Integration between different basal ganglia-thalamocortical circuits is essential for producing coherent behavior. The question is how this integration takes place through the BG?

4. New perspectives?

a. Joel and Weiner model: the “split circuits”

Joel and Weiner (1994) introduced an architecture called the “split circuit”, in which input from one cortical area splits into two circuits: one that terminates in the original cortical area (a closed loop) and another that terminates in some other cortical area (an open loop). For example, a motor split circuit contains a closed motor circuit that reenters the motor cortex and an open motor pathway that terminates in the prefrontal cortex. The associative split circuit contains a closed circuit that reenters associative prefrontal cortex and an open associative pathway that terminates in the pre-motor cortex, and so forth. This model reconciles parallel and associative processing which can occur simultaneously in the BG. The converging inputs may allow contextual processing, while the parallel frontal loops may prevent conflicting motor plans from interacting.

b. Striatal compartments (figure A10)

The neurochemically distinguished striosome and matrix compartments of the striatum represent not only anatomically distinct subdivisions of the striatum but also subdivisions that differ in terms of connectivity. Firstly, cortico-striatal neurons in infragranular layers project principally to striosomes while those in supragranular layers send their axons to the matrix (Gerfen, 1992). The striosomes receive essentially cortical

afferents from prefrontal and limbic cortices (orbitofrontal cortex and anterior cingulate cortex), while the matrix receives cortical afferents from primary motor, somatosensory cortex, as well as frontal, parietal and occipital cortex (Gerfen, 1992; Aosaki et al., 1994). Thalamic efferents project preferentially to the matrix (Ragsdale & Graybiel, 1991; Sadikot et al., 1992). Dopaminergic innervation to the striatum is also heterogeneous. The targets of the striatal compartments also differ, the striosomes targeting principally the SNc and the matrix targeting both pallidal segments and the SNr.

The different connections of the striosomes and matrix suggest that they participate differentially in limbic-based (striosome) and sensorimotor-associative (matrix) circuits. In this line, a recent study demonstrated that the highest metabolic activity in the striatum occurs in the matrix compartment rather than in striosomes in awake behaving animals under a range of behavioral conditions, including voluntary movement, light restraint, and focal stimulation of different parts of the body surface (Brown et al., 2002).

Finally, the subdivisions into striosomes/matrix functional compartments coexist with, and do not replace the functional compartmentalization of the striatum according to cortical projections (motor/limbic/sensorimotor). As proposed by Gerfen, striatal patch-matrix compartments may be viewed as two phylogenetically distinct neuroanatomical circuits through which cortical information is processed. Regionally, the mix of these two circuit systems varies such that in the ventromedial striatum, allo- and periallocortical circuitry dominates, whereas in the dorsolateral striatum, neocortical circuitry dominates. In much of the striatum the two circuits coexist, and interactions between them may provide mechanisms for regulating the balance in the striatopallidal and striatonigral systems (Gerfen, 1992)

In summary, these new perspectives, although interesting, do not provide a clear answer to the question as to how the integration of the multitude of incoming signals takes place in the organization of the BG and across the complex multiple interactions between the different BG components.

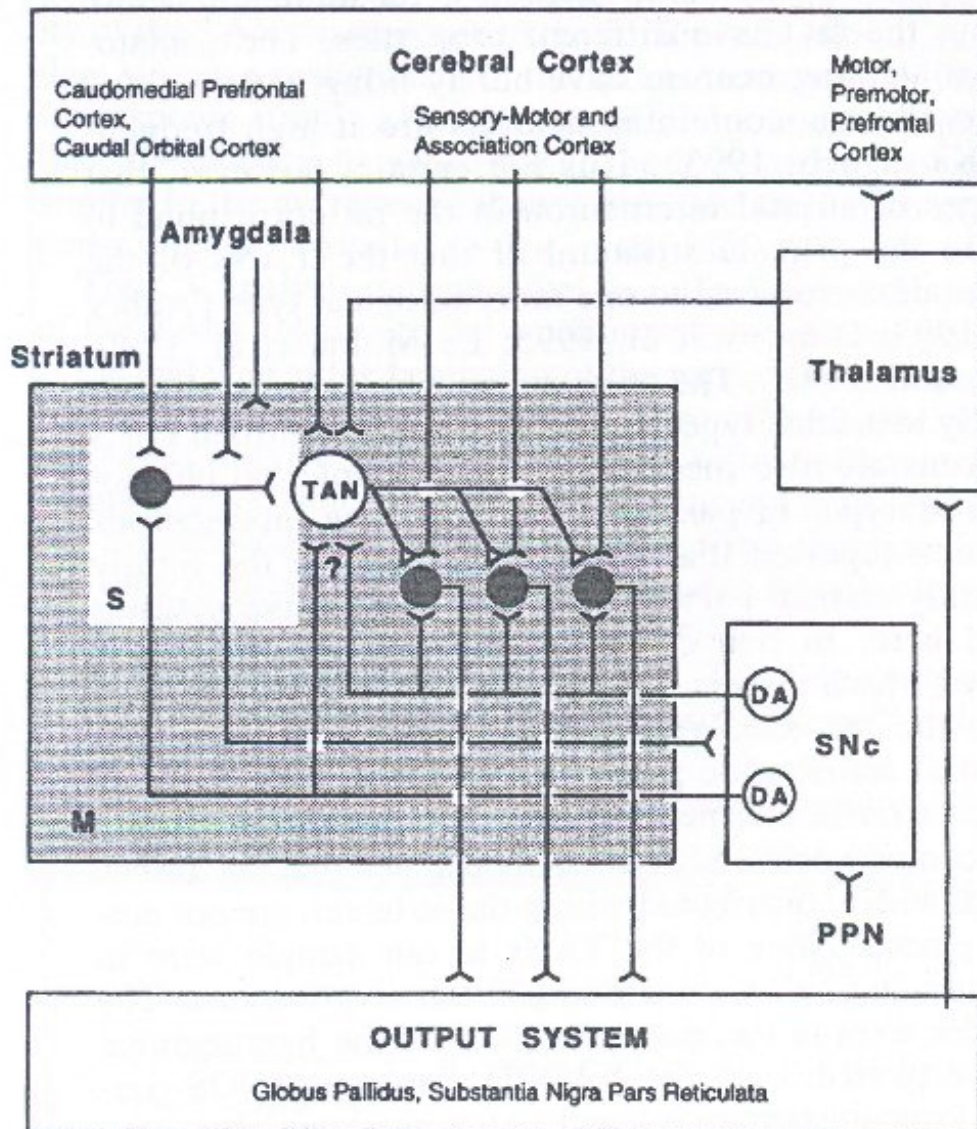


Figure A10 : Functional compartmentalization in the striatum. The striatum is functionally divided into two compartments, the striosomes (S) and the matrix (M). The TANs are largely confined to the borders of the striosomes and the matrix.

Models are necessary because they try to provide an integrated view of a variety of data. However, in doing so, they often tend to oversimplify the reality. Regarding this issue, Parent & Cicchetti wrote: *“Models in science tend to reassure and appease researchers who do not like to wander alone in the universe of knowledge. However, models may have a perverse effect, such as the selective neglect of data that do not fit into the model (modellus deformans disease). It would be unwise to rush into the formulation of a new basal ganglia model until the real significance of the enormous amount of new data on basal ganglia becomes clear. Furthermore, formulating models is a difficult task. On the one hand, efficient models have to be simple, but simple models can provide only part of the reality and are thus bound to be wrong (for example, current basal ganglia model). On the other hand, an elaborated model that would embody all the complexities of a given reality (for example, any new basal ganglia model) is doomed to be useless. We therefore suggest to stay away from basal ganglia model for some time. This will give us the opportunity to appreciate the real value of raw data and to realize that the beauty of nature lies in details.”*

Parent A. & Cicchetti F.

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SECTION 2 - CONDITIONAL VISUO-MOTOR LEARNING IN PRIMATES :

A KEY ROLE FOR THE BASAL GANGLIA

The basal ganglia have been considered as a motor substrate since the end of the nineteenth century: 'the corpus striatum contained the centers of automatic or sub-voluntary integration of the various motor centers where habitual or automatic movements become organized' (Marsden, 1982). However, there is now a large agreement that the basal ganglia are also important for cognitive and motivational functions.

In monkeys, early observations showed that lesions of the striatum elicit changes in emotional behavior, including a lack of emotional expression, display of dominance, motivation and curiosity (Mettler, 1945; MacLean, 1972). In the 1950's, Rosvold and colleagues proposed that lesion in the caudate nucleus, receiving projections from the prefrontal cortex, could evoke deficits in the delayed alternation task, a memory task which depends on the prefrontal cortex (Rosvold & Delgado, 1956). This hypothesis was confirmed and extended by Divac et al. (1967) who demonstrated that the delayed alternation deficit produced by dorsolateral prefrontal lesions, the object reversal learning impairment typically following orbital frontal lesions, and the visual discrimination difficulties known to follow inferior temporal cortex, could each be mimicked by discrete lesions targeting the specific striatal regions to which each of these cortical regions projects.

The idea that the basal ganglia are important for learning and memory was subsequently developed by Mishkin and colleagues (1984). This proposal emerged with the discovery that memory is not a unitary function, but rather comprise several anatomic-functional systems (Schacter & Tulving, 1994; Squire & Zola, 1996). Briefly, short-term or working memory depends on the prefrontal cortex, whereas long-term memory comprises at least two systems. One, often termed declarative memory, ensures the storage of facts and events, and depends on the medial temporal lobe. The other was denominated habit memory by Mishkin, and was thought to ensure the storage of stimulus-response associations, via the basal ganglia. A 'habit' was defined as an automatic stimulus-response bond which develops with repetition; it is learned slowly and possibly unconsciously, and, once established, is remarkably resistant to forgetting. Habit memory is more primitive, ontogenically and phylogenetically, than the knowledge-based declarative memory. Thus, the striatum, an evolutionarily ancient part of the brain which 1) receives massive inputs for the cortex,

including the sensory systems, 2) has access to motor regions, and 3) is the target of dopaminergic reward-related signals, appeared well suited to provide the relatively direct links between stimulus, action, and reward which are implicit in the notion of habit. Mishkin's view is now largely accepted (see for example Brown et al., 1995; White, 1997; Gaffan et al., 1996; Wise et al., 1996; Graybiel, 1995; 1998; Packard & Knowlton, 2002) and is supported by numerous results (see for example Knowlton et al., 1996; Packard & McGaugh, 1996; Passingham 1993; Curran and Keele 1993; Brashers-Krug et al. 1996; Deiber et al. 1997; Karni et al. 1998; Honda et al. 1998; Grafton et al. 1998; Toni et al. 1998; Krakauer et al. 1999, Jog et al., 1999, Hollerman et al.,1998). In particular, the striatum is now thought to contribute to various forms of motor learning, including sequential motor learning (Jueptner et al., 1997a,b; Miyachi et al., 1997; Miyachi et al., 2002, Hikosaka et al., 1999), skill learning (Jog et al., 1999; Sarazin et al., 2002), and reward-based learning (Hollermann et al., 1998; Tremblay et al., 1998). The following paragraphs will focus on conditional sensorimotor learning which, although undoubtedly recruiting short-term (working memory) processes during its acquisition phase, nevertheless can be viewed as one of the major forms of habit memory once established.

I. ROLE OF THE FRONTO-STRIATAL SYSTEM IN CONDITIONAL VISUOMOTOR ASSOCIATIONS

1. The frontal cortex: brief anatomical description

The frontal lobe lies anterior to the central sulcus and includes both the agranular motor (M1) and premotor regions (PM), and the granular prefrontal cortex (PF) (Figure A11). Multiple subdivisions have been identified within both the PM and PF cortices, based on anatomical, physiological and neuropsychological evidences (Petrides & Pandya, 1999; Preuss & Goldman-Rakic, 1991; Rajkowska & Goldman-Rakic, 1995). Schematically, PM comprises two main regions. The medial one includes the supplementary motor area (SMA), subdivided in a rostral (pre-SMA) and a caudal region (SMA proper), and the cingulate motor area (CMA). The lateral one includes the dorsal (PMd) and ventral (PMv) premotor areas. Finer subdivisions have been proposed, but this distinction will suffice for the purpose of the present review. PF is subdivided in at least three major regions, the orbitofrontal (PFo), the dorsolateral (PFdl), and the ventrolateral (PFvl).

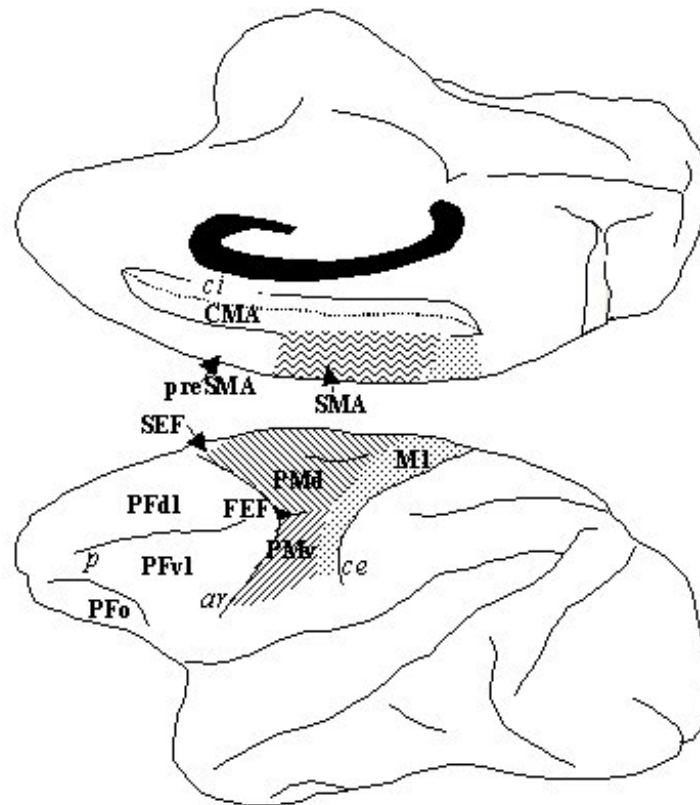


Figure A11. Frontal cortex subdivisions shown on lateral (bottom) and medial (top) views of a macaque brain. The corpus callosum is shown in black. The cingulate sulcus (ci) is opened. Abbreviations: ar, arcuate sulcus; ce, central sulcus; p, principal sulcus; M1, primary motor cortex; PMd, PMv, dorsal and ventral premotor cortex, respectively; SMA, supplementary motor area; SEF, supplementary eye field; FEF, frontal eye field; CMA; cingulate motor area; PFdl, PFvl, dorsolateral and ventrolateral prefrontal cortex, respectively, PFo, orbitofrontal cortex.

2. Role of the frontal cortex in conditional visuomotor associations

a. Neuropsychology in humans and monkeys

In humans, extensive unilateral frontal excisions, including a large portion of prefrontal cortex and often extending into premotor cortex, severely impair trial-and-error learning of a set of arbitrary associations between visual or spatial stimuli and motor responses (Canavan et al., 1989; Petrides, 1985). This impairment persists even when the correct response is provided verbally before testing and after each error (Petrides, 1997). The patients can discriminate the visual stimuli, and are also able to perform the motor responses, hence, their deficit seems due to a specific difficulty in selecting, from a set of competing responses, the appropriate one for each stimulus (Petrides, 1997). A profound impairment was also reported by Halsband and Freund (1990) after smaller unilateral lesions centered on the premotor cortex. These patients acquired sensory-sensory associations normally (between a

visual cue and a spatial location), but failed to learn sensory-motor associations linking six different visual, tactile, or auditory stimuli with six different arm movements.

Of course, in patients, lesions are rarely confined to specific anatomical regions. Experimental lesions or reversible inactivations in monkeys have therefore helped to identify the contribution of the different frontal areas to conditional sensory-motor associations (Delacour et al., 1972; Kurata & Hoffman, 1994, Passingham, 1986; Petrides, 1985). Bilateral lesions of the ventral premotor, medial premotor or primary motor cortex leave the animals' performance largely unaffected (Kurata & Hoffman, 1994; Passingham, 1987). By contrast, bilateral PMd lesions severely disrupt both the retention of pre-operatively learned associations and the acquisition of novel visual or spatial ones (Crowne et al., 1989; Kurata & Hoffman, 1994). As in humans (Halsband & Freund, 1990), the deficits following PMd lesions in monkeys are specific to sensory-motor tasks requiring non-standard mapping. Indeed, visuo-visual and visuo-motor tasks that can be solved using standard mapping (e.g. to push a blue lever *versus* to pull a red one, note that in these cases the visual cues are not spatially dissociated from the handle used to execute the motor response) are readily acquired by the animals (Halsband & Passingham, 1982; 1985; Passingham, 1985; Petrides, 1985). Thus, PMd, a region well-known for its role in motor preparation, seems to be particularly important for the selection of action in response to a sensory cue based on arbitrary rules, and to be equally critical for both the formation of these rules and their later use.

Lesion studies in monkeys have also somewhat clarified the role of PF in conditional sensory-motor associations (Delacour et al., 1972; Passingham, 1986; Petrides, 1985). Bilateral PFdl lesions involving the periprincipalis region do not affect retention of tasks requiring for example to either grasp a handle or touch a button depending on the visual or auditory stimulus presented (Passingham, 1986; Petrides, 1982; 1986), but can yield a mild retardation in learning new visuo-motor associations (Gaffan & Harrison, 1989). The most severe impairment has however been found after bilateral lesions of the ventral aspect of PF (PFvl and Pfo). Animals with such damage executed familiar sensori-motor associations almost normally, but failed to learn new ones (Bussey et al., 2001). These data suggest that, unlike PMd, PF, in particular its ventral aspect, is selectively involved in the acquisition of new conditional visuo-motor associations. The other difference between the two regions is that the deficits following PF lesions are not restricted to sensory-motor associations, but extend to sensory-sensory associations as well (Parker & Gaffan, 1998; Petrides, 1985). A summary of the effect of damage to the fronto-striatal system in conditional learning is provided in [Figure A12](#).

b. Brain imaging in humans and neurophysiology in monkeys

A number of neuroimaging studies in humans using either Positron Emission Tomography (PET) or functional Magnetic Resonance Magnetic (fMRI) have confirmed an implication of the PF and the PMd in non-standard mapping (Deiber et al., 1997; Toni & Passingham, 1999). In two recent PET studies (Grafton et al., 1998; Toni et al., 2001a; see also Deiber et al., 1997), brain activation was compared during performance of two tasks requiring the transformation of visual stimuli into motor responses. The first task was a reaching task requiring standard sensorimotor mapping. The second required the subject to associate a hand gesture with a visual cue, the association between the cue and the movement being arbitrary. The two tasks elicited different cortical activation, the reaching task activating preferentially PMv and the parietal cortex, whereas the conditional task preferentially activated PFvl and PMd. Likewise, an fMRI study showed that PMd was significantly more activated during execution of well learned auditory-motor associations than during execution of auditorily instructed sequences of finger movements (Kurata et al., 2000). In addition, in order to determine the regions specifically involved in the acquisition of arbitrary associations, visuo-motor conditional learning was compared with visuo-motor sequence learning (Toni & Passingham, 1999). In agreement with neuropsychological data, learning new visuo-motor associations elicited a preferential activation in PFvl (Toni & Passingham, 1999). Furthermore, direct comparison between learning of new visuo-motor associations *versus* execution of well-known ones revealed a selective involvement of PFvl and, also of PFdl, in early stages of learning (Toni et al., 2001b). PMd was, by contrast, equally activated during both the execution and the acquisition phases.

In monkeys, several studies have demonstrated that both PMd and PFdl possess neural properties subserving execution of familiar visuo-motor associations (Boussaoud & Kermadi, 1997; Boussaoud & Wise, 1993a,b). These findings will be described in part II below. By contrast, only few studies have addressed the neuronal changes within these areas during learning. In one study, Germain and Lamarre (1993) recorded two samples of neurons from PMd and M1, one before and one after monkeys acquired associations between auditory tones and specific limb movements. Prior to learning (i.e. when the animal performed at chance levels), 34% of M1 cells and 35% of PMd cells were modulated by the tones. After learning, the proportion of M1 cells that were sensitive to the tone did not change, whereas the proportion of such cells increased dramatically in PMd (76%). These findings suggest that

learning increases the representation of the conditional cue in PMd. In another study, Mitz and colleagues (1991) used a different approach. They recorded cells from PMd during learning, by trial-and-error, of associations between visual cues and specific movements of a manipulandum. They found that the activity of over half of the PMd neurons studied changed with learning, and that these changes followed the improvement of the behavioral performance. Chen and Wise (1995a,b) used a similar task, but requiring eye rather than arm movements, and also found learning-related changes in cell activity in the two premotor regions involved in the control of ocular saccades, the supplementary eye field (SEF) and the frontal eye field (FEF).

There has been no systematic study of the changes of PF neurons during learning of conditionally instructed arm movements. However, Asaad and colleagues (1998) described such learning-related changes in a conditional oculomotor task. They recorded neuronal activity in PFdl and PFvl and found cells with activity that reflects a particular association between a stimulus and the appropriate response. An interesting finding in Asaad and colleagues' study was that the selectivity for saccadic eye movements made in response to conditional cues appeared earlier in the trial as the animals mastered the associations, suggesting a role for PF in the learning of conditional sensorimotor associations.

To summarize, among the frontal areas, PF as well as PMd are critical for conditional sensori-motor mapping. PF is specifically involved in the formation of new associations whereas PMd is needed during both learning and consolidation. Note, that surprisingly, within PF, the dorsolateral aspect, which is directly connected with PMd, seems to make a less crucial contribution to conditional learning than the ventrolateral aspect, which lacks such direct connections, but receives direct inputs from temporal visual cortical areas.

3. The basal ganglia and conditional visuomotor associations

a. Neuropsychology in humans and monkeys

Indirect evidence of the contribution of the BG to arbitrary mapping comes from the study of patients with either Parkinson or Huntington disease. These two pathologies affect BG function due to degeneration of the SNc and of the striatal spiny neurons, respectively. Patients suffering from these diseases are impaired in learning various conditional tasks including visuo-motor tasks (Canavan et al., 1989a, Gotham et al., 1988, Sprengelmeyer et al., 1995; Taylor et al., 1990; Vriezen & Moscovitch, 1990). Of course, these neurodegenerative diseases lead to dysfunction in other parts of the brain as well, in particular the frontal cortex

(Marié et al., 1999), which could be partly responsible for the impairment. Nevertheless, the deficits observed in Parkinson patients (Vriezen & Moscovitch, 1990) differ from those reported in frontal patients (Petrides, 1997). Both populations have difficulties to learn by trial-and-error. The difference is that when the arbitrary associations are explicitly given by the experimenter, performance of Parkinson patients improves, whereas that of frontal patients does not. This suggests that Parkinson disease does not interfere with motor selection once the rule is provided, but selectively alters the learning of arbitrary rules. The BG thus seem to play a specific role in the formation and long-term storage of visuo-motor associations.

The idea of an implication of the BG in conditional learning is strengthened by the finding that lesions of the ventral anterior thalamic nucleus (which projects to PMd) induce deficits in postoperative relearning of visuo-motor associations, whereas lesions of the ventral lateral (oralis) nucleus (which projects to SMA and M1) do not cause any impairment (Canavan et al., 1989b). These results demonstrate that the integrity of the basal ganglia-thalamo-cortical circuitry involving PMd is necessary for arbitrary sensory-motor mapping.

b. Brain imaging in humans and neurophysiology in monkeys

In their comparison of standard *versus* conditional visuo-motor mapping, Toni and colleagues (Toni et al., 2001a) found subcortical activation in the striatum that was preferentially elicited by the conditional task. Comparison of learning visuo-motor associations with learning of visuo-motor sequences also revealed a selective activation in the striatal region (Toni & Passingham, 1999). In addition, using event fMRI to follow the temporal dynamic of brain activity while subjects learned to associate visual cues with different finger movements, Toni and colleagues (Toni et al., 2001b) found selective activation in the caudate nucleus that correlated with performance. According to this study, the ventrolateral prefrontal cortex and the hippocampal formation are first recruited before the implication of the striatum.

Few neurophysiological studies have investigated the role of the striatum in conditional tasks. Boussaoud and Kermadi (1997) have recorded neuronal activity in the striatum while monkeys were performing well-learned visuo-motor associations. They found an important population of neurons coding specific associations between a particular cue and a particular movement (for detail, see part II-2 below). Tremblay and colleagues (1998) have recorded cells in the anterior part of the striatum during learning of novel associations between visual stimuli and behavioral responses. They found a substantial proportion of cells

whose activity changes with learning. Although these changes were mainly related to reward expectation, their existence suggests that the striatum undergoes adaptive changes during the formation of new visuomotor associations.

In conclusion, despite the scarcity of neurophysiological evidence, available data are consistent with an implication of the BG, and perhaps more precisely of the striatum, in both learning and execution of arbitrary conditional rules.

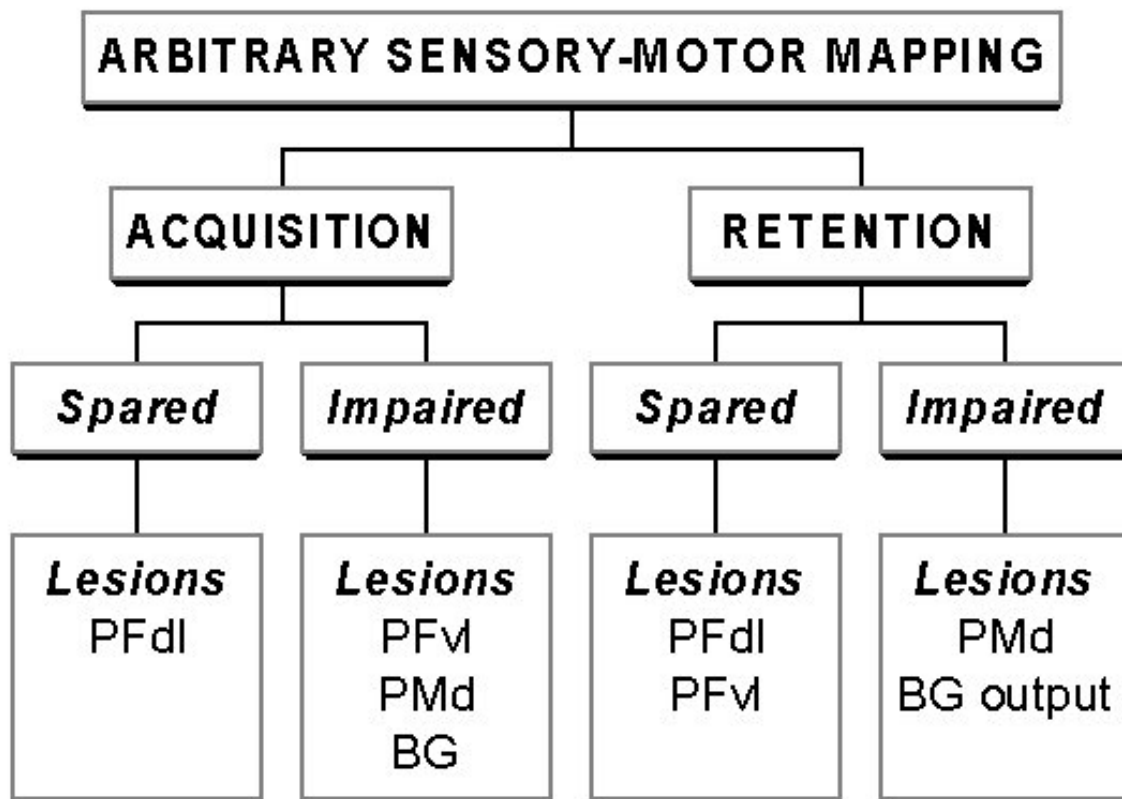


Figure A12. Effects of damage to the fronto-striatal system on arbitrary mapping in human and non-human primates. Note that during acquisition of arbitrary sensory-motor mapping, a network involving PFvl, PMd and BG is involved, whereas during the retention phase, PFvl is no longer necessary.

BG, basal ganglia, PFdl, PFvl, dorsolateral and ventrolateral prefrontal cortex, respectively, PMd, dorsal premotor cortex.

II. LINKING SENSORY INFORMATION TO MOTOR RESPONSES: A SPECIFIC ROLE FOR THE STRIATUM

Traditionally, the BG have been thought to play a modulatory role, through a disinhibitory mechanism, of voluntary movements planned at the cerebral cortex level (Allen & Tsukahara, 1974; Marsden, 1982). In this view, the fronto-striatal system functions in a serial mode, without any contribution of the BG in the selection of action. This view has been challenged by the discovery that the BG contribute to complex cognitive processes including movement initiation, anticipation of events, learning, and memory (Apicella et al., 1992; Gardiner & Nelson, 1992; Hikosaka et al., 1989a,b,c; Kermadi & Joseph, 1995; Schultz et al., 1993). For instance, Divac and colleagues (1967), and later, Fernandez-Ruiz and colleagues (2001) showed that lesions involving the ventrocaudal striatum impaired visual discrimination learning. Also, Miyachi and colleagues (1997) found a deficit during learning of sequential hand movements following inactivation of the striatum with muscimol. Inactivation of the anterior part selectively impaired learning of new sequences, whereas inactivation of the middle or posterior part of the striatum altered both learning of new sequences and execution of learned sequences.

1. The striatum: a site of convergence for sensory, motor, and reward signals

The BG are the largest subcortical structures in the human forebrain, within which the striatum constitutes an important site of convergence of information. As already mentioned, one characteristic of the striatum is that it receives sensory as well as motor information from cortical areas, and thus is in an ideal position to link these two types of information, as in arbitrary sensory-motor mapping. However, another important characteristic of the striatum, is that it is the target of massive dopaminergic inputs from the midbrain systems, i.e, the retrorubral area (RRA), the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Schematically, the striatum can be divided in two distinct parts, each receiving a different dopaminergic input. The dorsal striatum, formed by most of the caudate-putamen complex, receives its input mainly from the SNc (nigro-striatal pathway). The ventral striatum, including the ventromedial part of the caudate-putamen and the nucleus accumbens receives its input essentially from the VTA (meso-limbic pathway).

Traditionally, the nigrostriatal dopaminergic system was thought to play a role in motor acts whereas the mesolimbic system was thought to be involved in reinforcement and motivational processes (Carli et al., 1985). More recently, however, new evidence revealed

some common features of these two pathways. In particular, dopamine neurons share reward-related neuronal properties, as elegantly demonstrated by Schultz and colleagues. Midbrain dopamine neurons are activated by the unpredictable occurrence of reward (Hollerman et al., 1998; Ljungberg et al., 1992; Mirenowicz & Schultz, 1994; Schultz et al., 1993), during free delivery reward tasks, or early stages of visual discrimination learning. Once the reward becomes predictable (when the paired stimuli are learned, or in a simple visual or auditory reaction time task), these neurons no longer respond to the reward but instead respond to the instruction cue, although even this response is abolished following extensive overtraining (response habituation). Conversely, if an expected reward is not given, the activity of dopamine neurons is depressed (Hollerman et al., 1998). Based on these results, Schultz and colleagues suggested that these dopaminergic neurons could deliver reward-predictive signals to the striatum. This signal reinforces behaviors by strengthening associations between stimuli and behavioral responses as first stated by Thorndike (1911) ('Law of Effect: Any act which in a given situation produces satisfaction becomes associated with the situation so that when the situation recurs the act is more likely than before to recur also'). This reward-predictive signal is of particular interest for non-standard mapping, which in fact requires to link a stimulus with a response, according to an outcome. Furthermore, dopaminergic inputs to the striatum are critical for normal striatum functioning, as demonstrated in pathology such as Parkinson disease. Dopamine depletion using local infusion of drugs such as dopamine antagonists, suppresses for instance previously acquired behavior-related neuronal activities in the striatum (Aosaki et al., 1994; Watanabe & Kimura, 1998) as well as long term potentiation and depression in this structure (Calabresi et al., 1997).

As a result, the striatum can be seen as funnel-shaped. It receives many types of different sensory, motor and reward predicting signals. Sending output essentially to the frontal areas, puts this structure in an ideal position to influence frontal cortex functions.

2. Coding for stimulus *versus* movement in frontal cortex and striatum

The capacity of the brain to link sensory information to action relies not only on the existence of structures that receive both sensory and motor information but also on the existence of neuronal networks whose activity combines stimulus features with movement attributes, such that a given cell's activity reflects specific input-output combinations. Dissociating "sensory" activity from "motor" activity has been a challenging task for neurophysiologists, especially in higher order brain areas such as the frontal cortex and BG.

One way to do so has been to develop tasks with instructed delays, whose rationale was to establish temporal correlation between neuronal activity and specific task events (Weinrich et al., 1984). Neuronal activity of a cell would reflect stimulus properties if locked to the onset of the instructional cue, or movement parameters if locked to the onset of movement.

Based on the above principle, Boussaoud and colleagues trained monkeys to perform a conditional visuomotor task where the color of a visual cue instructed a limb movement to the right (red cue) or to left (green) (Boussaoud & Kermadi, 1997; Boussaoud & Wise, 1993a,b). One of the aims of these studies was to determine the degree to which motor preparatory activity reflected the stimulus parameters, the direction of the motor response, or specific combinations of both. [Figure A13](#) summarizes the proportions of cells with stimulus and movement effects across frontal areas (PFdl and PMd) and the striatum. Stimulus effect is highly frequent in PFdl (57%), but extremely rare in PMd (2-5%). The proportions are reversed for movement effect. Relatively few cells varied their discharge rate in relation to movement direction in PFdl, whereas 71-75% of PMd cells did so. [Figure A14](#) illustrates this property. Interestingly, the proportions of cells with combined stimulus and movement effects are predominant in the striatum ([Figure A15](#)). For example, the neuron shown in [Figure A16](#) is active shortly after the onset of the instructional cue. However, its activity depends on both movement direction (compare a-d and e) and the location of the cue (compare a and b-d). Activity in half of the striatum cells reflected specific stimulus-movement combinations, a property that was present in less than 30 % of frontal cells.

The striatum, unlike the PMd and PFdl, is in an ideal position to link sensory, motor and motivational signals (Dominey et al., 1995; Graybiel, 1995; Houk & Wise, 1995). According to this hypothesis, the striatum would receive incoming signals about the current status of events as well as signals predicting future events. One of the striatal functions would be to compare sensory inputs with previously learned repertoire of possible motor responses, and generate an output signal, which would mediate the selected response, to motor and premotor cortex, via the thalamus (Alexander et al., 1986). In instructed delay tasks, it is plausible that sustained activity during the delay period is maintained by repeated reverberations through the cortico-basal ganglia-thalamo-cortical loop, as has been proposed by Schultz and Romo (1992). Alternatively, Houk and Wise (1995) proposed that sustained cortical activity provides a positive cortico-thalamic feedback which serves to register that a context has been recently selected at the level of the striatum.

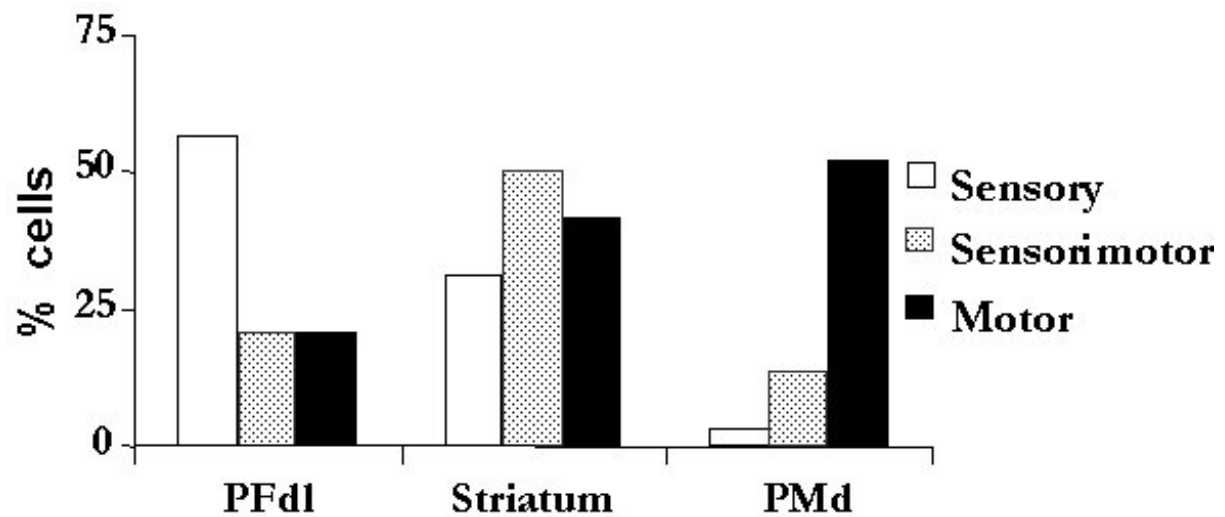


Figure A13. Comparison of neuronal properties in frontal cortex and striatum during execution of a well-learned conditional task. Three categories of neurons were found, depending on whether cell activity was correlated with stimulus (Sensory), movement direction (Motor), or both (Sensorimotor). Cells were recorded from PFdl, PMd and the striatum. The striatum differs from both frontal areas, containing the largest proportion of cells selectively activated by specific associations between one stimulus and one movement (*from Boussaoud & Kermadi, 1997*).

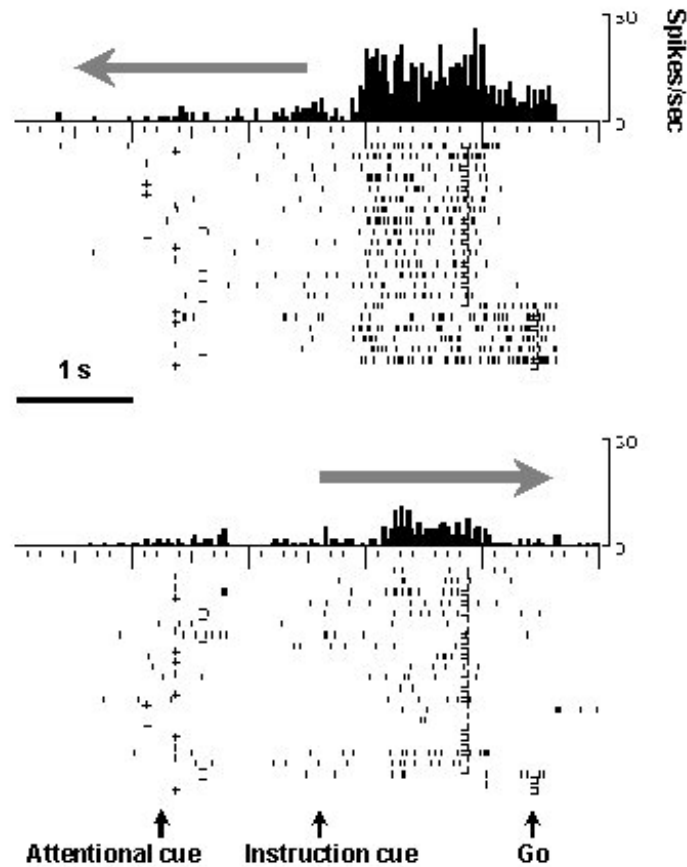


Figure A14. Motor preparation related activity of a dorsal premotor cell. Each tick indicates the time of occurrence of an action potential. Each horizontal line of ticks represents one trial. The trials are aligned (vertical lines) on the onset of instruction cue. The open squares denote the Go signal and the plus signs, the onset of the attentional cue. Note that this neuron is not active following attentional cues, and that its activity following motor instructional cues is selective for movement to the left (*from Boussaoud & Wise, 1993 a,b*)

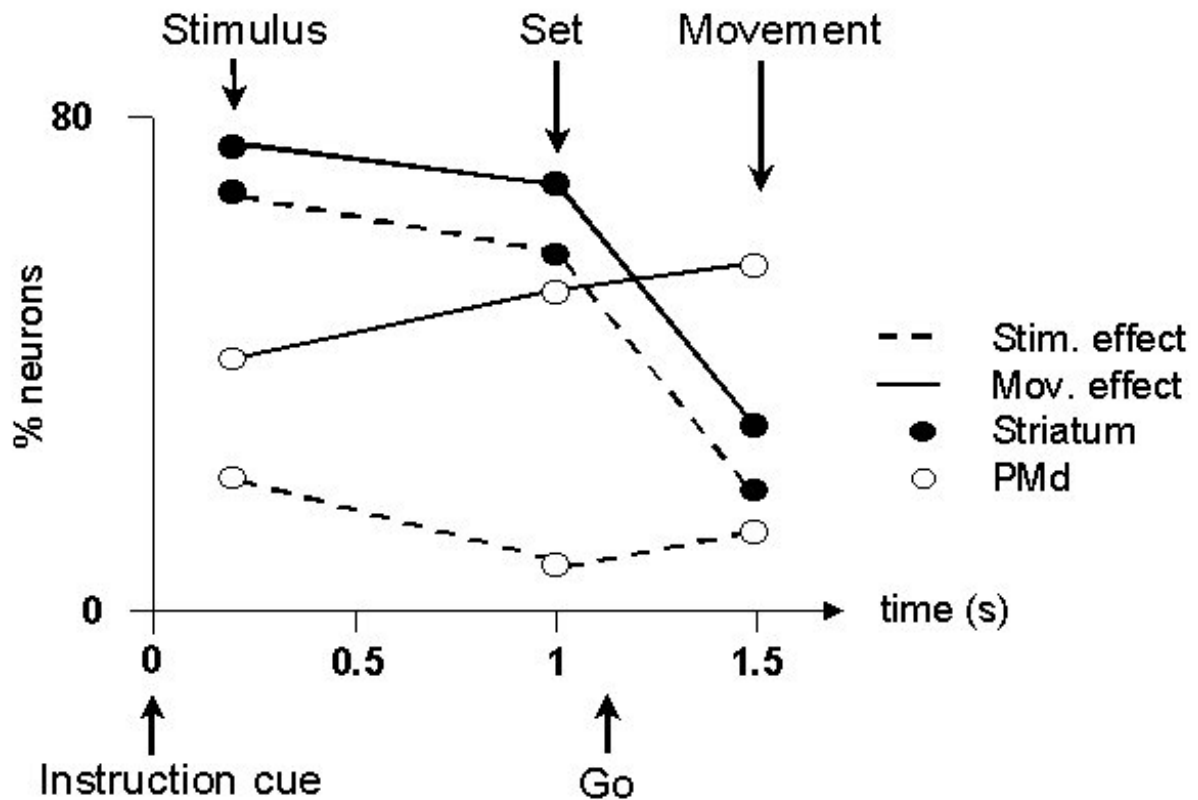


Figure A15. Information content of neural activity in the striatum *versus* the dorsal premotor cortex : within-trial temporal evolution. Data from Boussaoud & Wise (1993a,b) and Boussaoud & Kermadi (1997) were analyzed to calculate the proportions of neurons with stimulus *versus* movement related activity at three different epochs during the trial : after the instruction cue (Stimulus), before the Go signal (Set) and at response execution (Movement). Note that the striatum exhibits both stimulus and movement related properties, which diminish before the Go signal. By contrast, PMd shows mainly movement related activity which gradually increases up to movement execution.

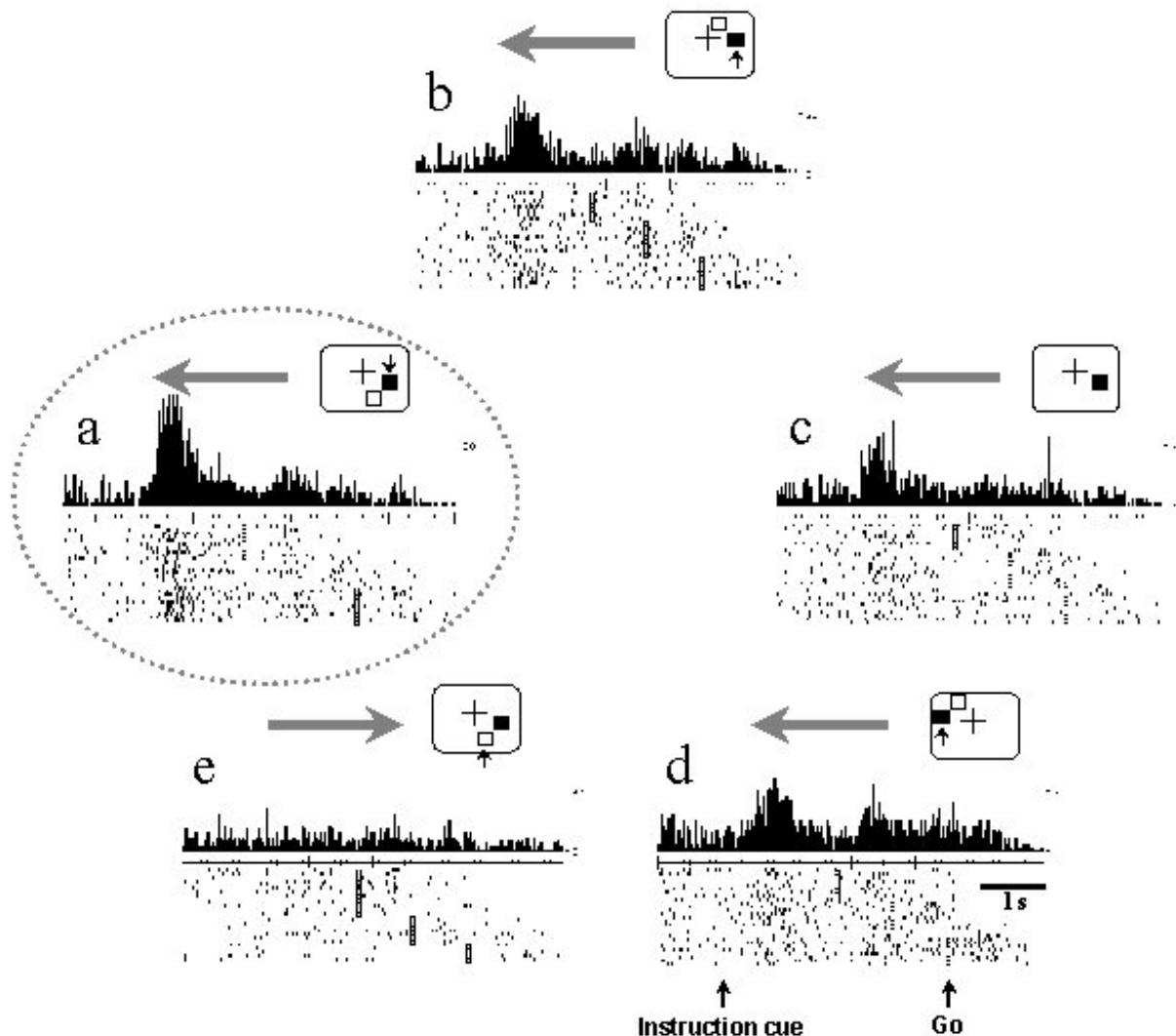


Figure A16. A striatal neuron whose activity reflects a particular stimulus-response combination. On top of each histogram, the large square represents the video screen, the central cross the fixation point and the squares the motor instructional stimulus. A stimulus can be composed of one square (red = filled; green = open) or two squares. In the latter case, the arrow points to the square that the monkey had to select as the instruction for movement direction, red instructed a leftward movement and green a rightward movement (horizontal grey arrows). Note that this neuron is preferentially active for one particular stimulus-response combination (a). Other conventions as in Figure A14 (from Boussaoud & Wise, 1993a,b).

III. A MODEL FOR DISTRIBUTED PROCESSING IN THE FRONTO-STRIATAL SYSTEM DURING LEARNING

Arbitrary sensori-motor learning is complex and involves several processes. First, one needs to discriminate the different stimuli presented and, subsequently, recognize and memorize each of them. Second, because there is no direct link between the stimuli and the appropriate response, one has to learn by trial-and-error the correct associations. This implies on-line monitoring of the associations already tried and of their consequences (correct or incorrect). Finally, once learned, the associations have to be consolidated. Each component of the large network involved in this type of learning likely makes a specific contribution to these different processes (Figure A17).

1. Lateral prefrontal cortex (PFdl and PFvl)

The specific role of the dorsal and ventral aspects of the lateral PF remains controversial. One view (Goldman-Rakic, 1995) considers that PFdl and PFvl are concerned with the type of information processed, such that PFdl is involved principally with spatial locations, whereas PFvl is involved with visual object information ("domain specific" modularity). This regional bias is based on the organization of the cortical visual system. The visual cortex contains two relatively separate anatomical pathways, a dorsal and a ventral one (Ungerleider & Mishkin, 1982), which have preferential (albeit overlapping) connections with PFdl and PFvl, respectively. The dorsal pathway is thought to be devoted to the "where" information, whereas the ventral one is thought to be devoted to the "what" information. However, recent neuroimaging studies in humans (Haxby et al., 2000; Postle et al., 2000) and neurophysiology studies in monkeys (Rainer et al., 1998a,b; Rao et al., 1997) report an intermixing of "what" and "where" properties in the lateral PF cortex. Accordingly, Petrides and Owen have suggested that the dorsal and ventral regions mediate distinct processes ("process specific" modularity). In their view, PFvl is concerned with 'first order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long term memory' [Petrides, 1996, page 1457] whereas PFdl is concerned with more demanding processes, such as the active manipulation and monitoring of series of information (Petrides, 1995). The data reviewed in this paper are more in accordance with this second view.

PFdl seems not to make a major contribution to arbitrary sensory-motor mapping, whether the information is spatial or not (Deiber et al., 1997, Toni et al., 2001a). Although arbitrary sensory-motor mapping likely requires organizing and manipulating information in working memory, the contribution of PFdl to these processes does not seem essential, probably because most conditional tasks reviewed here involve simple movements, rather than planification of complex sequences of actions (Pochon et al., 2001; Rowe et al., 2000).

By contrast, PFvl seems particularly involved during the acquisition and to a lesser degree during the retention phase. PFvl receives different types of sensory information, including visual inputs from the infero-temporal cortex, and auditory inputs from the superior temporal cortex (see Passingham, 1993). Neurons with activity reflecting the sensory stimulus have been recorded in this area (Fuster et al., 2000; Rao et al., 1997). In addition, neuronal activity in this area is modulated by cues predicting a specific reward (Watanabe, 1996). Thus, like the striatum, PFvl possesses stimulus and reward-related properties. Nevertheless, unlike the striatum, this structure lacks direct motor projections, suggesting that the establishment of sensory-motor associations is more likely to take place in the striatum. The early contribution of PFvl in arbitrary sensori-motor mapping (together probably with the hippocampal system, see Wise & Murray, 1999), might thus be to hold in memory the stimuli presented, as well as the consequences of the already tried associations (see also Murray et al., 2000; Passingham et al., 2000; Wallis et al., 2001; White & Wise, 1999).

2. The dorsal premotor cortex (PMd)

PMd is involved in both the execution and the learning of arbitrary sensory-motor mapping. In light of its well-known importance for motor preparation, PMd is in the position to select a motor program in response to an incoming stimulus, and then send it to the primary motor cortex, which is responsible for the execution of the movements. In our network dedicated to arbitrary sensory-motor mapping, PMd thus constitutes the output stage (see [Figure A17](#)), a position that explains why it is equally critical whether the associations are new or well known. An important finding in Mitz and colleagues' study (1991) was that the learning-related changes observed in the neuronal activity of PMd lagged behind the improvement of the behavioral performance. This finding indicates that plasticity in PMd is the consequence, rather than the cause of learning.

3. The striatum

As mentioned earlier, there is no evidence for a direct connection between PFvl and PMd. It seems that one way for PMd to receive information from PFvl is via the BG loops. Thus, despite the scarcity of neuropsychological and neurophysiological data in monkeys, we postulate that the striatum, under PFvl influence, occupies a privileged position to link visual inputs with motor responses through arbitrary rules, and that its output signal to PMd contains information on these rules. On the basis of such information that PMd could select the appropriate motor response. The interaction between the striatum and PMd is illustrated by the within-trial temporal evolution of the percentage of neurons that code for stimulus attributes *versus* movement direction, in a well-learned conditional visuo-motor task (Figure A16). Neural activity was analyzed at three epochs between stimulus presentation and movement execution. Shortly after cue onset, the proportions of neurons in the striatum that code for stimulus or for movement are both high. They remain so during the preparatory phase until the monkey receives instruction to execute movement (go signal), and then fall to a low level. In PMd, stimulus representation is weak throughout time, whereas movement representation increases progressively to reach its maximum level after the go signal. Thus, in a well learned task, striatal neurons maintain both stimulus and movement representations as long as response execution is not required, as if the appearance of a particular cue activates, in the striatum, the representation of the particular rule associated with it, until the intervention of PMd for the selection of the appropriate motor response.

In summary, learning to associate visuo-motor information through arbitrary rules requires the integrity of a network including PFvl, PMd and the striatum. Figure A17 schematically summarizes how these structures might contribute to learning. The striatum integrates sensory, motor and reward information, and under PFvl influence, links these information through arbitrary rules. PFvl contribution might be to hold in memory the stimuli presented, as well as the consequences of the already tried associations. Finally, information flow from the BG, via the thalamus, influences PMd which is responsible for the selection of the motor response. Once learned, use of the visuo-motor rules requires particularly the striatum, that seems to contain a representation of these rules, as well as PMd, the output stage of the circuit.

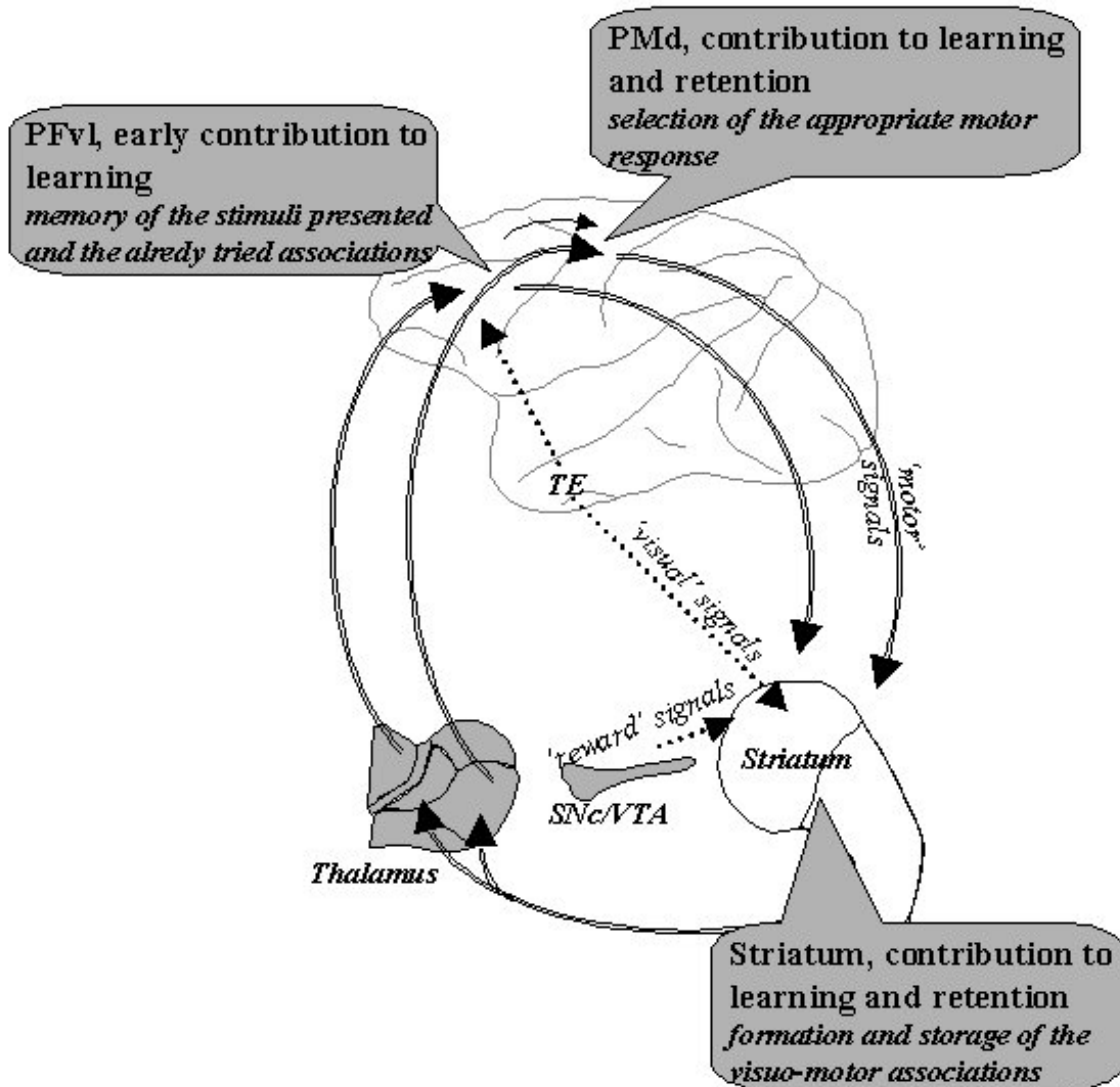


Figure A17. A functional model describing how the fronto-striatal system may subserve conditional visuo-motor associations. The model postulates that the striatum, under PFvl influence, plays a key role in integrating sensory, motor and motivational information, thereby ensuring the formation and long-term storage of visuo-motor associations. In this model, PFvl contribution is to hold in memory the stimuli presented and the consequences of the already tried associations. PMd, the output stage of the system responsible for the selection of the appropriate motor response based on incoming signals from basal ganglia, via the thalamus. Abbreviations: TE, inferior temporal cortex; VTA, ventral tegmental area; PFvl, ventrolateral prefrontal cortex; PMd, dorsal premotor cortex.

B - Neurophysiological study in monkeys

I. INTRODUCTION

The basal ganglia have been proposed as structures critical for reward-based learning. Indeed, as already developed in part A, the striatum occupies an ideal position to link sensory inputs with motor responses according to their behavioral outcomes. Previous neurophysiological studies have reported learning-related activity changes in both the TANs (Aosaki et al., 1994) and PANs (Jog et al., 1999; Miyashi et al., 2002; Tremblay et al., 1998) striatal neurons. Among them, one study has investigated striatal activity during learning of a visuo-motor conditional associative task (Tremblay et al., 1998). However, in this study, activity from the anterior striatum was recorded while monkeys learned a go/no-go task, during which learning usually took only two trials. It was therefore difficult to follow the temporal dynamics of learning-specific modifications of the activity.

In order to further examine this issue, we used a task similar to that of Mitz et al. (1991), allowing the comparison between the striatum and the premotor cortex (PMd), an important area for conditional visuo-motor behavior. In PMd, transient or long-lasting, albeit relatively late, activity changes were recorded during the acquisition of visuo-motor associations. These changes were thought to participate to the selection of the appropriate motor response (Mitz et al., 1991). Our prediction was that, in the striatum, changes of neuronal activity during conditional visuo-motor learning would reflect an involvement in the early processes leading to the acquisition of conditional visuo-motor associations. These data are in the process of publication in *Experimental Brain Research* (Hadj-Bouziane & Boussaoud, in press).

II. MATERIALS AND METHODS

1. Subjects and apparatus

Three rhesus monkeys (*Macaca mulatta*) were subjects in this study: 2 males, MO and MH, weighing 8 and 9 kg, respectively, and a female (MS) weighing 5 KG. The training took several months during which each monkey learned to sit quietly in a primate chair and perform a rather complex task. The monkey faced a video screen where visual stimuli were presented, and had access to a joystick which was constrained to move in 4 orthogonal directions (referred to as right, left, up and down). All three animals used their right arm, the

left one did not have access to the joystick, but was free to move inside the monkey chair. In the early phase of training, monkeys worked with their head free to move. After surgery, the head was fixed using a head fixation device implanted surgically. Eye position was monitored with the use of a scleral search coil.

2. Training and behavioral paradigm

Each monkey was taught a conditional visuo-motor task that required to associate complex visual cues with joystick movements. They were first trained with a set of four stimulus/movement pairs, presented concurrently, until they reached the criterion of 80 percent correct responses (familiar condition). These 4 familiar pairs remained unchanged throughout the whole experiment. Then, the animal was taught to search, by trial and error, for the correct responses to cues never presented before. This was the 'novel condition', where 2 to 4 new cues were presented concurrently until the animal reached the criterion of 4 correct responses out of 5 consecutive presentations of each cue.

Figure B1 illustrates the sequencing of events during the task. Typically, a trial started when the animal held the joystick at a central position for 0.25s (Figure B1). A stimulus was then presented at the center of the screen for a delay of 0.75 to 2s (with a 0.25 s step), after which it blinked, instructing the monkey to respond (go signal) within 1s by moving the joystick in one of the 4 directions. If movement direction was correct (i.e. if it was in the predetermined direction associated with the stimulus), a reward (fruit juice) was delivered after a fixed delay of 0.8 s; if it was incorrect, a purple circle appeared for 1.5s as an error signal.

3. Surgery and recordings

Surgery was performed under aseptic conditions and deep anesthesia using propofol or isoflurane. A stainless steel (monkey MO) or cilux (compatible with magnetic resonance imaging, monkeys MH and MS) recording chamber (Crist Instruments®) was implanted on the left hemisphere. The center of the chamber (ϕ : 18 mm) was positioned at an antero-posterior coordinate of +17 mm, with an angle of 30° from the vertical plane, giving access to the anterior striatum. A head restraining device and a scleral search coil were also implanted for head fixation and monitoring of eye movements, respectively. The animals received antibiotics and analgesics postoperatively.

During daily recording sessions, tungsten electrodes (FHC Instruments®, impedance: 1-3 MΩ) were inserted into the brain, through the dura mater, and advanced with a hydraulic microdrive into the striatum. Action potentials were then amplified, filtered with a bandpass of 300 Hz to 3 kHz, and discriminated on the basis of their waveform, using a multi-spike detector (Alpha-Omega Engineering®). For monkey MH, the recording sites were verified by magnetic resonance imaging (MRI).

In a typical recording session, the animal performed first the familiar associations, while searching to isolate neurons. Each isolated neuron was then tested first with the four familiar associations, then with up to 4 sets of novel associations. The data were analyzed off line, and activity during the novel condition was compared to the activity during the familiar one.

4. Data analysis

Single neuron activity and behavior. Data analysis was carried out, in parallel, on the behavioral performance (% correct responses and mean response times) and neuronal activity. For neuronal activity, raster displays and histograms of the discharge rates were constructed, and activity was identified in different task epochs by visual inspection, and compared to a reference period (500 ms before the cue onset) using a t-test. These epochs were as follows: reference period, 500 ms before the cue onset; stimulus-related, following the cue onset (maximum duration: 500 ms); instructed delay, from the end of stimulus period until the go signal; movement-related, starting at the go signal and extending until the end of the movement execution; expectation of reward, from the end of movement to reward delivery; reward, from delivery up to the end of the trial (500ms). These time windows were adapted to particular activity profiles. Task-related activity and directional selectivity were assessed and then compared for familiar *versus* novel condition, using paired *t*-tests ($P < 0.05$). Changes of activity and behavioral performance across the learning process were plotted using a 5-point moving average window.

Population analysis. In order to perform a population analysis, neuronal activity was standardized and realigned on the learning criterion. However, individual neurons may be active in relation with different task events, and they may undergo different modulations of their activity depending on epochs in the trial. For example, during learning, the activity of a given cell may decrease for one epoch (e.g. IS-related activity) and increase for another epoch (e.g. reward related activity). The question is how to include such neurons in the population

analysis. Our approach was to consider each epoch with task-related activity and learning-related modulation, as one case. A neuron may thus contribute more than once to the population signal. We then made two groups of cases, one where modulation is a transient increase of activity, and one where the modulation is more long lasting. As was done for individual neurons, behavioral performance was also averaged across the different cases. This analysis produced curves representing changes of activity within populations of cells and behavioral performance during the learning process.

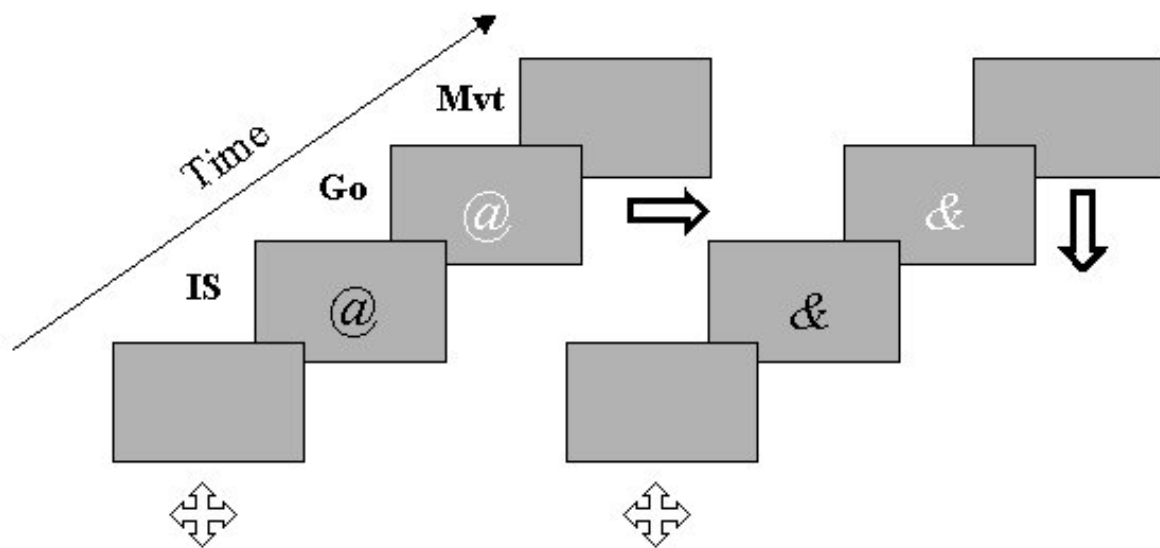


Figure B1. Behavioral paradigm. The two diagonally oriented columns represent examples of trials. Time progresses from bottom left to upper right, as represented by the arrow on the left. The panels represent the video screen, and the joystick is represented at the bottom. Before trial is initiated, the screen is blank. When the monkey holds the joystick, a cue (Instruction stimulus, IS) is presented for a delay of 0.75 - 2 s, after which it blinks (Go signal). Each particular cue is arbitrarily associated with one of the four possible joystick movement. In the 2 examples illustrated, the character "@" is associated with a rightward movement, whereas the "&" is associated with a downward movement. When a new cue is presented, the monkey had to find the predetermined movement by trial and error. Four association were maintained constant throughout the whole experiment. Neuronal activity in the striatum was recorded both during execution of these well-learned associations (familiar condition) and during trial-and-error learning of new associations (novel condition).

III. RESULTS

1. Behavior

During the recording sessions, the performance in the familiar condition reached 85% correct responses for monkey MO and 97% for monkey MH. For the novel condition, the two monkeys learned at different rates, but they used a similar strategy, which is illustrated in Figure B2 for monkey MH. This monkey usually learned up to 4 sets of 4 associations in one session, and was more consistent than monkey MO. Figure B2 shows the number of trials necessary to reach the learning criterion for each association, as well as the mean response times, averaged over 30 new sets. It appears that new associations, although presented in a pseudorandom order within each block of 4 trials, were learned sequentially, as the number of trials required to learn a single association increased exponentially ($R^2 = 0.99$). Learning took between 4.5 trials on average, for the first-learned association, and 25.8 trials for the last one, with progressive increase in between. As illustrated in Figure B2, mean response times were significantly longer in the novel condition as compared to the familiar one. Furthermore, there was a significant decrease in response times during learning, which is represented by the difference in response time between correct and incorrect trials.

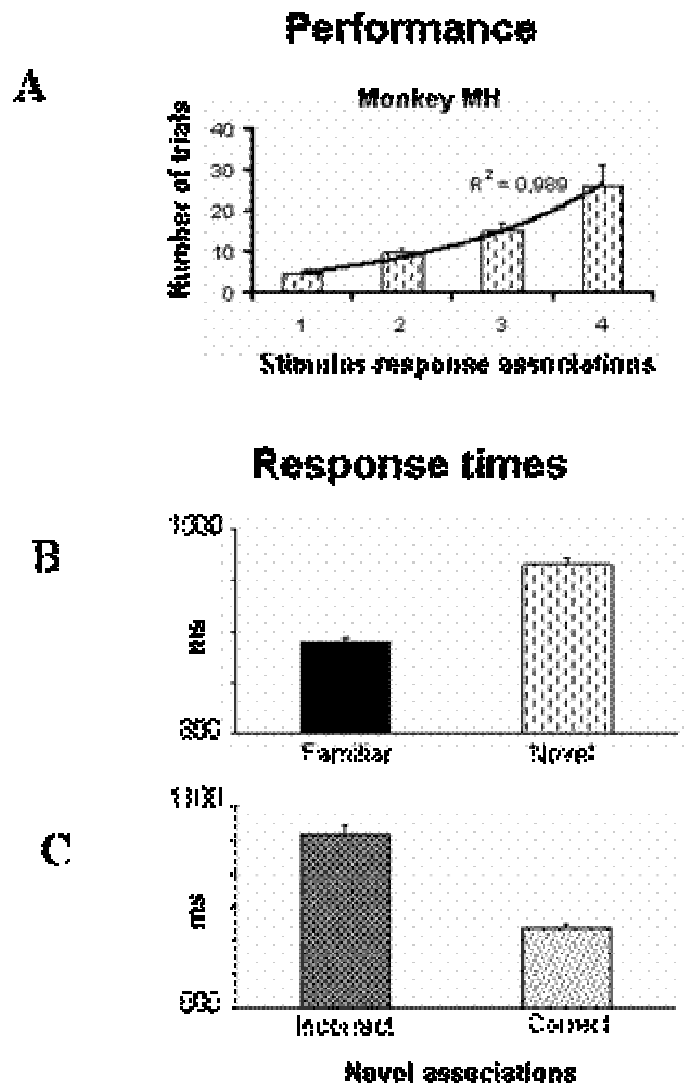


Figure B1. (A) Behavioral performance : learning strategy of Monkey MH. The bars indicate the mean (±SEM) number of trials needed to learn each association calculated over 30 sets of 4 new associations. Note that the associations are learned sequentially. The best fitting curve is an exponential curve ($R^2 = 0.989$). **Response times during the familiar and novel conditions (B)** **Response times for correct and incorrect trials in the Novel condition (C).**

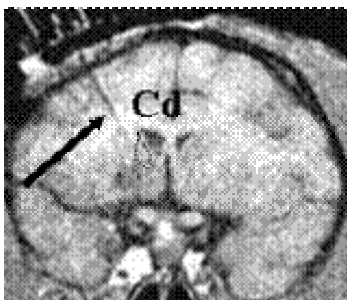


Figure B3. Coronal MR image of monkey MH, showing the trajectory of an electrode pointing to the head of the caudate nucleus (Cd).

2. Neuronal activity

The results presented here are based on a sample of 72 neurons recorded from the striatum of monkeys MO (18 cells) and MH (54 cells). The recordings from monkey MS are still ongoing and will not be included in this thesis. The location of recording sites in the striatum was verified in monkey MH using MRI. Figure B3 shows the trajectory of an electrode pointing toward the head of the caudate nucleus. Monkey MO is still involved in the experiment and was implanted with a non MRI compatible device. Histological verification has yet to confirm the precise location of the recorded neurons, but according to stereotaxic coordinates, the recordings were made from the dorso-medial portion of the putamen and caudate nucleus.

a. General properties of the striatal neurons

In the familiar condition, 50 out of 72 neurons displayed a modification of activity in relation with one or several events of the task. Task-related activity was observed in relation with the IS onset (n= 30) or anticipating the IS onset (n= 5), during the preparatory period (n= 20), the execution of the movement (n= 20) and/or reward (n= 4). These modifications of the activity consisted most often (80 % of the cases) in increases of activity relative to the baseline discharge rate.

When no learning was required, i.e. when the monkey performed familiar trials, the majority of neurons exhibited complex patterns of task-related activity, showing activity changes with more than one task event. Examples of the different patterns of activity observed are illustrated in Figure B4. This figure shows the activity of 4 different striatal cells. The first examples (B4-A and B4-B) illustrate the case of striatal neurons with a typical phasic response in relation with either the instructional cue (B4-A) or with execution of the movement (B4-B). Figure B4-C and B4-D show cases with more complex properties. The neuron illustrated in B4-C responds both during movement execution and continues to discharge during later phases of the trial including expectation of reward and its delivery. In the case shown in Figure B4-D, a strong phasic activity was observed in relation with reward delivery. However, this activity started well before the reward delivery. Indeed, after the end of the movement, there was a delay of 800ms, during which the activity increased progressively (reward expectation).

In the previous examples, the activity for the four different directions of movement was pooled to show the general patterns of activity of different neurons. However, the activity

associated with the different cue-response associations was rarely the same. The majority of striatal neurons were selectively active for one or two particular associations. Such selectivity could be observed during different trial epochs as illustrated in Figures B5 and B6. Figure B5 shows the case of a neuron with a significant increase of activity in relation to the onset of the IS and to the execution of the movement. The neuron responded similarly to the 4 cues, but its discharge rate during movement execution varied markedly depending on movement direction. This particular neuron “preferred” the upward movement. The examples shown in Figure B6 illustrate selectivity for the cues (B6-A), or for the expectation of reward (B6-B).

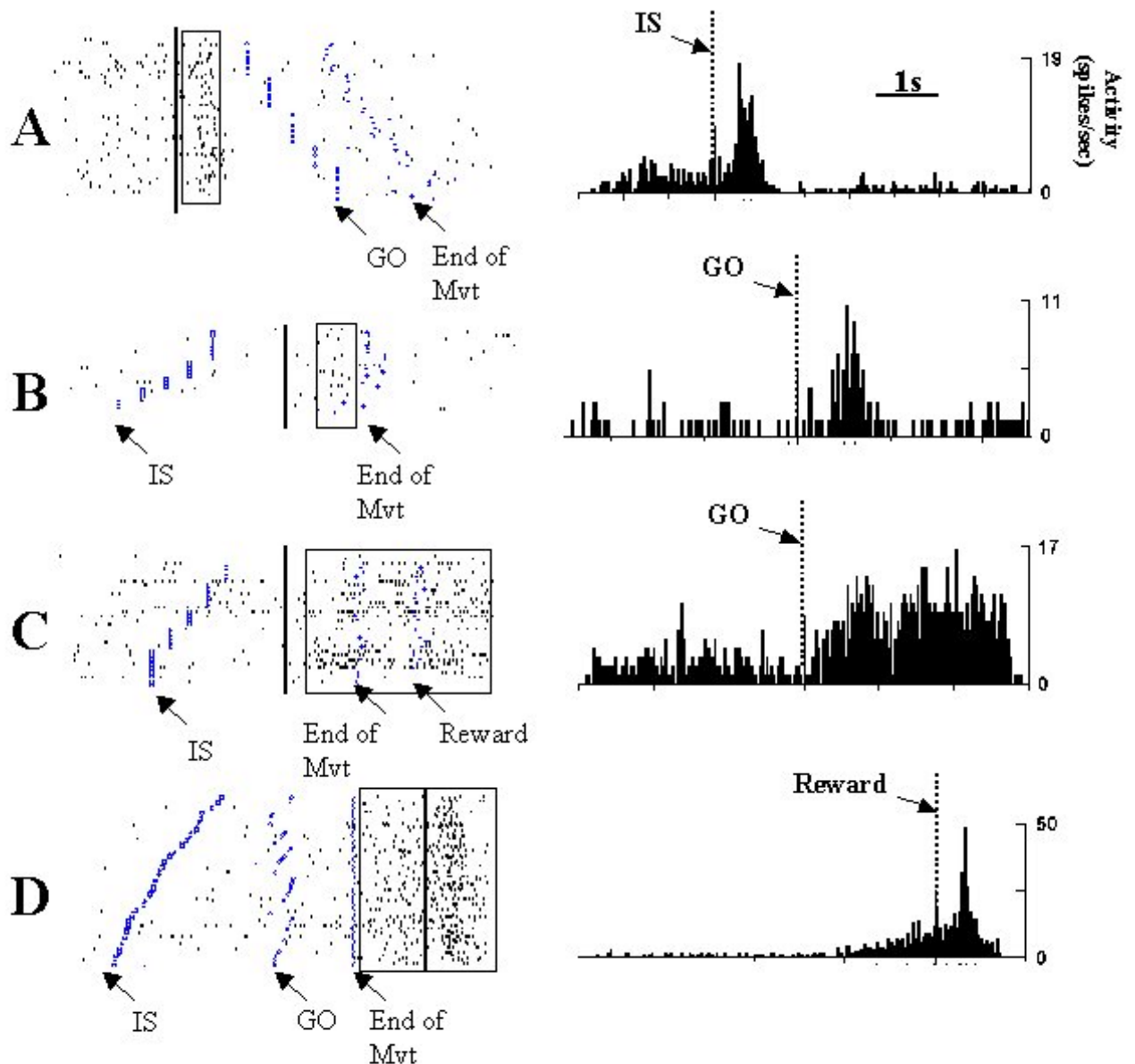


Figure B4. General properties of striatal neurons. Example of four different striatal neurons exhibiting a significant activation in relation with the onset of IS (A), the execution of the movement (B), the execution of the movement and the reward (C), the expectation of reward and its delivery (D). Note that neurons in the striatum show significant phasic activation in relation to one or several epochs of the tasks
Left, In raster displays, each tick indicates the time of occurrence of an action potential. A horizontal line of ticks represents one trial.
Right, the histograms represent the discharge frequency of the neurons across trials (bin = 30ms). The trials are aligned (vertical lines) on the onset of the IS (A), on the go signal (B,C), or reward delivery (D).
 Abbreviations: IS, Instruction Stimulus; GO, go signal; End of Mvt, end of the execution of the movement.

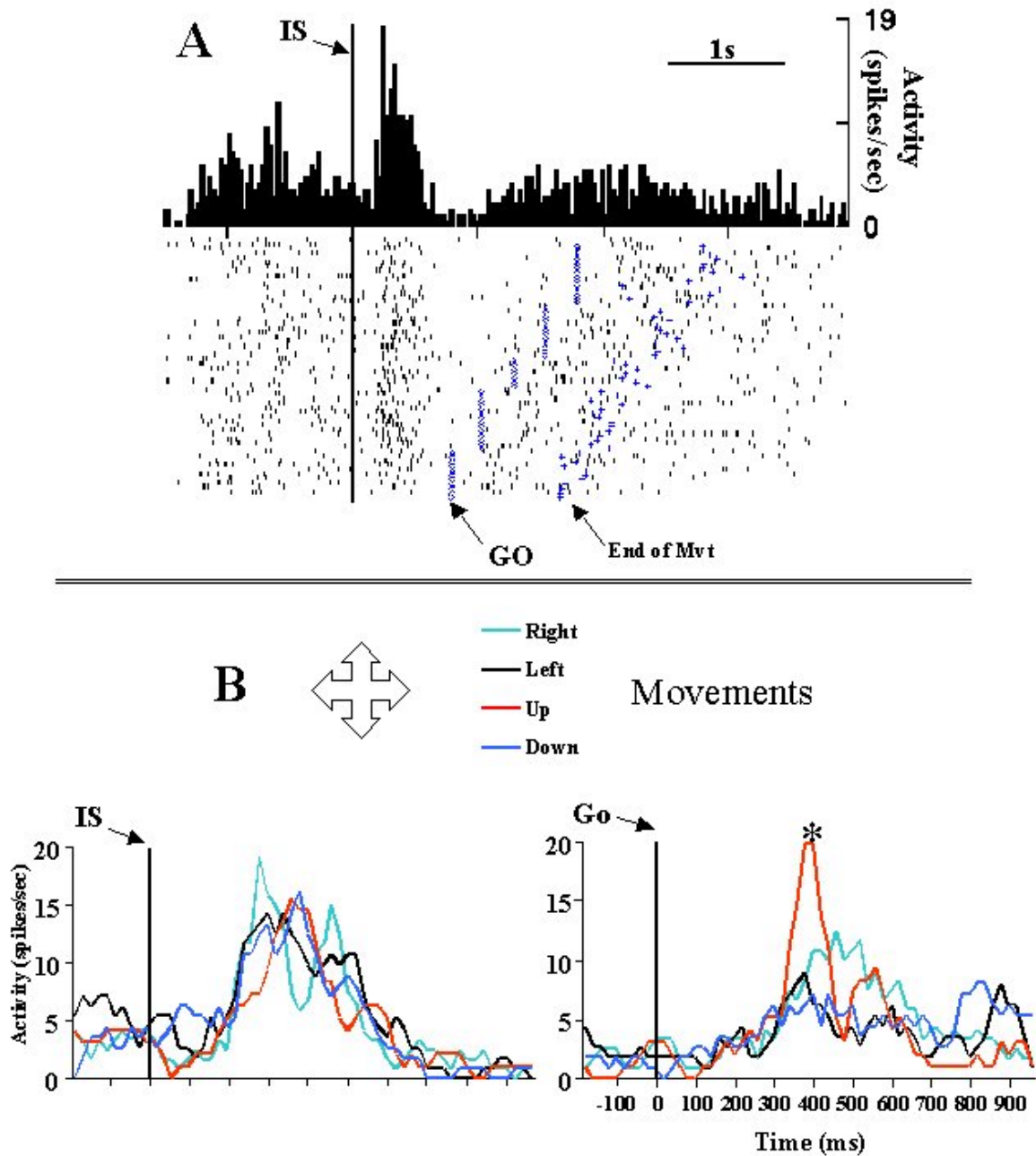


Figure B5. Striatal cell exhibiting a selectivity for one condition during execution of the movement. A) Histogram and raster display of a striatal cell exhibiting a phasic increased activity in relation to the IS onset and to the execution of the movement. The 4 conditions (right, left, up, down) were pooled. The activity is aligned on the onset of the IS (same conventions as in Figure B4).

B) Activity per condition (bin=20ms) averaged across several trials. This activity was calculated around the IS (left) and the GO signal (right). Note that this neuron does not shown selectivity for a particular stimulus. However, a significantly stronger response was observed in relation to the execution of an upward movement (*).

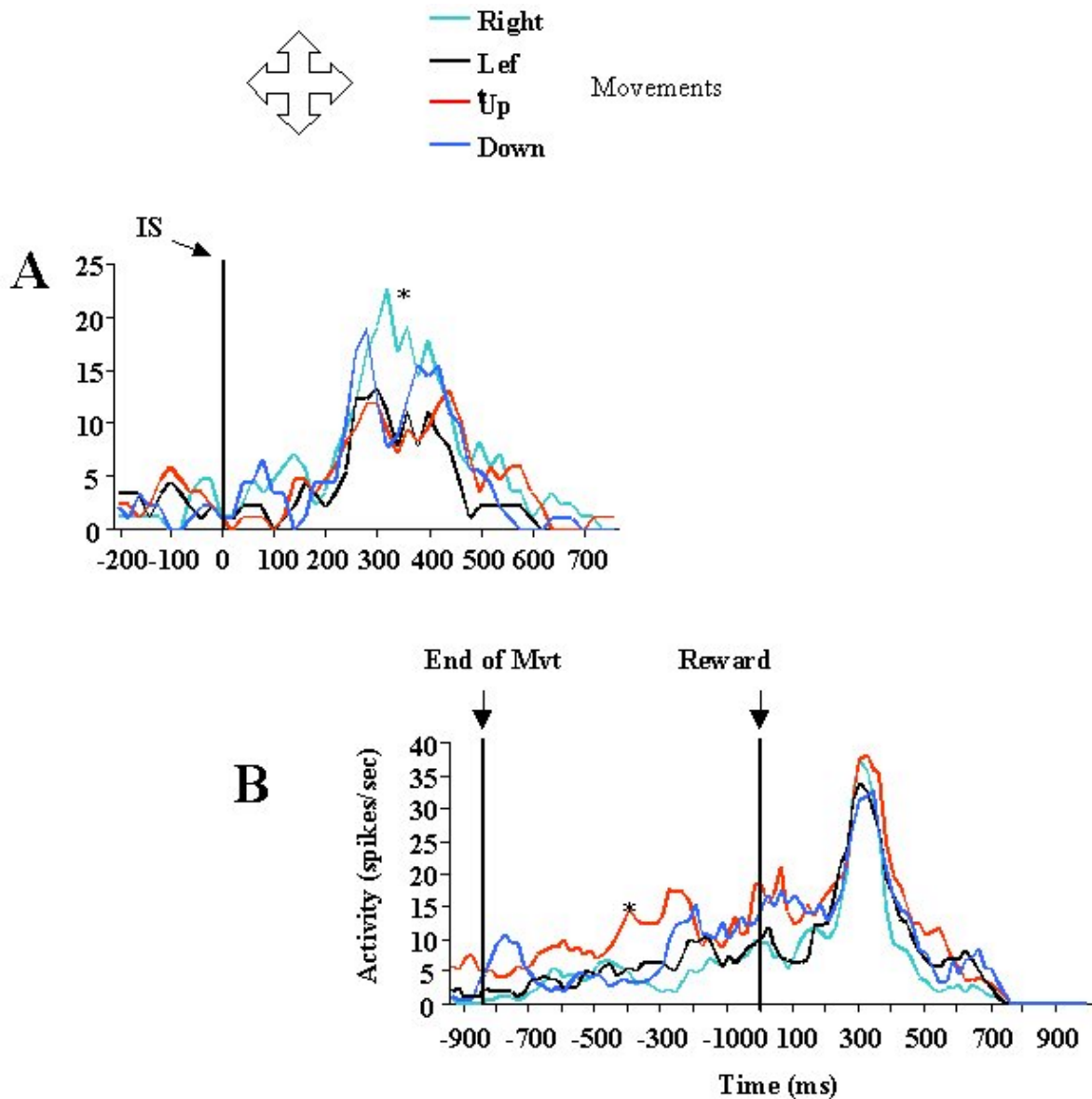


Figure B6. Striatal cells exhibiting a selectivity for one condition during stimulus onset and reward expectation. A) A striatal cell with a stronger response in relation to the stimulus instructing a movement to the right. B) A striatal cell exhibiting a stronger response following the execution of an upward movement.

Activity per condition (bin = 20ms) averaged across several trials. This activity was calculated around the IS (A) and between the end of the movement and reward delivery (B).

b. Modification of striatal activity during learning

A sample of forty neurons was studied under both familiar and novel conditions, and it was thus possible to examine their activity during learning. In 60% of the cases, significant activity changes occurred as the monkey learned new associations during at least one epoch of the task. The learning related changes of activity were either transient or long lasting modulations of task related activity as the behavioral performance improved. These changes were often relatively simple increases (observed in 36 % of the cases, MH n=11, MO n=3) or decreases (38 %, MH n=13, MO n=2) in the firing rate relative to the familiar condition. In some cells, however, modulations of activity were more complex with combinations of increases and decreases in activity (26 %, MH n=9, MO n=1).

□ *Various types of modulation during learning*

Modulation of activity during learning could affect any type of task-related activity, and there was no clear relationship between the type of modulation and the type of activity. In other words, stimulus-related activity was not modulated in a particular way during learning, and movement-related activity in another way. In fact, a given cell may show different modulations depending on the task period considered. Examples of the most frequently observed modulations are illustrated in Figures B7-10.

Figure B7 illustrates a cell with a long lasting increase of activity during learning. In the familiar condition, with a cue instructing a rightward movement, this cell showed a phasic discharge following stimulus onset and during movement execution (B7-a). In the novel condition, when a cue instructed the same movement direction, stimulus related activity was higher than that observed for the familiar condition (dashed lines), and this increase persisted throughout the entire learning process (B7-b, left panel). By contrast, movement related activity was nearly absent in the early stage of learning but emerged progressively during later stages (B7-b, right panel). The profile of activity changes was closely linked to the fluctuations of the animal's performance, and it stabilized at a high discharge rate when the monkey's performance reached 100% correct responses. An additional analysis dissociating correct trials (i.e. rightward movements) from incorrect ones (all other motor responses) confirmed that the movement related activity appeared with learning. Indeed, this activity slowly emerged with a repetition of correct responses, and with progressively shorter latencies, whereas it remained weak in all incorrect trials (B7-c).

Figure B8 illustrates a neuron whose activity decreased during learning. For the familiar condition, the neuron showed a phasic discharge in relation with movement

execution, especially for downward movements (directional preference). This response was initially increased by the presentation of novel associations but then rapidly regained the level observed for the familiar condition. In addition, novel associations triggered a phasic discharge in relation to the stimulus onset. Like movement related activity, this stimulus related activity was transient, the neuron's activity regaining the level observed for familiar associations after few correct trials (Figure 8-A/B).

Figure B9 illustrates a neuron with more complex transient modulations of activity during learning. For the familiar condition, this neuron showed a low (but significant) activity during the expectation of reward, and a strong activity with reward delivery. The activity, illustrated for two familiar and two new associations, developed when the monkey successfully learned a new association, but was absent for a novel association that the animal failed to learn. When learning did occur, both the reward expectation and the reward delivery activities increased significantly with the improvement of performance. After the animal reached 100% correct responses, both activity types decreased slowly, to a level below that recorded for the familiar condition. Note that in the novel condition, the magnitude of the increase was significantly higher for the reward delivery activity than for the reward expectation activity.

Figure B10 illustrates a neuron with increased activity during anticipation of the onset of the IS. Interestingly, as illustrated in the previous example, when the monkey failed to learn a novel association, the neuron remained silent during the anticipatory period and the rest of the trial. It appears as if this activity developed with learning.

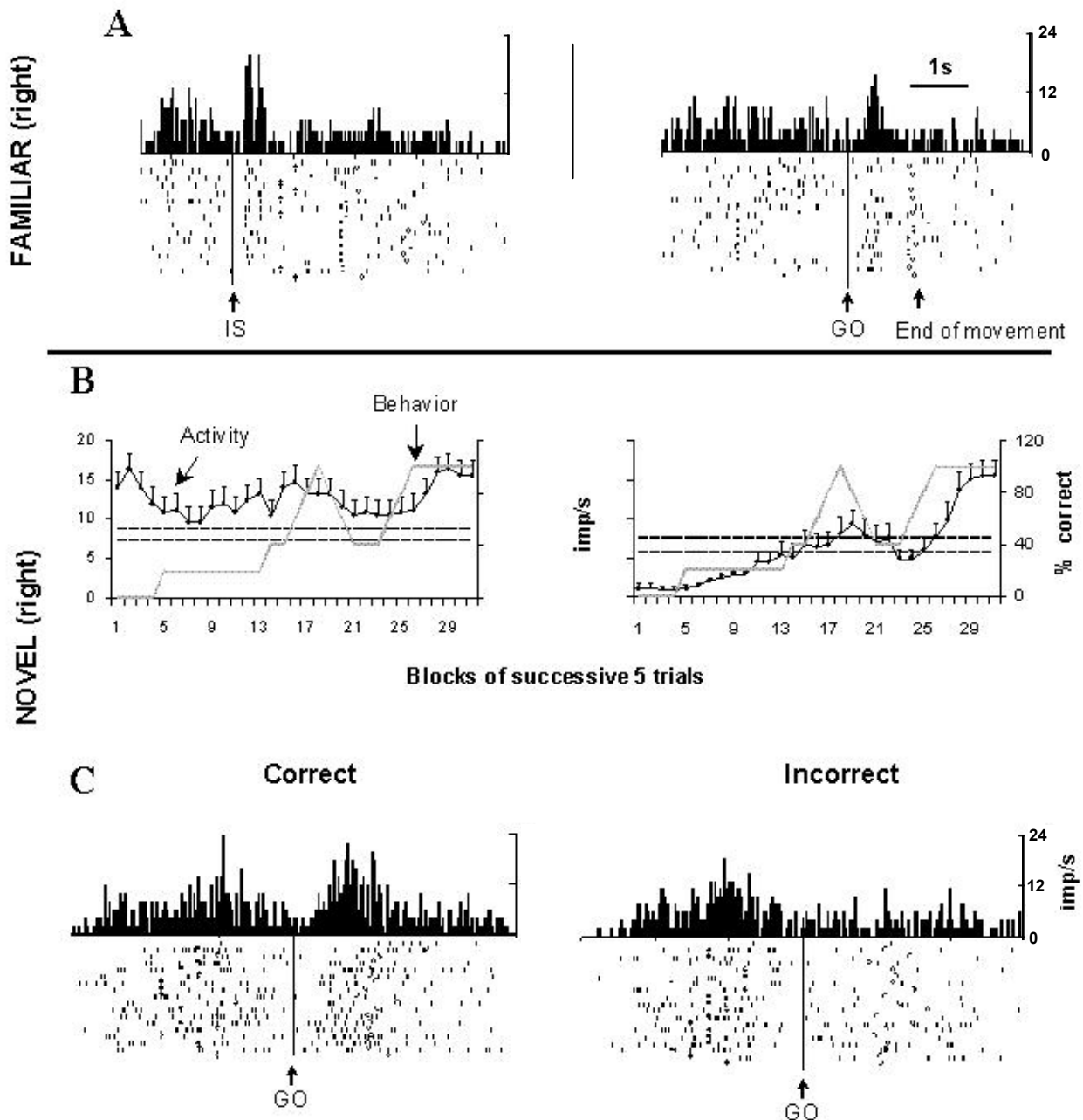


Figure B7. Increase of stimulus and movement related activities during learning in a striatal neuron. Same conventions as in Figure B4. Activity of an individual striatal neuron for a familiar (A), and a novel (B&C) associations, both instructing a rightward movement. This neuron shows a phasic discharge after the presentation of the cue (A, left), and during movement execution (A, right). The trials are aligned (vertical lines) on the onset of the IS (A, left) or on the go signal (A, right & C). The graphs (B) illustrate the changes of activity for the same neuron during learning of a new association instructing a rightward movement. Each graph is a plot of the percentage correct responses and discharge frequency, both calculated as a moving average across blocks of 5 trials (\pm SEM). The two horizontal dashed lines, in each graph indicate \pm 1 SEM of the mean IS-related (B, left) or movement-related activity (B, right) recorded in the familiar condition (i.e. activities illustrated in panel A). IS-related activity was measured from 200 to 500 ms after IS onset and movement-related activity, from 200 to 400 ms after the GO signal. The IS-related activity in the novel condition was higher than that observed for the familiar condition, and remains relatively stable throughout the entire learning process (B, left). By contrast, movement related activity emerged progressively during the learning process (B, right). C. Correct and incorrect trials for the novel condition are plotted separately. Note that learning-related activity emerged gradually with the repetition of correct trials but remained absent during incorrect trials.

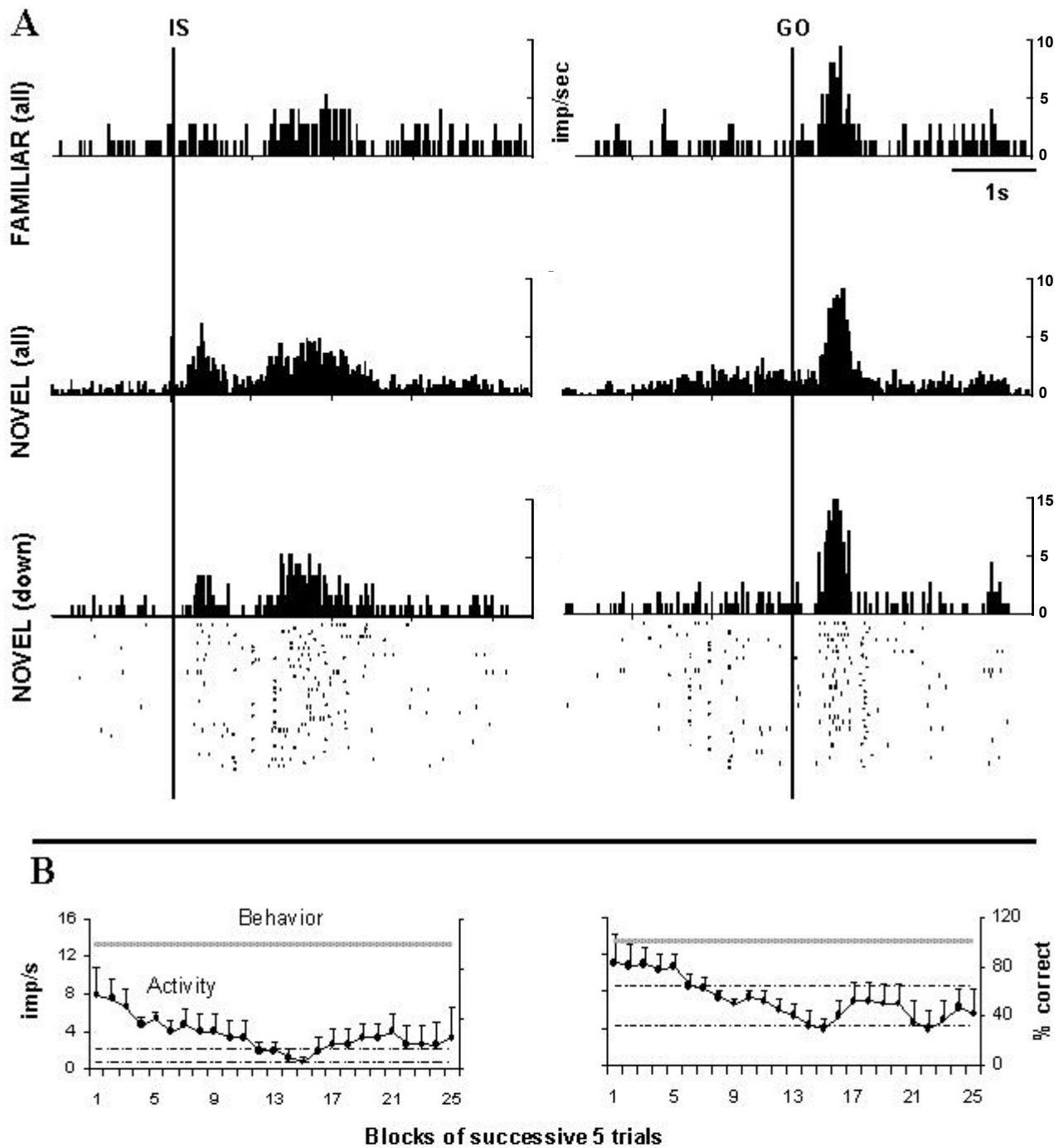


Figure B8. Decrease of stimulus and movement related activities during learning in a striatal neuron. Same conventions as in Figures B4 and B7. Trials are aligned on the IS (left) or on the go signal (right). **A.** From top to bottom: Familiar condition (all four associations); novel conditions (all four learned associations); novel condition for the preferred direction (down). Note that stimulus related activity is absent in the familiar (top left), but present in the novel condition (middle left). Movement related activity is present in both conditions (top and middle right, for familiar and novel conditions respectively). **B. Activity versus behavior during learning.** The IS (B, left) and movement-related (B, right) activities for the novel condition instructing a downward movement was compared to the activity recorded in the familiar condition also instructing a downward movement (dashed lines.)

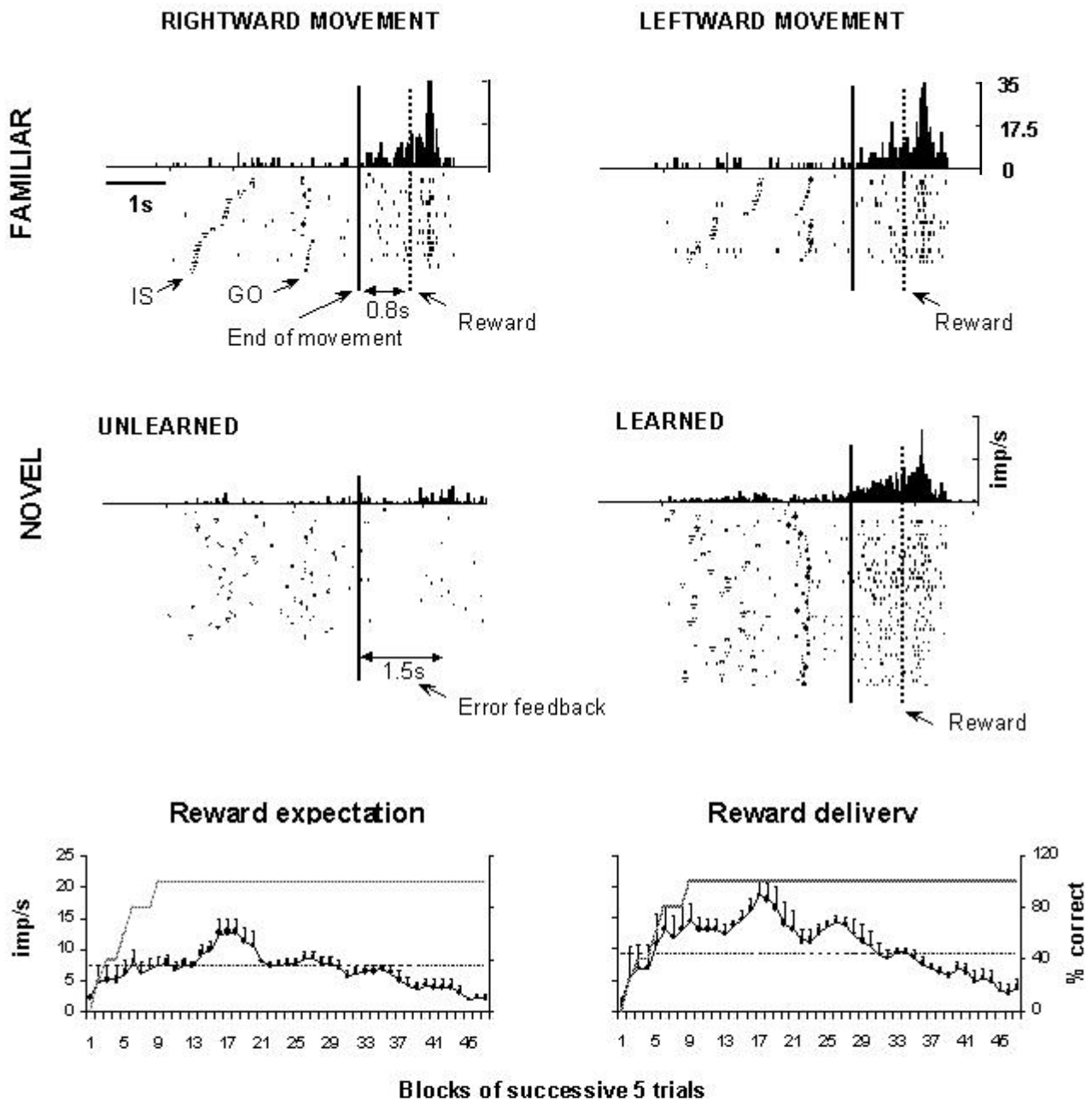


Figure B9. Complex, transient learning modulation of reward related activity of a striatal neuron. Same conventions as in Figures B4 and B7. Trials are aligned on the end of the movement. Reward delivery or error feedback occurs at the vertical dotted line, and during 1.5s after the end of movement, respectively. Reward expectation is measured between the end of movement and the reward delivery (dotted line, 0.8s). Reward delivery is measured from the moment of reward delivery for 0.5s. *Bottom.* Activity *versus* behavior for the learned associations. Note that modifications of the activity occurred only when the animals successfully learned the association (right panel).

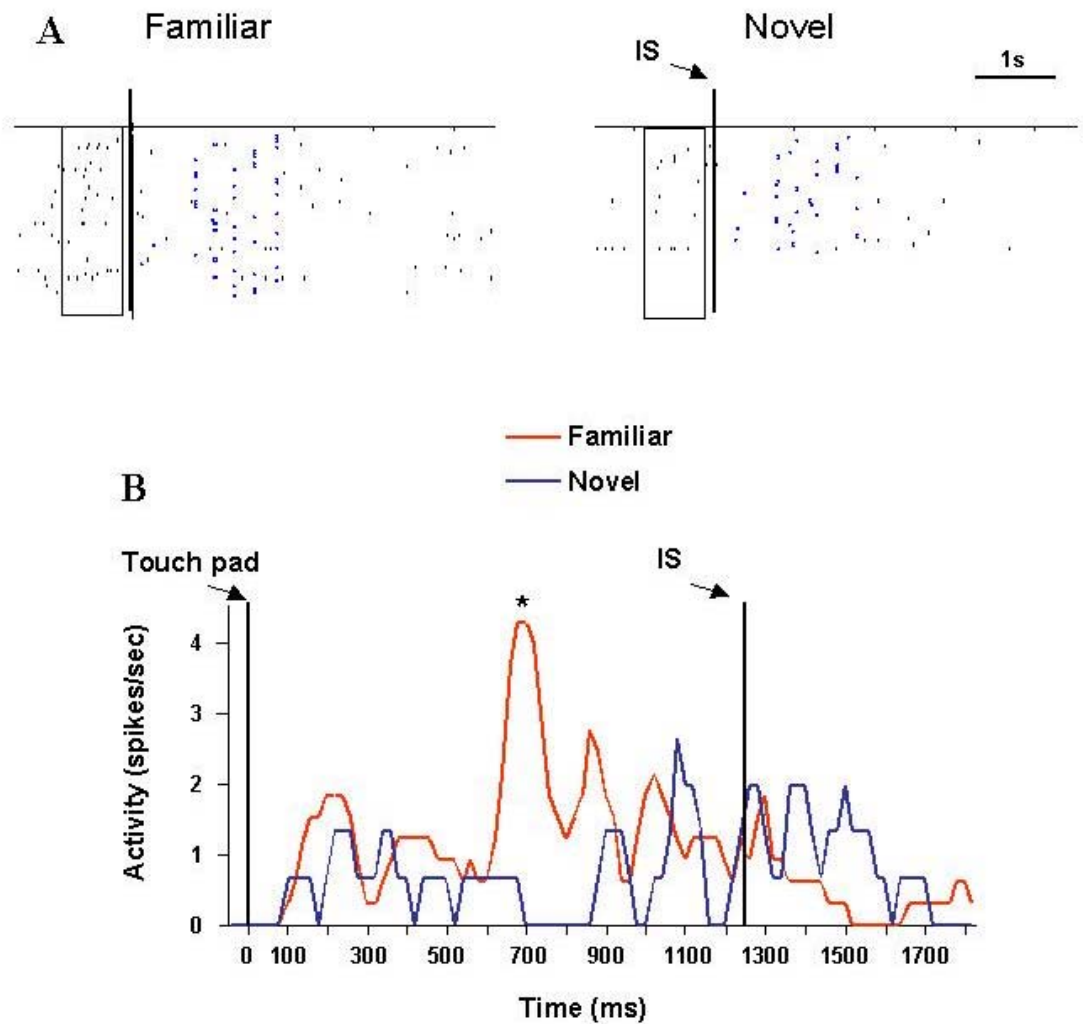


Figure B10. Anticipatory activity associated with well-learned associations. A) Raster display in the Familiar (left) and Novel (right) conditions. B) Activity in the familiar and novel conditions (bin = 20ms) averaged across several trials. This neuron fired before the onset of the IS only in the Familiar condition. In the novel condition, the animal failed to learned any association, and the neuron remained silent.

□

Population analysis

Overall, in the familiar condition, the activity of striatal cells remained relatively stable throughout the recording period as illustrated in Figure B11. The standardized neuronal activity and behavioral performance, averaged over several sessions, are represented for one association (cue instructing a movement to the right). The monkeys' performance was stable and tended to 100 % correct responses. The activity of striatal cells while animals performed these well-learned associations did not show any significant changes across time. An identical pattern was observed for the 3 remaining conditions (not illustrated).

As already described for individual cells, the firing rate of the striatal neurons underwent dramatic changes during learning of new conditional visuo-motor associations. As stated before, two types of changes were observed, and classified as “transient” or “long lasting”. We pooled together the cases with transient activity and found that the modulation consisted of an early increase of activity followed by a progressive decrease along the learning period and after the learning criterion was reached (Figure B12). In early stages of learning, i.e. before the animals reached the learning criterion, the activity of the striatal neurons was relatively high. However, in later stages of learning, i.e. once the performance of the animals tended to reach 100% correct responses, the activity decreased progressively. When the performance stabilized, the activity of striatal cells also tended to stabilize around the level of activity seen in the familiar condition and in some cases even below this level.

The other important pattern of modulation observed in the striatum during learning consisted of a slow increase of activity as learning occurred. Figure B13 illustrates the pooled activity of neurons in 19 cases. The dynamics of activity changes paralleled that of the improvement of the animal's behavior. Contrary to the transient modulation described above, here the activity increased progressively with the percent correct responses and then stabilized, after performance had reached 100 % correct responses, around the level of activity measured during execution of familiar associations. In the very few cases (5/19) which could be recorded over a long post-criterion period (i.e. more than 22 trials), the acquired learning-related activity eventually decreased. It is unclear, however, whether this final decrease would have been observed had a larger sample of neurons been recorded during over training.

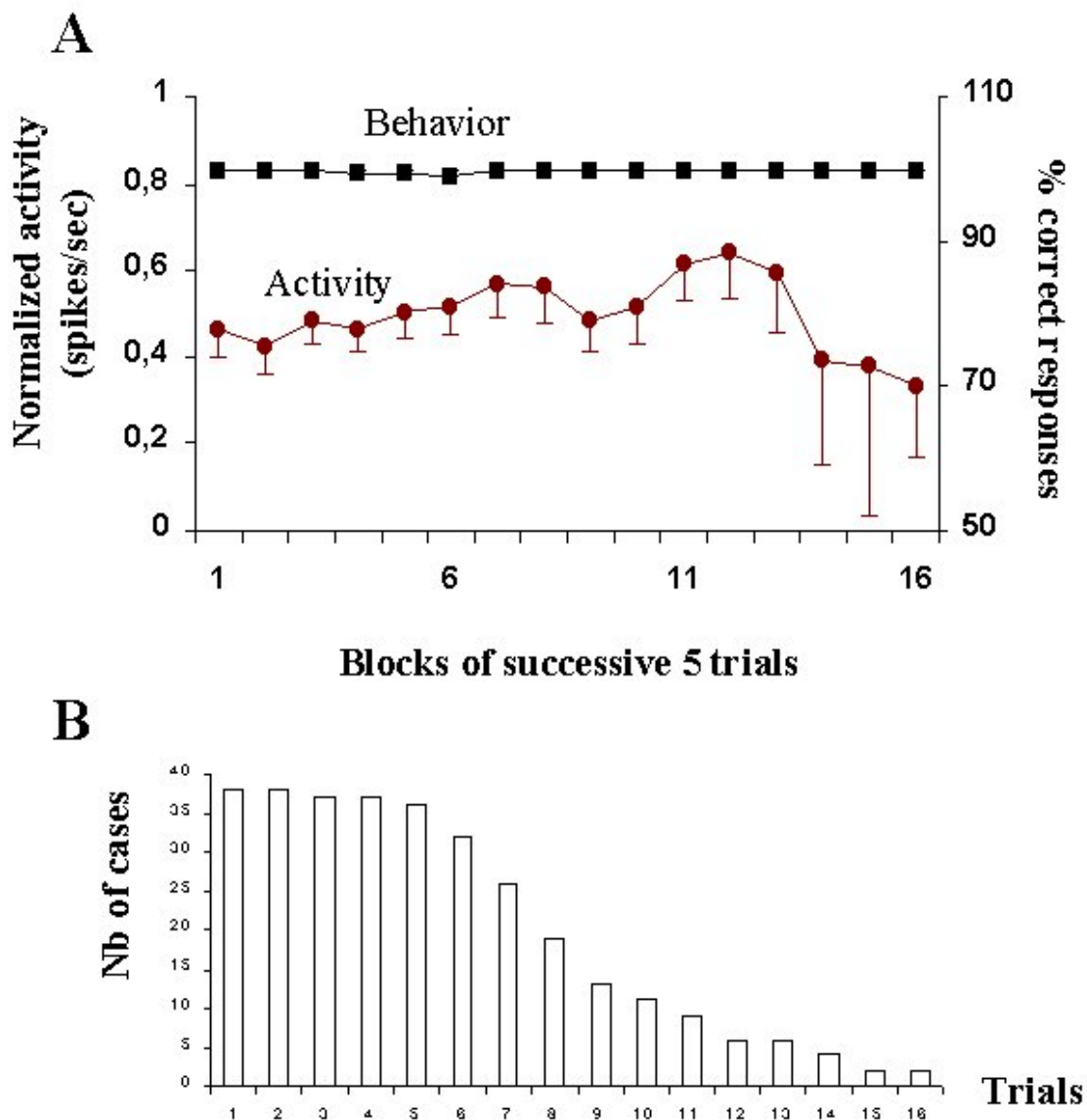


Figure B11. Population analysis : familiar condition (association instructing a movement to the right). **A.** Mean standardized activity across cases for epochs during which a modulation of activity was observed in the novel condition. **B.** Number of cases studied across trials.

Note that the activity of the striatal neurons remained relatively stable across trials (except for a decrease during the last three blocks of trials which was recorded in only 2 to 3 cases and might therefore not be representative of the entire striatal population of neurons)

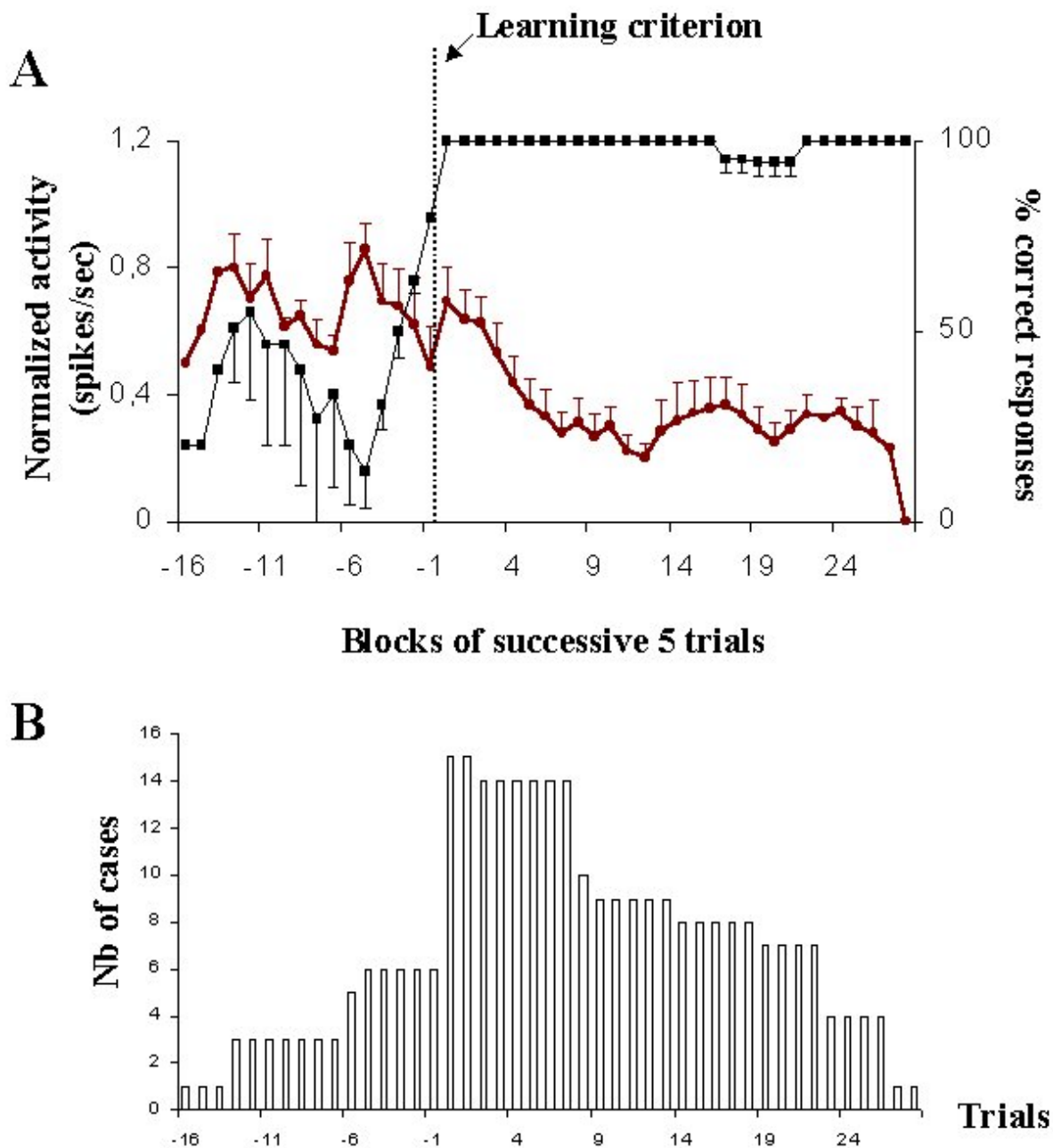


Figure B12. Population analysis : Novel condition - pattern 1. A. Mean standardized activity across cases for which activity increases during learning. **B.** Number of cases studied across trials. Note that these neurons were strongly activated during the early stage of learning. Before the animals reached the learning criterion (dotted line), this activity decreased progressively.

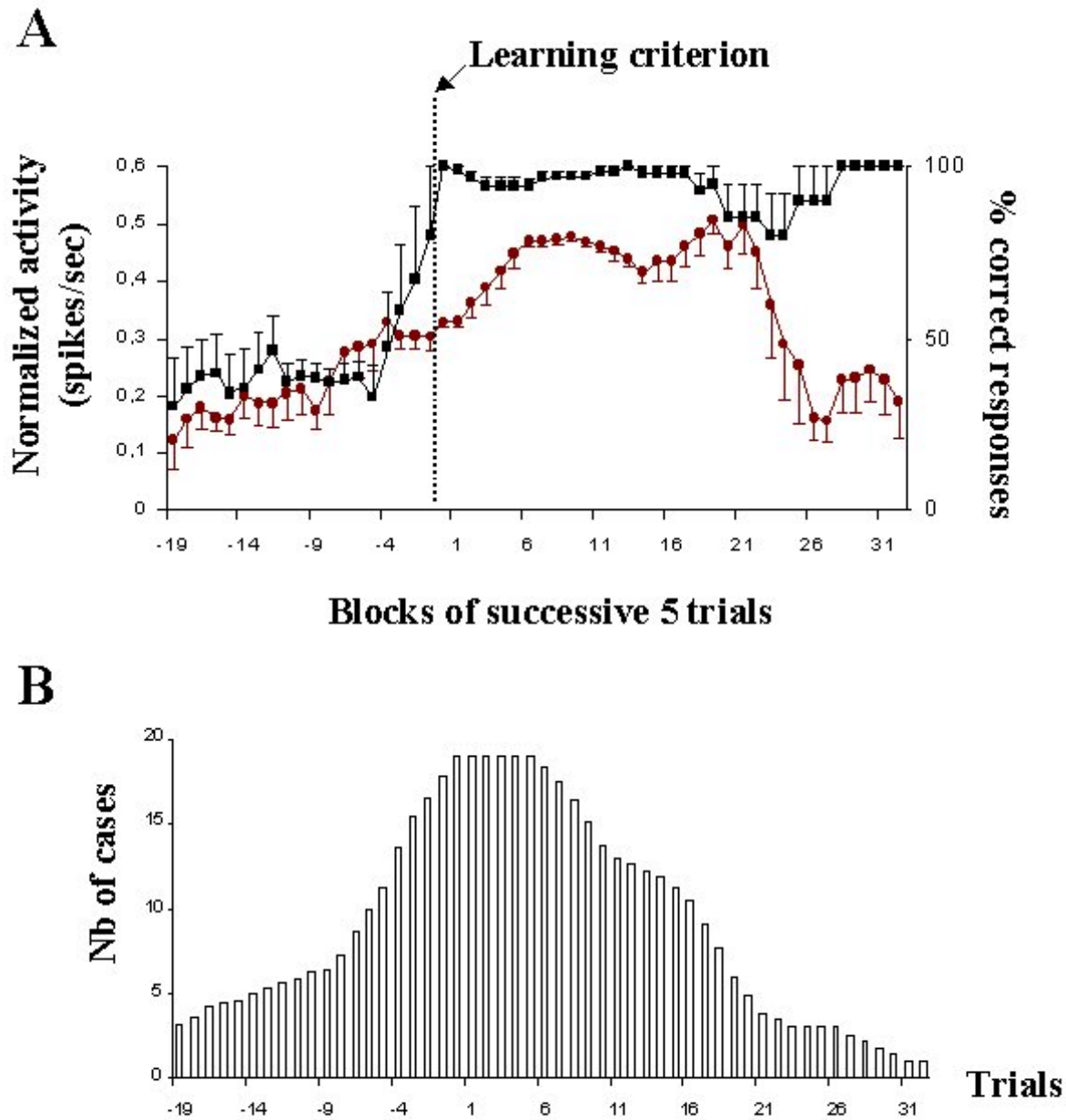


Figure B13. Population analysis : Novel condition - pattern 2. A. Mean standardized activity across cases for which activity decreases during learning. **B.** Number of cases studied across trials.

Note that these neurons had relatively low firing rate during the early stage of learning, that subsequently increased in parallel with the improvement of the animals' behavioral performance.

IV. DISCUSSION

1. Summary of the principal findings

In the present study, activity of phasically active neurons (PANs) was recorded while monkeys executed FAMILIAR arbitrary visuo-motor associations and learn NOVEL ones. The results shows that neuronal activity in the striatum undergoes strong modulations during learning of conditional visuo-motor associations. Task-related activity recorded during execution of well learned associations changes during learning of new associations. Learning-related effects are complex, but they can be summarized as three types of modulations. In some cases, cell activity increased gradually as the animals learned and it stabilized at the end of learning. In others, activity appeared only during the early phase of learning and disappeared when the monkey's performance reached a plateau. Finally, in some instances, activity modulations during learning were combinations of increases and decreases, depending on the level of learning. Overall, these activity modulations are either transient or long lasting. We will discuss their possible functional implications, in relation with previously published data.

2. General properties of striatal neurons during the execution of well-learned arbitrary visuo-motor associations.

During execution of familiar associations, striatal neurons display a phasic discharge in relation with a variety of task events including anticipation of the cues, the onset of the cues, movement preparation and/or execution, and reward (see Figure B4). Single neurons may present activity in relation with more than one of these events. These properties are well known in the striatum (Hikosaka et al., 1989a,b,c; Alexander & Crutcher, 1990; Kawagoe et al., 1998; Kimura & Matsumoto, 1997; Rolls, 1994, Schultz et al., 2003; Boussaoud & Kermadi, 1997), and there have been several interpretations of their functional implications. One important aspect is that this divers pattern of activity has led to the now accepted view of basal ganglia role in more than motor control. Indeed, it now well accepted that these structures play a crucial role in complex processes such as context dependent selection of action, memory, and motivational states in relation with reward. In fact, previous studies have shown that instead of serving as a motor relay for cortical information, basal ganglia may control high level processes of action selection by influencing cortical activity via the

thalamus (e.g. Alexander & Crutcher, 1990; Boussaoud & Kermadi, 1997). With recent work on dopamine neurons (Schultz, 2002, Fiorillo et al., 2003), and striatal plasticity (Jog et al., 1999), basal ganglia appear in a key position to use these multiple signals to optimize learning capacity.

3. Modulation of activity in the striatum during learning of novel visuo-motor arbitrary associations: a comparison with changes in the frontal lobe

As summarized above, the multiple types of striatal activity undergo transient and/or long lasting changes during learning. One important observation is the labile neuronal properties of striatum cells. If, for example, a cell has a preferred direction during the familiar task, during learning of a new set of associations, its preferred direction may not be the same. One may interpret this observation in the following way: each new experience or learning creates a new distribution of activity among the population of striatal neurons. By comparison, neurons in the cortex tend to have relatively fixed properties which are retrieved after new learning (Mitz et al., 1991).

Comparison of the present results with frontal cortex data suggests that the same modulations exist at both levels. Indeed, our “transient” and “long lasting” effects of learning have an equivalent in frontal cortex described as "learning-selective" and "learning-dependent or learning-static", respectively (Chen and Wise, 1995a,b). Thus, the present study, as well as the study by Tremblay et al. (1998), suggest that the striatum and frontal cortex share common, and possibly related, adaptive mechanisms during the acquisition of conditional visuo-motor behavior. The question remains as to whether and how the striatum and frontal cortex contribute differentially to such learning.

Wise and colleagues proposed that in the premotor cortex (i.e., SEF and PMd), the long lasting and the transient activity changes "may underlie responses selected on the basis of learned associations, and those selected by trial and error", respectively (Chen and Wise, 1995a; Mitz et al., 1991). Here we propose that distinct processes may underlie the changes observed in the striatum. Our conjecture is that transient changes in the striatum may play a critical role in the short-term maintenance in memory of the stimulus previously seen, the already tried associations and their outcome. This is consistent with the transient modulations of stimulus and reward related activities observed here (Figure B8 and B9) as well as in a previous study (Tremblay et al., 1998). Indeed, the increased activity related to the stimulus or to the reward might reflect increased processing of the new stimulus and its behavioral

outcome (reward expectation as a positive feedback). This is probably mediated in close relationship with the PFvl and the hippocampus, which have been shown to participate in the earliest stages of learning (e.g. Passingham et al., 2000; Wise & Murray, 1999). By contrast, the long lasting striatal changes might contribute to the long term storage of learned associations. Indeed, as observed in well-learned associations, activity does not reflect a specific stimulus, or a specific motor response, rather it seems to reflect a specific association between one particular stimulus and one particular movement (Figure B7). As previously said, this finding is in agreement with a previous study showing that, in a well-learned conditional task, striatal activity was correlated with specific stimulus-response associations (Boussaoud & Kermadi, 1997). Interestingly, the proportion of such cells was higher in the striatum than in PMd, suggesting that the new stimulus-response associations might be stored, at least in part, in the striatum.

One important issue is the interaction between the striatum and the PMd. During learning, both transient and long lasting changes of striatal activity may modulate neuronal activity in PMd, via the basal ganglia output nuclei and thalamus. This conjecture is supported by recent evidence of early neuronal changes in the GPi (internal globus pallidus), one of the output nuclei of the basal ganglia to the frontal cortex during acquisition of conditional visuo-motor associations (Inase et al., 2001). Additional support of this idea comes from a recent fMRI study by Toni et al. (2002), who found that learning visuo-motor rules strengthens effective connectivity between the striatum and PMd. In this regard, transient modulations are of particular interest, as they might first drive the changes observed in the PMd, before the reinforcement by the long lasting changes. After learning, the strengthened connectivity between basal ganglia and PMd is crucial for task performance, as demonstrated by lesion studies (Canavan et al., 1989b; Passingham, 1986; Petrides, 1985).

4. Alternative explanations

Alternative explanations could account for the modifications of activity observed in the NOVEL conditions. These modifications could indeed be related to attentional processes following the presentation of a novel stimulus (Boussaoud & Kermadi, 1997). First, one might argue that the observed activity changes during learning could reflect the changes in attentional demands, which decrease as the monkeys become familiar with the new associations. This interpretation does not appear to be compatible with our observation. This interpretation would require that the activity would be higher for the first trials and would

decreases progressively with learning. However, during learning, activity was low for the first trials and increased progressively as the animal learned. Second, if activity reflected the novelty, the changes of activity in relation to attention would be expected to occur for both learned and unlearned associations (see Figure B9).

Another possible interpretation could be that the changes of activity in the striatum could reflect the expectation of reward, which increases as the animals learn. This interpretation can indeed account for the cases where activity increased as the animal acquired the novel associations, but for the cases with transient modifications (where activity of these neurons decreased).

5. Limits

It is important to point out that the sample of neurons recorded here may introduce a bias. Indeed, in a typical recording session, the animal performed first the FAMILIAR associations, while searching to isolate neurons. We usually isolated 1 to 2 neurons from the electrode. In order to isolate neurons, we slowly advanced the electrode toward a region showing phasic task-related activities. Activity of the neurons was recorded during the FAMILIAR condition. Then, novel stimuli were presented and activity of the neurons was recorded while the animals learned these NOVEL associations. However, during the FAMILIAR condition, the neurons could be silent (not showing any task-related response). When presented with NOVEL associations, this neuron will started to fire, either for a short or a longer period of time. Our sampling method may have underestimated these cases. This is indeed likely as Miyachi et al. (2002) reported neurons specifically active in relation with either NOVEL (new preferring neurons) or FAMILIAR (learned preferring neurons) visuo-motor sequences, which followed an anteroposterior gradient. The former were more numerous in the anterior striatum ('associative') whereas the latter were predominant in the posterior striatum ('sensorimotor'). According to the MRI scan obtained for monkey MH, our recording sites were located in both of these regions.

**C - Neuropsychological study in Parkinson's
patients**

in collaboration with :

**Pr. Emmanuel Broussolle,
Dr. Isabelle Benatru,
Hélène Klinger.**

INTRODUCTION

Various forms of conditional associative learning (CAL) have been studied in patients suffering from Parkinson's disease (PD), as summarized in Table C1 (Canavan et al., 1989; Gotham et al., 1988; Marié et al., 1999; Pillon et al., 1998; Postle et al., 1997; Sprengelmeyer et al., 1995; Taylor et al., 1990; Vriezen & Moscovitch, 1990). These studies have yielded contradictory results. Although PD patients were often found to perform less efficiently than controls, a lack of impairment was also reported in several instances. As typical in neuropsychology, several parameters vary across studies, including the age of the patients, their stage in the disease, their pharmacological treatment, the task modalities and the stimulus presentation mode.

The age of the patients may influence the patients' performance. For example, although Canavan et al. (1989) reported no significant impairment in either visuo-motor or visuo-visual CAL in a group of 19 early PD patients, some of the oldest patients (over 70 years of age) did perform poorly compared to controls. However, given that there is an age-related decline in CAL in normal subjects (Levine et al., 1997), the poor performance of old PD patients (over 70 years) may reflect normal aging rather than a disease effect. Since the age of the control subjects in the Canavan et al.'s study ranged from 54 to 67 years, this possibility cannot be ruled out.

The stage of the disease does not appear to be a determinant factor as both Early and 'Standard' PD patients² were found to be equally impaired in several studies (see for example, Pillon et al., 1998).

Pharmacological treatment with anticholinergic drugs does not seem to influence PD patients' performance in CAL (Canavan et al., 1989). By contrast, L-dopa, despite its beneficial effects on motor symptoms, could have a negative impact. First, Gotham et al. (1988) reported that the same patients that performed well during L-dopa withdrawal, were impaired under L-dopa treatment. Second, among the two studies that used a visuo-visual task based on color-shape associations to evaluate early PD patients (Canavan et al. 1989, and Marié et al. 1999), only the one carried out in patients treated with L-dopa (Marié et al. 1999) reported an impairment. This negative effect of the L-dopa may be due to an overstimulation

² Early *versus* 'Standard' (or advanced) patients correspond approximately to patients with less *versus* more than 10 years of disease, respectively.

of the dopaminergic (DA) system projecting to the prefrontal cortex, which is supposed to be spared in the early stage of the disease (Marié et al. 1999).

In addition, it seems that whenever a spatial component is introduced in the task, whether in the stimulus or in the response arrays, the performance of PD patients is systematically impaired. It is the case for Early as well as 'Standard' PD patients, with or without treatment, and whether stimuli were successively or simultaneously presented (Pillon et al., 1998; Postle et al., 1997; Taylor et al., 1990; Vriezen & Moscovitch, 1990).

Finally, presenting complex abstract visual stimuli simultaneously, as opposed to successively, seems to ameliorate PD patients performance. In the simultaneous mode of presentation, all the visual stimuli are presented at the same time and one is highlighted, the one for which the subject has to give a response. This mode of presentation offers the possibility to directly compare the different stimuli, thereby facilitating their discrimination and recognition (Postle et al., 1997; Vriezen & Moscovitch, 1990).

In summary, earlier studies on CAL in PD patients suggest that dopaminergic treatment, tasks involving a spatial component, and successive presentation of the stimuli, all deteriorate the performance. By contrast, these earlier studies provide little insight on the exact type of difficulty PD patients encounter when they are impaired on CAL.

As already mentioned in the previous section, the defining characteristic of conditional associative tasks is that there are several, competing responses, each being correct when performed in the presence of the appropriate stimulus (Petrides, 1985). Several processes are confounded when subjects are asked to learn by trial and error a set of stimulus-response associations. For each stimulus presented, subjects have first to discriminate it from the other stimuli (recognition memory). Subsequently, they need to select a response and most importantly to hold its consequence (i.e correct versus incorrect) in working memory. A correct or an incorrect response must be integrated, probably under the influence of reward and error signals. All this information needs to be organized and monitored in working memory across trials before each stimulus-response association can be first established and then consolidated. In addition, because several associations are learned concurrently, specific strategies (e.g. focusing on one association at a time) may be used to optimize performance. Thus, cognitive processes such as recognition memory, on-line maintenance and organization of information in working memory, response selection, and feedback use are all confounded in CAL. Each of these different processes may be impaired in PD patients (for a review, see Dubois & Pillon, 1997), thus measuring global performance can not provide clues about the specific process that is altered in PD patients during conditional associative learning.

One study (Vriezen & Moscovitch, 1990) has shown that verbally providing the correct response to PD patients after each error did alleviate their impairment on visuo-verbal CAL. This suggested that, unlike frontal lobe damage (Petrides, 1997), Parkinson's disease does not interfere with motor selection once the rule is provided, but selectively alters trial-and-error learning of arbitrary rules. Other studies have calculated the number of times subjects tried the same incorrect association. In Postle et al.'s study (1997), PD patients made more of these errors than controls only in the spatial condition. These types of errors were also reported in the Pillon et al.'s study (1998), except for the Early PD in the visuo-spatial condition. Overall, according to these two studies, PD patients tend to repeat the same incorrect association more often than controls. In addition, Pillon et al. (1998) calculated the number of times PD subjects failed to inhibit a response for which they had already found the correct stimulus. They found that Early as well as Standard PD groups made significantly more of these perseveration errors than the controls groups.

Thus, neurophysiological studies (see previous part) suggested clearly a role of the basal ganglia in CAL task, but it is not obvious whether their dysfunction alters learning in this tasks. We reasoned that a systematic investigation using the same task as in the neurophysiological study would reveal an impairment in PD patients. We have thus tested the ability of a group of 'Standard' PD patients first to form a single stimulus-response association with and without using working memory, and then to learn, by trial-and-error, a conditional task during which sets of three visual stimuli had to be mapped onto four possible movements. For CAL, we have attempted to analyze the patients' performance in detail so as to gain some insight on the specific difficulty they encounter when impaired.

Table C1. Conditional Associative Learning (CAL) in PD patients : a summary

Studies	Age mean±SD (range)	Stage of the disease ¹		PD Diagnosis	Treatment	Task modality ²	Stimulus presentation ³	Performance
		EARLY	LATE					
Postle et al., 1997	64.9±8.2	×	—	H&Y : 0-II	ON L-dopa	Visuo-visual (6)	Simultaneous	Preserved
		×	—	—	ON L-dopa	Spatio-spatial (6)	Simultaneous	Impaired
Taylor et al., 1990	64±9	×	—	H&Y : 0-II 1-3 months	CFF L-dopa	Spatio-spatial (4)	Simultaneous	Impaired
Canavan et al., 1989	57.9±11.6 (52-74)	×	—	0.5-7 years	10/19 ON anticholinergics	Visuo-motor (6)	Successive	Preserved
					1/19 ON L- dopa	Visuo-visual (6)		Preserved
Marie et al., 1999		×	—	H&Y : 0-II	ON L-dopa	Visuo-visual (6)	Successive	Impaired
Pillon et al., 1998	60.4±11.1 63.2±9.6	×		Mean H&Y : II	CFF L-dopa	Visuo-spatial (6)	Successive	Impaired
			×	2 years Mean H&Y : III 10 years	ON L-dopa	Verbo-verbal (6) Visuo-spatial (6) Verbo-verbal (6)		Impaired Impaired Impaired

1 The stages of the disease are termed EARLY versus LATE according to either the Hoehn and Yahr's scale when available or the duration of the disease (× and —: tested and not tested, respectively).

2 The task modality refers to the nature of the stimulus-response associations to be made. Numbers in brackets correspond to the number of associations to be learned.

3 The presentation mode is termed successive when stimuli were presented one at a time, and simultaneous when all stimuli were present for each trial, the one requiring a response being highlighted.

SUBJECTS AND METHODS

Subjects

Nine patients with Parkinson's disease (PD) and eight controls were tested in these experiments. The main characteristics of these two groups are summarized in Table C2. The protocol was approved by the local Ethics Committee for clinical investigations, and informed consent was obtained from all subjects.

a. Patients

Nine patients with idiopathic PD were recruited from the clinical department of Neurology of the Hospital of LYON. The diagnosis of PD was established on the basis of the following criteria: 1) existence of either an akinetorigid syndrome, resting tremor, or both; 2) good sensitivity to levodopa treatment. All patients selected in this study were treated with levodopa and were candidates for a surgical implantation of chronically implanted electrodes in the subthalamic nucleus. They were thus selected following strict criteria (Limousin et al, 1998; Thobois et al, 2002). All patients had marked "on" state dyskinesias and on-off fluctuations. Details concerning motor, cognitive states as well as treatments are summarized in Tables C3 and C4 for each patient. A routine neuropsychological tests were administrated only in the ON condition, and their details are provided in annex.

The Patients were tested under two conditions: 'ON' and 'OFF' levodopa state. In this preliminary study, seven patients were first tested in the 'OFF' condition, i.e. after overnight withdrawal of medication (12 hours). In the 'ON' condition, the testing lasted approximately one hour after (levodopa) treatment with a standard dose of levodopa (= 1.5 times their current dose). The two remaining patients were first tested in the 'ON' condition (same as above) and then in the OFF condition.

b. Controls

Eight control subjects, recruited from local advertisements in the Lyon area, participated in this study. They had no neurological or psychiatric history, and matched the PD patients for age and level of education.

TABLE C2. MAIN CHARACTERISTICS OF THE CONTROL AND PD PATIENT GROUPS

CHARACTERISTICS OF CONTROL GROUP				CHARACTERISTICS OF THE PD PATIENT GROUP			
CONTROLS	SEX	AGE	EDUCATION LEVEL (years)	PATIENTS	SEX	AGE	EDUCATION LEVEL (years)
1	F	57	12	1	M	52	19
2	M	58	15	2	M	60	9
3	F	51	9	3	F	42	9
4	M	52	9	4	F	50	12
5	F	55	12	5	M	52	9
6	F	56	15	6	M	53	10
7	M	48	12	7	M	54	19
8	F	66	9	8	M	61	9
				9	M	49	12
Mean		55.4	11.6	Mean		52.6	12.0
SEM		1.9	0.9	SEM		1.9	1.4
Minimum		48	9	Minimum		42	9
Maximum		66	15	Maximum		61	19

TABLE C3. PD PATIENT GROUP: DURATION OF THE DISEASE, TREATMENT AND MOTOR STATES

CASE/AGE/SEX	DURATION OF THE DISEASE(YEARS)	DOPAMINERGIC TREATMENT*		HOEHN & YAHR SCORES		UPDRS MOTOR SCORES	
		Duration	Dose (mg/day)	OFF dopa	ON dopa	OFF dopa	ON dopa
1/52/M	10	10	1500	3	1.5	42	7
2/60/M	10	10	1200	3	2	31	9
3/42/F	12	12	500	3	2.5	43	10
4/50/F	13	12	1125	3	2	36	10
5/52/M	13	13	1775	4	2	48	20
6/53/M	11	11	1500	4	2	48	9
7/54/M	10	10	1500	3	1	30	8
8/61/M	7	7	1290	3	1.5	29	8
9/49/M	9	7	1260	3	1.5	34.5	13
Minimum	7	7	500	3	1	29	7
Maximum	13	13	1775	4	2.5	48	20

* Dopaminergic treatment included both levodopa and dopaminergic agonists (Doses were calculated as L-dopa equivalent in mg/day)

TABLE C4. PD PATIENT GROUPS : NEUROPSYCHOLOGICAL SCORES

CASE/AGE/SEX	BDI	MATTIS DEMENTIA RATING SCALE					
		Total (/144)	Attention (/37)	Initiation (/37)	Construction (/6)	Concepts (/39)	Memory (/25)
1/52/M	10	138	37	37	6	38	20
2/60/M	33	128*	37	29	5	37	20
3/42/F	21	141	36	37	6	37	25
4/50/F	10	138	36	37	6	36	23
5/52/M	10	132	34	35	6	33	24
6/53/M	14	133	36	35	5	34	23
7/54/M	9	141	37	37	6	36	25
8/61/M	6	124*	34	28	6	33	23
9/49/M	21	142	37	37	6	39	23
Minimum	6	124	34	28	5	33	20
Maximum	33	142	37	37	6	39	25

CASE/AGE/SEX	GROBER & BUSCHKE-MEMORY				
	Immediat recall (/48)		Delayed recall (/16)		Recognition (/16)
	free	indexed	free	indexed	
1/52/M	-	-	-	-	-
2/60/M	-	-	-	-	-
3/42/F	41	48	13	16	16
4/50/F	35	47	15	16	16
5/52/M	25	47	12	16	16
6/53/M	22	48	13	16	16
7/54/M	27	48	10	16	16
8/61/M	20	44	11	15	16
9/49/M	22	47	8	16	16
Minimum	20	44	8	13	16
Maximum	41	48	16	16	16

CASE/AGE/SEX	WISCONSIN CARD SORTING TASK – FRONTAL SCORES				
	Total scores (20)	Categories (/6)	Perseverative errors	Maintenance errors	Total errors
1/52/M	-	-	-	-	-
2/60/M	-	-	-	-	-
3/42/F	18	6	0	1	1
4/50/F	20	6	1	0	4
5/52/M	9	3	9	1	21
6/53/M	18	6	1	1	5
7/54/M	15	5	2	1	11
8/61/M	12	4	6	1	15
9/49/M	6	6	0	0	0
Minimum	6	3	0	0	0
Maximum	20	6	9	1	21

BDI, Beck Depression Inventory

- data not available

* These low scores are to be related to the social background of the patients.

Materials

Subjects sat in front a computer screen where visual stimuli were presented (Figure C1). Visual stimuli consisted of complex geometric colored patterns that were difficult to verbalize. They were presented on a dark background. All the experiments were controlled by a home-made program running under Windows. Subjects gave their responses using a joystick which could be moved in four directions (referred to as right, left, up and down). They practiced to move the joystick before testing started. None of the patients included in the study had difficulty using the joystick.

Procedure

The experiment consisted of a series of tasks presenting an increasing level of difficulty (Figure C2). In all tasks, a trial started by the presentation of a yellow central fixation cross during 1s, instructing to the subject to pay attention to the screen, and the subjects were informed about the result of their response after each trial. If the subject gave a correct response, a green smiley face appeared for 1s, if the response was incorrect, a red unhappy face was presented for 1s. In the task involving learning, we considered that subjects had learned when they responded correctly over 3 consecutive presentations of a given stimulus.

Each subject completed a series of tasks in the following order (Figure C2): 1) a standard mapping task, 2) a learning task where they had to associate by trial and error one visual stimulus with the correct response, with or without load in working memory, 3) a conditional learning task where they had to associate by trial and error three visual stimuli with their correct responses. In all tasks, the same categories of visual stimuli were used and subjects were asked to respond as quickly as possible.

Standard mapping task (SM)

In this task, after the presentation of the fixation point, a visual stimulus was presented at one of four positions on the screen : UP - RIGHT - LEFT - DOWN. The position of the visual stimulus varied pseudo-randomly within each block of four trials. The subject was asked to displace the joystick in the direction indicated by the stimuli. A feedback was presented in the direction chosen by the subject. A block of 12 trials were completed by each subject for all (three per direction). The same visual stimulus was used for all 12 trials.

Single association learning without working memory (SLnoWM)

For this task, a new visual stimulus was presented at the center of the screen after the extinction of the fixation point. The subjects were asked to find the correct joystick movement associated with this stimulus. They were explicitly informed that there was no direct link between the physical features of stimulus and the correct motor response. Every time the subject tried a response, he/she received a feedback which remained on the screen during the rest of the trials. For example, if the subject moved the joystick to the right and the right was not the correct direction, a negative feedback (unhappy face) was presented on the right side of the screen and remained on during the following trials. In such a situation, the subject did not have to hold in memory the outcomes of preceding trials. The aim here was to test the subject's capacity to select one movement among the still possible ones and the ability to refrain from perseverating in incorrect choices. The testing lasted until the learning criterion was reached. Two separate associations were successively presented until the learning criterion of three correct consecutive responses was achieved.

Single association learning with working memory (SL_WM)

This task was identical to the previous one except that feedback was presented on the center of the screen. The subjects were asked to remember their different responses and their consequences (correct/incorrect). Two associations were successively presented until the learning criterion was achieved.

Visuo-motor Conditional associative learning task (CAL)

In this task, sets of three visual stimuli were used. The stimuli were presented one at a time, at the center of the screen, in a pseudo-random order within each block of three trials. As in the previous experiments, the subjects were asked to learn by trial and error the correct movement associated with each stimulus, until they reach the learning criterion for each visuo-motor associations. One to three sets of three stimulus-response associations were completed by each subject. In each block, three different novel stimuli chosen within the same family (e.g. same color) were used. One block was completed when subjects reached the learning criterion for the three stimulus-response associations.

As compared to the SL_WM task, in this task, subjects had to handle a large amount of information in working memory. They had to discriminate the different stimuli presented and to remember the responses tried for each stimulus and whether that response was correct or incorrect.

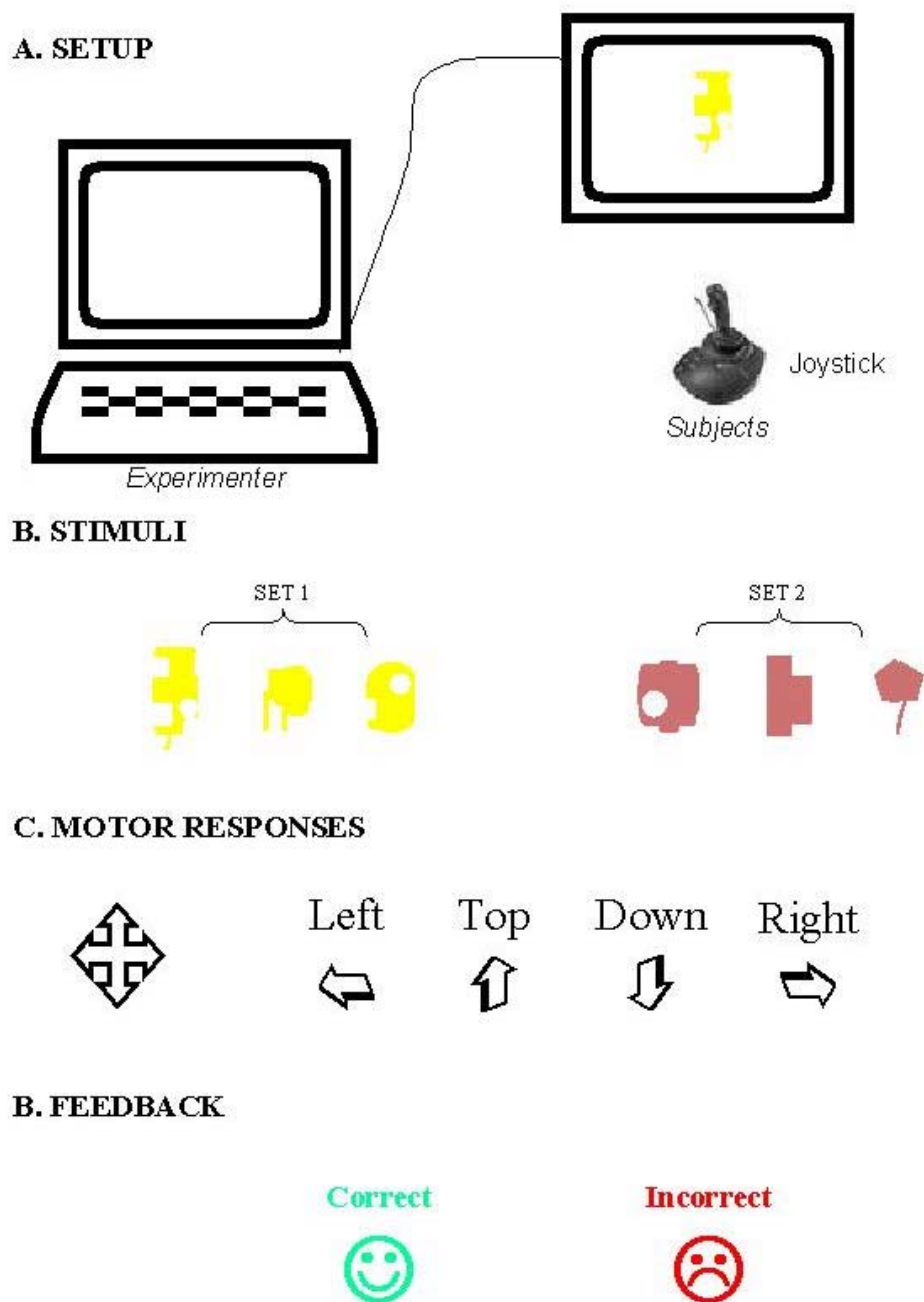
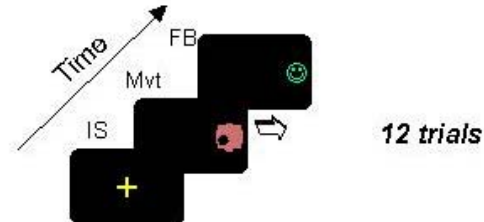
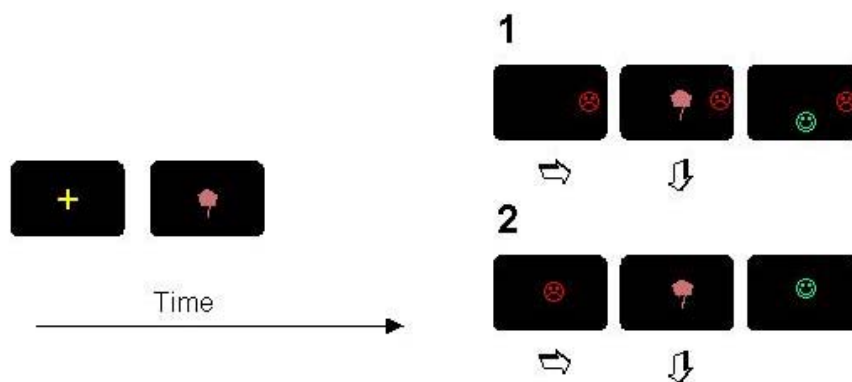


Figure C1. Experimental setup. A. Subjects sat in front of a video monitor and held a joystick in their hand. B. The stimuli used were complex geometric colored patterns. For conditional associative learning, sets of three stimuli from the same family were presented to the subjects. C. Joystick movements were constrained in four directions, represented by the four arrows. D. After each response, the subjects were given either a positive or a negative feedback.

A - STANDARD MAPPING



B - SINGLE ASSOCIATION LEARNING



C - CONDITIONAL ASSOCIATIVE LEARNING (CAL)

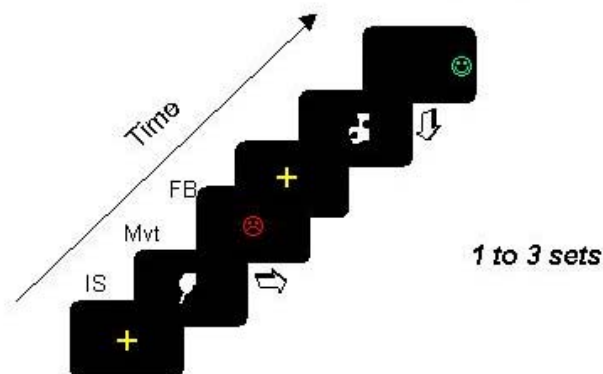


Figure C2. Task design. A. In the standard mapping task, subjects moved the joystick in the direction indicated by the stimulus. B. In the single association learning tasks, they had to find which of the four possible motor responses was arbitrarily associated with one stimulus, either (1) with a feedback indicating the direction and accuracy of responses from previous trials, or (2) with only a brief feedback presented at the center of the screen after each trial. C. In the conditional associative learning task, three associations (presented in a pseudo-random order over each three-trial blocks) were to be mapped onto the four possible responses. In this example, two successive trials are represented. IS, instruction stimulus; Mvt, Movement; FB, feedback.

Data analysis

Performance as well as response times were collected for both groups in all tasks. Response times corresponded to the time from stimulus presentation until the end of the subject responses. In the SM task, performance referred to the percent correct responses. In the SLnoWM and the SL_WM tasks, performance corresponded to the mean number of trials necessary to reach the learning criterion (the 3 trials of the learning criterion was always included).

In CAL task, we calculated the total number of trials to achieve learning criterion for each of the 3 associations. If subjects failed to achieve the criterion, we also used the total number of trials performed by these subjects. We also calculated the number of errors and the percentage of error (number of errors/total numbers of trials). As in SLnoWM and SL_WM tasks, we then calculated the number of trials needed to learn each stimulus-response association (3 stimulus-response associations).

Once the subjects reached the learning criterion for a given stimulus-response association, we evaluated the number of times they executed an incorrect response for this association (**Post-criterion memorization errors**). This measure was intended to detect difficulties in holding in memory a successfully learned association. We also calculated the number of times an incorrect response to a given stimulus was repeated (**Incorrect association perseveration**). This measure could either denote a working memory problem (if subjects did not remember their previous choices and/or their consequences) or a difficulty in switching to another response.

We then examined the chronological order of the subjects' responses. Each of the three stimuli appeared once per three-trial blocks, hence, a given stimulus was seldom repeated over two consecutive trials. We calculated the number of times the subjects: 1) inappropriately repeated a correct response when a different stimulus was presented (**motor perseverative errors**) and 2) appropriately repeated the same motor response until they found the correct stimulus associated to this response (**motor strategy**).

Statistical analysis. The controls, PD patients ON medication and PD patients OFF medication were compared using one-way ANOVAs, following by 1-sided Dunnett's tests. The effect of L-Dopa medication in the PD patients was assessed using paired t-tests. Finally, the links between the different variables measured were explored using Pearson correlations.

III. RESULTS

The patients and controls did not significantly differ in age [$F(1,15) = 1.079$, $p = 0.315$], nor in their level of education [$F(1,15) = 0.049$, $p = 0.828$]. They both used labels to identify the visual stimuli.

1. Standard Mapping task (SM)

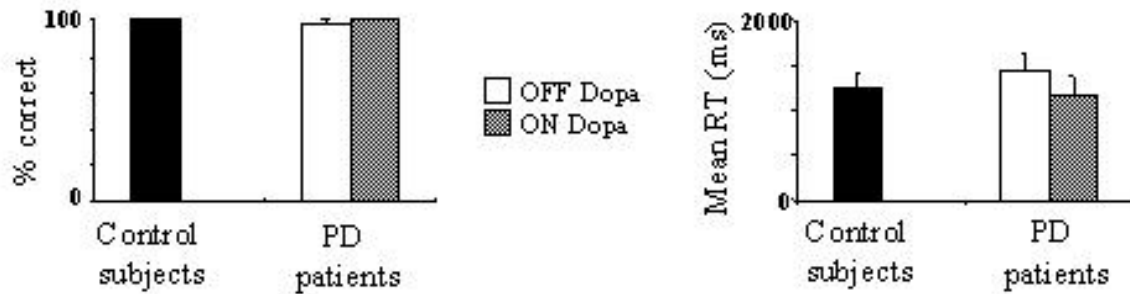
Both groups performed this task without any difficulty (Figure C3-A). There were no significant difference in the performance or in the mean response times between the controls and the PD groups, OFF or ON medication. Not surprisingly, PD patients tended to be slower OFF medication as compared to the ON state. However, this difference failed to reach the significance level.

Single association learning, without (SLnoWM) or with (SL_WM) working memory.

Theoretically, learning to associate a single visual stimulus with the correct motor response among four possible ones requires 1 to 4 trials if the 3 trials of the learning criterion are excluded, that is between 3 and 6 trials if the learning criterion is included. All subjects completed 2 associations per task (with or without working memory). As represented in Figure C3-B, the controls and PD (ON and OFF medication) groups learned the single associations within 3 to 6 trials (learning criterion included), irrespective of the demands imposed on working memory. Following an incorrect response, none of the subjects repeated the same error, instead they switched to another response until they found the correct one.

No significant difference was found in mean response times between groups in single association learning, without [$F(2,23) = 0.043$, $p = 0.958$] or with working memory [$F(2,23) = 0.095$, $p = 0.910$]. Furthermore, L-dopa treatment did not significantly ameliorate or deteriorate the performance or the response times in PD patients.

A – STANDARD MAPPING



B - SINGLE ASSOCIATION LEARNING

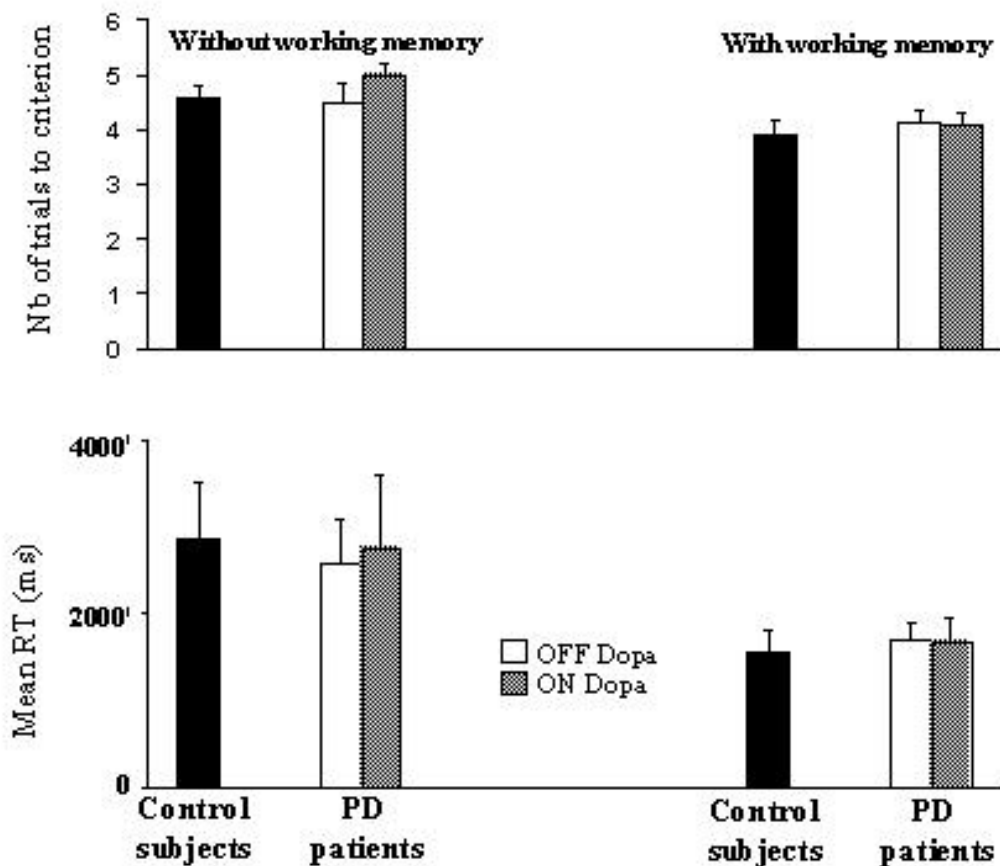


Figure C3. Performance (% correct) and response times (RT, expressed in ms) for the Control and PD groups in the standard mapping task (A) and the single association learning tasks (B). Patients did not differ from controls in these tasks. OFF Dopa, ON Dopa: without and with dopaminergic medication, respectively.

Visuo-motor Conditional Associative Learning

The number of sets actually completed by each subject (out of the intended three) is summarized in Table C5. All but one control subjects were tested on three sets each. By contrast, PD patients often completed only two sets, due to fatigue and/or to OFF/ON dependent motor difficulties (i.e. either dyskinesia or rigidity).

Overall, as compared to controls, the group of nine PD patients included in the present study were impaired in CAL, in the OFF medication condition. However, examination of individual scores indicated that this deficit was actually present in six patients (patients 1, 2, 3, 4, 5, and 8), but not in the remaining three (patients 6, 7, and 9). Therefore, in the following paragraphs, the results will be described separately for each of these two subgroups of patients that will be referred to as PD-I and PD-II, respectively. Under dopaminergic medication, neither of the two subgroups significantly differed from controls.

a. Comparison between the controls and PD-I OFF medication

As compared to controls, PD-I patients, OFF medication, first failed to reach the learning criterion for more than 50 % of the sets tested³ (Figure C4-A). Second, they needed significantly more trials to reach (or fail to reach) the learning criterion whether the three associations of each sets were considered together [Figure C4-B; $F(2,17) = 11.956$, $p = 0.001$; Dunnett $p < 0.001$], or separately (Figure C5-B; all Dunnett p 's < 0.05). Accordingly, they made more errors, whether expressed in terms of number of errors [Figure C4-B; $F(2,17) = 8.680$, $p = 0.003$; Dunnett $p = 0.001$], or in percent incorrect responses [Figure C4-C; $F(2,17) = 6.346$, $p = 0.009$; Dunnett $p = 0.004$]. In addition, detailed examination of individual performance revealed a non significant increase in post-criterion memorization errors, as well as a significantly greater number of association perseveration errors, i.e. repetition of the same incorrect association [Table C6; $(2,17) = 12.191$, $p < 0.001$; Dunnett $p < 0.001$].

b. Comparison between the control and PD-II OFF medication

Overall, PD-II patients, OFF medication did not significantly differ from controls. Learning criterion was achieved for all sets tested and all three patients learned the three associations at the same rate as controls. The only difficulty detectable in PD-II subgroup was a tendency to make more post-criterion memorization errors [Table C6; $F(2,11) = 1.875$, $p = 0.199$; Dunnett $p = 0.073$].

³ For the failed sets, patients' scores were based on the number of trials actually completed before interruption of testing. These scores therefore underestimate the severity of the difficulty encountered by the patients.

c. Strategies. As described in PART B in the monkey, humans learned the associations in a sequential manner and this strategy was present in controls and patients alike, and for the patients, irrespective of the medication condition. By contrast, differences emerged regarding the motor strategy. OFF medication, **none of the PD-I** patients developed it whereas, **all three PD-II** did so. Accordingly, when all PD patients were considered together, the use of the motor strategy was found to be negatively correlated (1) with the total number of trials ($p = 0.065$), (2) with the number of errors ($p = 0.052$), (3) with the percent errors ($p = 0.040$), (4) with the number of trials needed to reach the learning criterion for the second ($p = 0.026$) and third ($p = 0.083$) associations, and most significantly (5) with the perseveration in incorrect associations ($p = 0.008$, Figure C6). By contrast, only **four out of the eight controls** relied on the motor strategy, thus the use of this strategy was not correlated with any of the controls' scores.

d. L-Dopa treatment effect

Overall, L-Dopa treatment ameliorated PD performance. This effect was most salient for the PD-I subgroup (Figures C4 and C5). Paired t-tests revealed that, compared to the OFF state, these patients ON medication needed less trials to achieve the learning criterion (Dunnett $p = 0.057$), to learn the second (Dunnett $p = 0.034$) and third (Dunnett $p = 0.052$) associations, and made less errors (Dunnett $p = 0.06$) and perseveration in incorrect associations (Dunnett $p = 0.018$). L-Dopa treatment also increased the use of the motor strategy in PD-I subgroup (Dunnett $p = 0.006$, Table C6).

Under L-dopa treatment, PD-II subgroup tended to make less post-criterion memorization errors although this difference did not reach statistical significance (Table C6).

TABLE C5. Number of sets (out of the intended three) that were actually tested in Controls and PD patients

Subjects	CAL - number of sets tested		
	Controls	PD patients	
		Off dopa	On dopa
1	3	3	2
2	3	3	2
3	3	3	3
4	3	1	3
5	2	3	2
6	3	2	3
7	3	3	3
8	3	2	2
9	-	2	2
Total	23/24	22/27	22/27

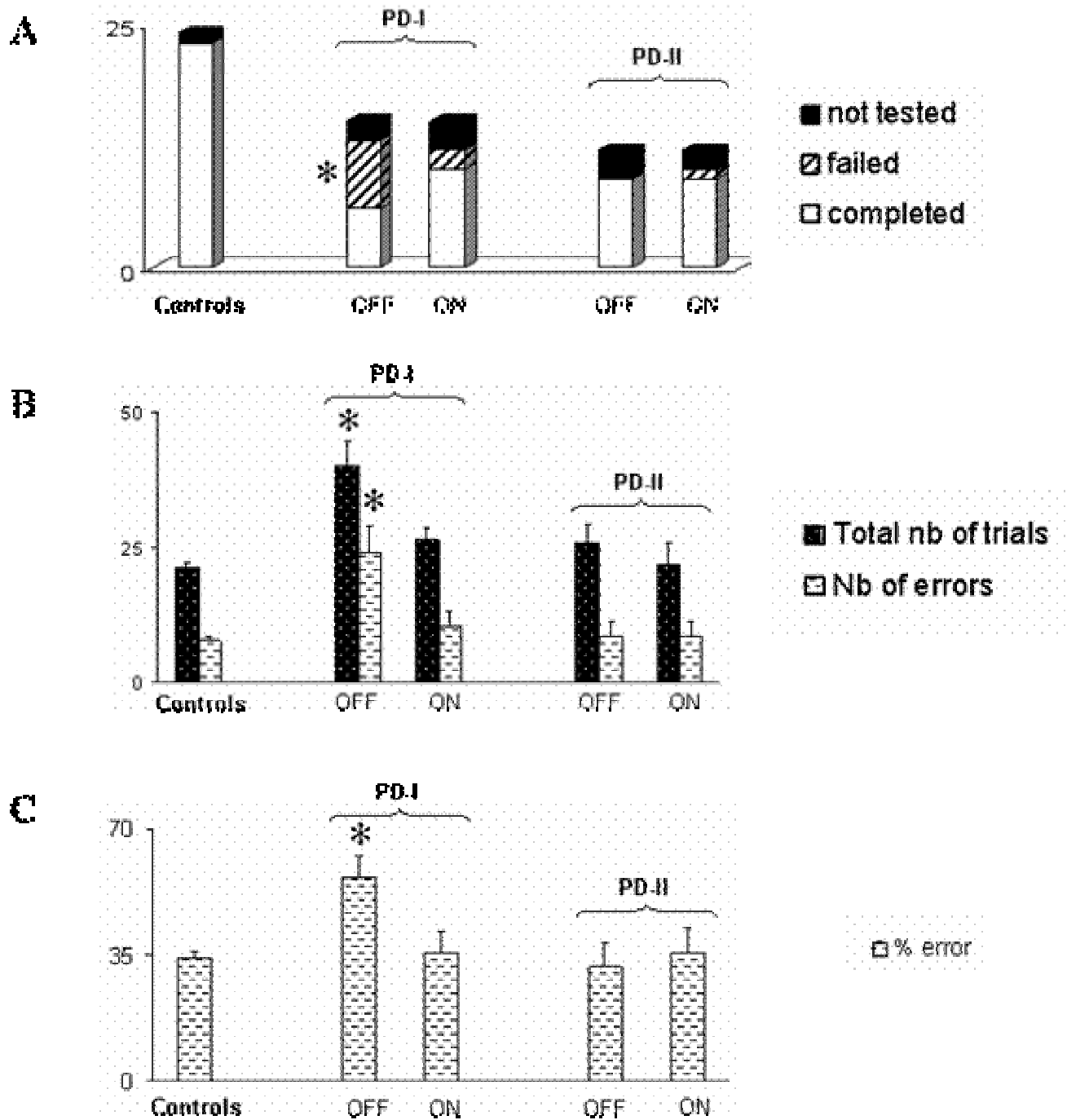


Figure C4. Conditional associative Learning – Global performance. A. Number of sets of three associations (out of the three prepared for each subject) that were learned to criterion (*completed*), interrupted before the learning criterion was reached (*failed*), or not evaluated (*not tested*) due to technical problems (in controls) or because of fatigue or motor dysfunctions (in patients). B. Total number of trials and errors. C. Percentage of incorrect responses (% errors). Six of the nine patients (PD-I), but not the remaining three (PD-II), were impaired relative to controls (*, Dunnett's tests, $p < 0.05$) when untreated with L-Dopa (OFF), this deficit was alleviated when dopaminergic medication was reinstated (ON).

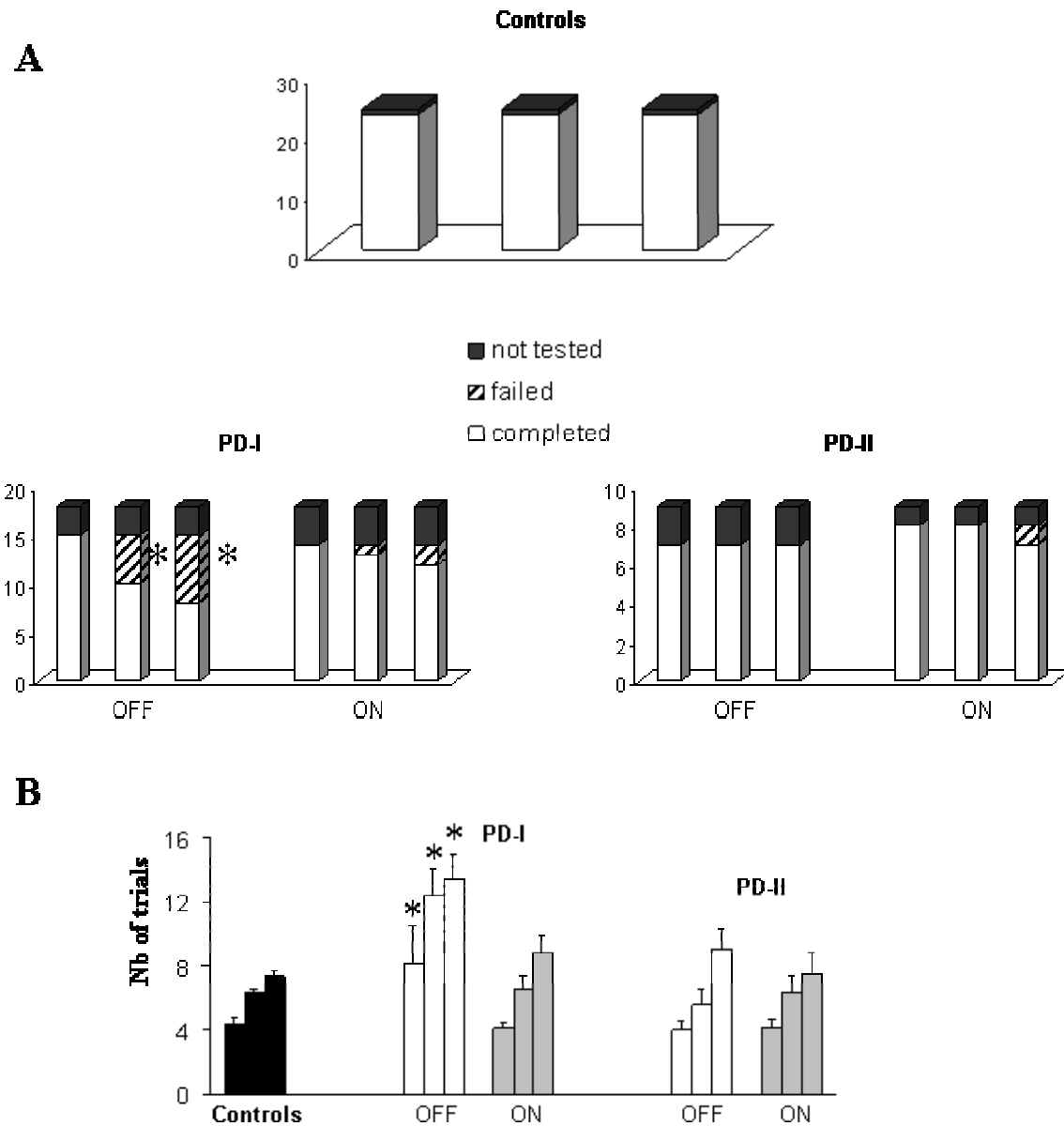


Figure C5. Conditional associative Learning - Sequential learning. Like controls, the two PD subgroups learned the sets of three associations sequentially. **A.** Numbers of 1st, 2nd, and 3rd associations completed, failed, vs. not tested (see Figure C4). **B.** Number of trials to reach the learning criterion for each association (*, significant difference relative to controls as revealed by Dunnett's tests, $p < 0.05$).

TABLE C6. ERROR TYPES AND MOTOR STRATEGY IN CONTROLS AND PD GROUPS

	CONTROLS	PD PATIENTS			
		PD-I		PD-II	
		OFF	ON	OFF	ON
Post-criterion memorization error	2.77±0.97	6.82±3.06	4.13±1.58	7.87±3.96 [*] (p=0.073)	3.61±1.68
Motor perseveration	7.08±1.78	7.04±3.53	5.99±3.22	0 [*] (p=0.025)	1.11±0.96
Incorrect association perseveration	25.76±4.37	63.87±4.64 ^{*F} (p<0.001; p=0.018)	36.70±7.24	30.56±11.1	36.05±8.75
Motor strategy	38.91±10.37	8.91±1.17 ^{*F} (p=0.012; p=0.001)	24.07±4.55	45.83±2.41	34.72±11.18

Percent mean ±SEM

* Difference as compared to the control group (ANOVAs, with Dunnett p)

F Difference between the ON and OFF conditions in the PD patients groups (paired t-tests).

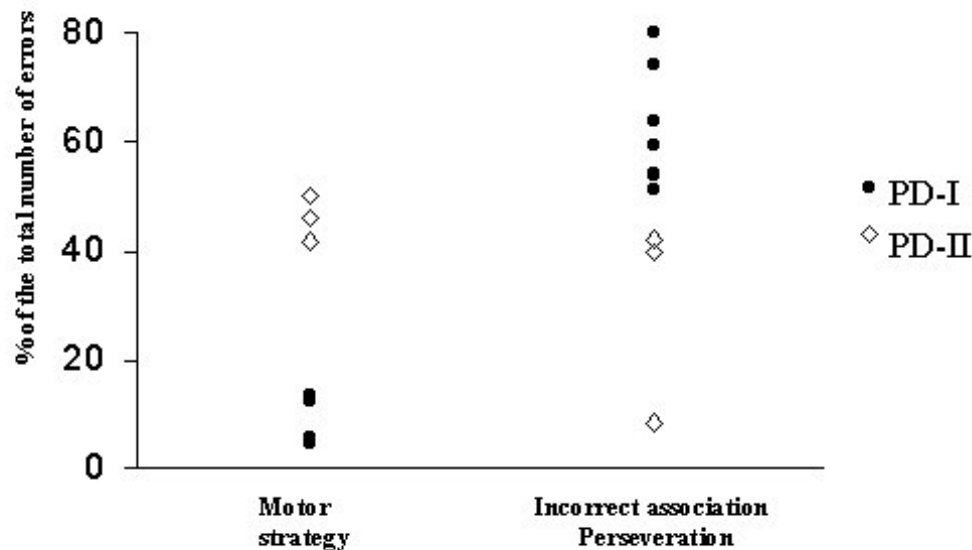


Figure C6. Motor strategy versus incorrect association perseveration in PD patients OFF medication. Interestingly, only PD-II subgroup was able to develop and/or use the motor strategy, and executed significantly less motor perseveration than PD-I subgroup.

IV. DISCUSSION

2. Summary of the results

Preserved performance on standard mapping and single association learning tasks

We used a series of tasks in order to rule out some alternative interpretations before coming to the conclusion that patients were specifically impaired in learning conditional visuo-motor associations. First, PD patients were not impaired because of a motor deficit. They were able to move the joystick in the four possible directions in the standard visuomotor task. Second, they were able to form single arbitrary associations between complex visual stimuli and motor responses, whether feedback was provided continuously or had to be stored in working memory. This indicated that our sample of patients retained the abilities to 1) select one particular movement among competing ones, 2) inhibit an incorrect response, and 3) ensure on-line maintenance of a limited number of items in working memory. All the above functions were found to be spared whether the patients were ON or OFF L-Dopa treatment.

Conditional associative learning impairment in a majority of PD patients

Like controls, all PD patients used verbal labels to discriminate the different stimuli forming a set, and learned the three concurrent associations sequentially. This suggested that the disease did not interfere with at least some forms of auto-generated strategies that can facilitate performance in conditional visuomotor learning, such as verbal organization of sensory information and breaking down a complex problem into several separate, more easily manageable elements. Nonetheless, six out of the nine patients (PD-I) displayed a significant deficit when tested OFF medication. These patients failed to reach the learning criterion for half of the sets tested, and even when they did reach criterion, took more trials and made more errors than controls. Detailed examination of their performance revealed two types of difficulty. The first type occurred early in learning (pre-criterion) and consisted in an abnormal number of repetitions of the same incorrect stimulus-response association. Two interpretations may account for this first type of difficulty. One is that the patients forgot incorrect associations from one block of (three) trials to the next, due to the intervening trials with the other stimuli, that is, presented a deficit in monitoring competing information in working memory. Another, not exclusive, possibility is suggested by the observation that some subjects seemed to display spontaneous preferences that led them to, *a priori*, favor one

specific response for a given stimulus. Thus, repetition of the same incorrect association might reflect a failure to inhibit those spontaneous biases following negative feedback information. The second type of difficulty detectable in PD-I subgroup was a tendency to make more post-criterion errors than controls. This could signal a problem in the late stages of learning, during which consolidation and automatization of stimulus-response bonds take place.

Spared conditional associative learning in some PD patients

Three of the nine patients acquired sets of three visuomotor associations as readily as control subjects, irrespective of the medication condition. No clear-cut difference could be found between these three patients and the remaining of the PD group in terms of age, duration of the disease, amount of dopatherapy, or education level. As a result, and pending testing of a greater number of patients, we favor the hypothesis that these three patients did suffer from the same deficit as that observed in the other patients, but successfully devised a compensatory strategy that allowed them to perform as accurately as control subjects. This hypothesis is based upon the fact that CAL performance within the PD group was tightly correlated with the use of a 'motor strategy' that consisted in repeating the same motor response until finding its associated stimulus. The three patients (PD-II) who performed as controls OFF medication, used this motor strategy, whereas the other six (PD-I) did not develop the strategy, and displayed a deficit. Since in controls, the motor strategy was present, but was not correlated with performance, it seems that only for the patients was this additional strategy mandatory to achieve normal learning. Focusing on a single motor response until its associated stimulus is found was appropriate in our protocol since each stimulus was presented once per three-trial block and stimuli were not re-presented after an incorrect response. The motor strategy could thus efficiently circumvent the difficulty in monitoring competing associations in working memory encountered by PD-I patients (see above). Finally, it is of interest to note that despite their normal pre-criterion performance, PD-II subgroup did show the same tendency to commit an abnormal number of post-criterion errors as that seen in PD-I. This suggests that difficulty in the automatization phase of CAL may be common to all PD patients.

L-Dopa treatment effect

Dopaminergic treatment did alleviate the deficit of PD-I subgroup. This improvement of performance was correlated with the use of the motor strategy, thereby raising the

possibility that L-Dopa did not restore normal functions, but rather facilitated the development of compensatory strategies. In addition, L-Dopa tended to decrease the number of post-criterion errors found in the two PD subgroups.

Comparison with earlier studies

As already summarized in the above introduction, the impairment of PD patients on CAL has been controversial in the literature (Canavan et al., 1989; Gotham et al., 1988; Marié et al., 1999; Pillon et al., 1998; Postle et al., 1997; Sprengelmeyer et al., 1995; Taylor et al., 1990; Vriezen & Moscovitch, 1990). Cross-study comparison is inevitably hindered by the fact that the conclusions of any single study, including the present one, depend not only on the particular sample of patients investigated, but also on the exact tasks used. Hence, the present data can usefully be confronted to the results of only two of the previous studies on CAL in PD patients. One because it constitutes the only other investigation of sensory-motor (rather than sensory-sensory) conditional learning (Canavan et al., 1989); the other because it constitutes the only other study including a homogeneous group of advanced PD patients (as opposed to a homogeneous group of early patients or a mixed group).

Canavan et al. (1989) submitted 19 early PD patients (mean age, 58 years; average disease duration, 34 months; testing done prior to initiation of L-Dopa therapy) to a visuo-motor task requiring trial-and-error mapping of six colors onto six possible handle displacements. The results can be viewed as a mirror-image of our findings in advanced PD patients (mean age 53 years, disease duration, 7-13 years). Namely, overall early patients were found not to be impaired (unlike patients with frontal lobe lesions), but examination of individual scores nevertheless revealed a deficit in a minority of subjects (six out of 19). It is therefore possible that a deficit in visuo-motor CAL is more likely to emerge in advanced than in early PD patients. Alternatively, the sparing of function observed by Canavan et al. might have been due to the method of testing. First, colors are simple visual stimuli that are easier to verbalize and remember than the complex stimuli used in the present study. Second, in Canavan et al's experiment (as in all previous neuropsychological investigations), after an incorrect response, subjects were presented with the same stimulus until they found the correct response, whereas in our protocol, no such correction method was used (in order to allow direct comparison with the monkey study).

Pillon et al. (1998) submitted 16 advanced PD patients (mean age, 63 years; average disease duration, 10 years) to two tasks requiring trial-and-error mapping of either six

complex visual stimuli onto six locations (visuo-spatial CAL), or six animal names onto six given names (verbo-verbal CAL). Unlike in our study, patients under L-Dopa treatment were found to be impaired (performance was not evaluated OFF medication). Since the main characteristics of Pillon et al.'s group of patients closely resembled that of our sample, this discrepancy likely results from task differences. One of them is the number of associations (six *versus* three). Another is the correction method evoked above. Indeed, although repetition of the same stimulus until the correct response is found may facilitate learning, it also precludes the use of the compensatory motor strategy seen in our protocol (where stimuli repetitions were rare). Notwithstanding, a finding common to the two studies is that, when occurring, CAL impairment in PD patients is accompanied by an excessive number of repetitions of the same incorrect association.

Basal ganglia and CAL

Behavioral studies of Parkinson's disease demonstrate that the characteristic clinical symptoms of bradykinesia, rigidity, and resting tremor are frequently accompanied by impairments in cognitive functions. The pattern of cognitive impairments seen even in the early stages of PD resembles that produced by frontal lobe damage, insofar as it includes deficits in executive functions such as planning and monitoring information in working memory (Taylor et al., 1990; Owen et al., 1997; Lewis et al., 2003; Dubois & Pillon, 1997).

Anatomically, Parkinson's disease is characterized first by a dopamine denervation in the nigrostriatal system, which although extensive is not complete. In later stages of the disease, this denervation extends into the mesocorticolimbic dopaminergic system (Agid et al., 1993). Additionally, other neuromodulatory systems are affected in Parkinson's disease (Javoy-Agid et al., 1984, Everitt & Robbins, 1997) and Lewis bodies have been found disseminated in different cortical brain areas such as the frontal and temporal lobes (Braak & Braak, 2000). Thus, although executive dysfunction in PD has been shown to be dopamine-dependent (Lange et al., 1992), one has to be cautious in interpreting the behavioral manifestations of this complex disease. In particular, it remains unclear whether cognitive parkinsonian symptoms are attributable to basal ganglia or to frontal lobe dysfunction.

The heterogeneity of the CAL performance in our group of patients denotes this complexity, and confirms the inter-individual variability reported previously in cognitive performance among PD patients who were otherwise matched for most clinical characteristics such as same disease duration (e.g. Lewis et al., 2003). As for the dopamine-dependent

compensatory mechanism observed here, it may be subserved either by the nigrostriatal or the mesocorticolimbic system (Rakshi et al., 1999; Kaasinen et al., 2001).

In light of electrophysiological data in monkeys (including those reported in Part B), we propose that the CAL deficits observed in PD patients result, at least in part, from basal ganglia dysfunction. Further, we hypothesize that the BG are involved in both the early (monitoring competing information in working memory) and late (consolidation and automatization of stimulus-response bonds) phases of CAL.

D - Neuroimaging study in healthy humans

in collaboration with :

**Dr. Christoph Segebarth,
Dr. Mathilde Pachot-Clouard,
Dr. Stéphane Simon,
Elenitsa Kitromilides.**

I. INTRODUCTION

As already mentioned in Part A, a few neuroimaging studies (using fMRI or PET)⁴ have investigated the cerebral network underlying arbitrary visuo-motor mapping (e.g. Toni et al., 2001a,b; Toni & Passingham, 1999, Toni et al., 2002; Deiber et al, 1997). According to these different studies, a large network, including prefrontal, premotor, temporal, and parietal cortical areas, as well as the cerebellum and the basal ganglia, was recruited during arbitrary visuo-motor mapping.

Among earlier studies using PET, one (Toni et al., 2001a) assessed the contribution of this network to two different types of visuo-motor transformation, i.e. standard versus non standard mapping. In the standard mapping task, subjects were instructed to grasp the presented object whereas in the non-standard mapping task (conditional task), they were instructed to perform the hand gesture arbitrarily associated with the presented stimuli, according to previously learned rules. No learning effect was measured during scanning in this study. Direct comparison between these two tasks revealed a selective activation of the anterior part of the left putamen/globus pallidus (Talairach coordinates : $x = -14$, $y = 6$, $z = -2$) while subjects performed the conditional task. In another PET study, CAL was studied using either spatial or object cues (Deiber et al., 1997). Depending on the task condition, subjects had to associate either the stimulus (object) or its location (spatial) with the correct motor response using a joystick. In this study, subjects were given the rules linking the sensory information and the movement to be performed before the scanning session. During scanning, no feedback was provided about the correctness of the response, and the errors were very rare (13/106 and 10/106 in the object and spatial paradigms, respectively). As in the previous study, performing such associations elicited a selective increase of activation in the left putamen in both the spatial (Talairach coordinates : $x = -28$, $y = -4$, $z = 4$) and object ((Talairach coordinates : $x = -30$, $y = -10$, $z = 8$) paradigms.

Learning to associate new visual cues to movements has also been investigated using functional imaging (Toni & Passingham, 1999, Toni et al., 2001b). In one PET study, Toni and Passingham (1999) compared the network recruited while subjects learned visuo-motor

⁴ functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) measure the hemodynamic or metabolic changes that accompany changes in neural activity.

arbitrary associations *versus* while they learned a visuo-motor sequence. In both tasks, subjects had to learn by trial and error. Direct comparison of these two tasks denoted a selective increase of activation over time in the left caudate nucleus (Talairach coordinates : $x = -12, y = 8, z = 18$) in relation to learning arbitrary rules. However, direct comparison of the baseline (sensory control) and CAL revealed a decreased activation over time of the right caudate nucleus (Talairach coordinates : $x = 24, y = 18, z = 16$). Thus, as previously mentioned, anterior striatal regions seem to be recruited during early stages of learning whereas posterior ones seem to be recruited during later stages. In another study using event fMRI, the same authors compared the execution of well-learned associations with learning of new ones (Toni et al, 2001b). In this study, before scanning, subjects were trained on a set of 4 associations between visual cues and motor responses (finger movements). During scanning, they were presented with these well-learned associations as well as new ones. Following the temporal dynamic of brain activity while subjects learned the new associations, the authors found a selective increase of activation for the caudate nucleus (Talairach coordinates : $x = -18, y = 18, z = 4$) that correlated with performance. According to this study, the ventrolateral prefrontal cortex and the hippocampal formation are first recruited before the implication of the striatum. Finally, this group also studied the effective connectivity, i.e. the strength of the cortico-striatal interactions, during learning (Toni et al., 2002). They found that during learning projections arising from the ventral prefrontal cortex and the medial temporal lobe and directed toward the striatum, as well as those arising from the striatum and directed toward the dorsal premotor cortex were strengthened. They concluded that the striatum is in a position to ‘bind together cortical sensory information (temporal) with action selection (anterior PF) in order to bias motor programs (PMd)’

To summarize, according to these studies, the striatum seems to be involved in CAL. Anterior striatal regions seem to be recruited during early stages of learning whereas more posterior regions are recruited during later stages. However, these results come from different studies. Only one study has investigated the role of striatum in the different stages of learning (Toni et al., 2001b), but subjects were trained occurred just prior to scanning, not allowing a strong consolidation (FAMILIAR condition, one training session : 93 blocks of 18 trials were performed by each subject). Furthermore, different types of stimuli were used in the FAMILIAR (simple arrows) and NOVEL (complex patterns) conditions. In addition, Toni et al. (2001b) used a single set of associations to study learning-related changes of brain activation.

Taking into account these different parameters, the aim of the present study was to pursue the investigation of brain activation across different stages of CAL. In this study, as in the previous Parts (B-C), subjects had to form arbitrary associations between visual cues and movements (in this case, finger movements). We overtrained subjects on 3 stimulus-response associations prior to scanning (Familiar). Training took place across several days (4 days) to ensure that the associations were perfectly learned and maintained in memory. During scanning, each subject was presented successively with 4 different sets of 3 novel stimulus-response associations (Novel) as well as the Familiar ones. The same types of stimuli were used in the Novel and Familiar conditions. In the Novel conditions, subject was required to learn by trial and error to associate each stimulus with the correct movement. Furthermore, 2 different modalities were used here. Likewise, using the same type of stimuli, subjects were either required to form the associations according to the stimulus (object) or its location (spatial).

II. MATERIALS AND METHODS

1. Subjects and setup

Ten healthy volunteers were studied (5 males, 5 females; mean age 24.7 ± 1.4 years). All subjects were strongly right-handed, as assessed by a French adaptation of the Edinburgh Handedness Scale (Oldfield, 1971). Experiments were conducted with the understanding and consent of each subject.

Visual stimuli were generated by a Power Macintosh 9600 computer (Apple, Cupertino, CA, USA) using Psyscope V1.2.2 software (Carnegie Mellon Department of Psychology; Cohen et al. 1993). They were presented using a video projector (Eiki LC 6000, Eiki Industrial Co. Ltd., Osaka, Japan), a projection screen fixed on the back of the magnet and a mirror placed atop of the head coil. The stimuli were taken from the "Greeble" series of objects provided courtesy of Michael J. Tarr (Brown University, Providence, RI; <http://www.cog.brown.edu/~tarr/stimuli.html>). As depicted in Figure D1-A, Greebles are computer-generated, abstract colored stimuli that are difficult to verbalize. The stimuli ($1.4^\circ \times 1.4^\circ$ each) were presented on a dark background at one of 15 predefined locations on the screen. Subjects responded by pressing one of the four keys positioned under their right thumb, index,

middle, and ring fingers. The computer was used for both stimulus presentation and data acquisition (key presses, and response times) in real time.

2. Behavioral paradigms

The subjects were tested using sets of three items presented over three of the 15 possible locations, with a pseudorandom order ensuring that each stimulus and location appeared once per block of three consecutive trials. The subjects were required to learn, by trial and error, which of the four possible motor responses was associated with each stimulus (OBJECT paradigm) or each location (SPATIAL paradigm). They were explicitly informed that there was no direct link between the stimulus or location and the correct motor response, i.e. that the associations were arbitrarily predetermined by the experimenter. The sequence and timing of events were identical in the two paradigms. As illustrated in Figure D1-B, a trial started with the presentation of one stimulus at one position for a maximum of 2 seconds. The subjects were asked to select and execute a motor response as quickly as possible. Immediately after response completion, a feedback was provided for 300 ms. A green square indicated a correct response and a red square an incorrect response. Then, a white fixation point was presented at the center of the screen until presentation of the next stimulus. The interstimulus interval lasted 4 seconds. The specific stimuli used for the OBJECT and SPATIAL paradigms were different in order to avoid interference. Otherwise, the two paradigms differed only by the instruction given to the subjects, i.e. to pay attention either to the morphological characteristics or to the spatial locations of the visual stimuli.

3. Testing procedure

The OBJECT and SPATIAL paradigms were administered separately over 2 consecutive weeks, with a counterbalanced order of presentation across subjects. For each paradigm, testing took place over five consecutive days and comprised four training sessions followed by one scanning session.

During the four days before scanning, subjects were trained with a single set of three stimulus-response or location-response associations. They performed a total of 600 trials (150 trials per day), which ensured that each subject reached a criterion of at least 90 % correct responses with stable reaction times at the end of training. This over-learned set of three associations will be referred to as the FAMILIAR task condition.

The scanning session occurred on the fifth day of testing and lasted a total of 80 min. It consisted of a sequence of five epochs of equal duration (4 min. each) that was repeated four times (Figure D1-C). The five epochs comprised a rest condition, the FAMILIAR task condition and three Novel conditions. Switching between epochs was signaled by a 2-sec text instruction. In the rest condition, subjects were asked to passively fixate a central fixation point. In the FAMILIAR task condition, subjects performed 12 trials during which they had to retrieve and execute the three associations acquired during the training sessions. In the Novel conditions, a new set of items was presented and the subjects performed 36 trials during which they were required to learn, by trial and error, to associate each stimulus or location with one of the four possible movements. Based on preliminary behavioral testing, the 36 trials performed with new sets of three associations were divided into three successive stages of learning, which included 12 trials each, and were respectively termed the EARLY, MIDDLE and LATE task conditions.

4. Behavioral analysis

Performance and response times during the scanning session were measured for each subject, and averaged over the four 12-trial blocks composing each task condition (EARLY, MIDDLE, LATE and FAMILIAR). Performance refers to the percentage of correct responses, and response times correspond to the time from the onset of the visual stimulus on the screen until the subject pressed a key. Comparisons between different conditions of the same paradigm or between the same conditions across the two paradigms were carried out using paired *t*-tests or parametric analyses of variance (ANOVAs) with repeated measures.

5. MR acquisition

Measurements were performed at 3 Tesla on a clinical MR imager (Brucker MedSpec S300). The body coil was used for excitation while the head coil was used for detection. A volume composed of 48 slices (slice thickness = 3 mm) parallel to the anterior commissure-posterior commissure (AC-PC) axis was measured 12 times during each epoch. The volume encompassed the whole brain except the posterior lobe of the cerebellum. Positioning of the volume was performed on scout images acquired in the sagittal plane. The volume was measured twice in a dummy fashion prior to testing, so that system stability could be achieved. The functional scans were performed by means of a gradient-recalled echo, echo-planar imaging MR sequence. T2*-weighted images were acquired. The major MR sequence

parameters were: TR = 4000 ms, TE = 45 ms, pulse angle = 90°, acquisition matrix = 72 * 72, field-of-view = 216 * 216 mm², in-plane resolution = 3 mm. Prior to acquisition, a chemically selective RF pulse was applied in order to suppress the signals from fat. Finally, a high-resolution 3D T1-weighted MR scan was acquired to provide anatomical information about the volume examined functionally.

6. Image processing and statistical analysis

Data analysis was performed using SPM-99 software (Wellcome Department of Cognitive Neurology, London, UK; see Friston et al. 1995a) running on a Unix workstation under the MATLAB environment (Mathworks, Sherbon, MA, USA). MR images were subjected to three pre-processing steps. All images within a functional scan were first realigned by means of a rigid body transformation for motion correction (Friston et al. 1995b). Then, the anatomical volume was spatially normalized using as template a representative brain from the MNI series (Montreal Neurological Institute, Quebec, Canada; Evans et al. 1993) and linear transformations (Friston et al. 1995b); these normalization parameters were subsequently applied to the functional images. Finally, the functional images were spatially smoothed with a Gaussian kernel of 8 mm width.

Statistical contrasts were performed both individually for each subject and for the overall group of subjects using the general linear model (fixed effects) (Worsley et al. 1992; Friston et al. 1995a, Worsley and Friston 1995). Clusters of activated voxels were then identified on the basis of the intensity of the individual responses and the spatial extent of the clusters. Statistical significance thresholds were established at $p = .00001$ for individual voxels, and at $p = .05$ for cluster size (corrected for multiple comparisons in both cases).

Analysis focused, as a first step, on the pattern of brain activation specifically related to the early stage of trial-and-error learning of arbitrary sensori-motor associations. To this aim, we compared the activation observed during the first twelve trials of learning novel associations (EARLY condition), first to that observed during execution of perfectly mastered associations (FAMILIAR condition), and then to that observed during the final phase of learning, that is, during the last 12 trials performed with novel associations (LATE condition). These single subtraction contrasts were computed separately for the OBJECT and SPATIAL paradigms. Then, to identify the brain areas that were equally involved in object and spatial learning, conjunction analyses were performed (Price and Friston 1997). These SPM conjunction analyses summed over the two paradigms [(EARLY_OBJECT +

EARLY_SPATIAL) – either (FAMILIAR_OBJECT + FAMILIAR_SPATIAL) or (LATE_OBJECT + LATE_SPATIAL)] and removed the voxels showing a significant interaction across paradigms. The resulting activation maps were masked ($p < 10^{-8}$) with the two single contrasts to ensure that all voxels identified by the conjunction analyses were significantly active in both paradigms. Finally, to identify the areas preferentially involved in spatial learning, two interaction analyses were performed. These analyses summed the two paradigms and retained the voxels for which the single subtraction contrasts [either (EARLY – FAMILIAR) or (EARLY – LATE)] were significantly larger for the SPATIAL than for the OBJECT paradigm. The resulting activation maps were masked ($p < 10^{-3}$) by the SPATIAL contrast to ensure that effects due to OBJECT negative activation were excluded. Similar interaction and masking procedures were used to identify the brain regions that were preferentially involved in object learning. For all analyses, coordinates of the activated brain areas in the MNI system of reference were transformed into the Talairach and Tournoux stereotaxic space (Talairach and Tournoux 1988), using the following equations : $X_T = 0.88 X_{MNI} + 0.8$; $Y_T = 0.97 Y_{MNI} - 3.32$; $Z_T = 0.05 Y_{MNI} + 0.88 Z_{MNI} - 0.44$.

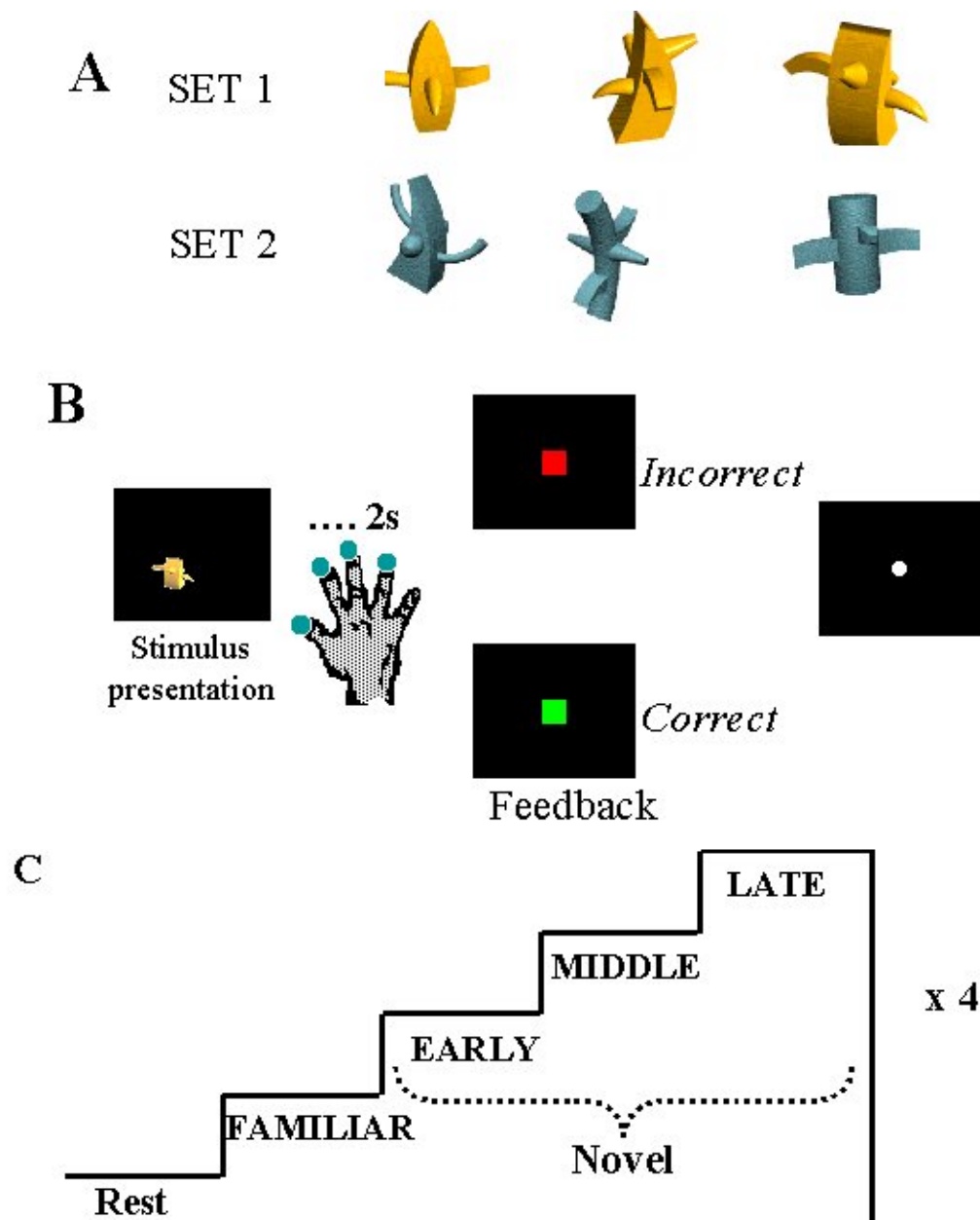


Figure D1. **A)** Two examples of the sets (each comprising three Greeble stimuli) used for both the OBJECT and SPATIAL paradigms. **B)** For both paradigms, a trial started with the presentation of one stimulus at one of 15 possible locations on the screen. The subject selected one among four finger movements. Colored squares were used for feedback, and followed, during the intertrial interval, by a fixation point. **C)** The scanning session consisted of four identical sequences, each including five successive epochs: Rest (central fixation), FAMILIAR (execution of associations learned prior to scanning, 12 trials), and Novel (trial-and error learning of novel associations; 36 trials divided in three 12-trial phases of learning, EARLY, MIDDLE, and LATE).

III. RESULTS

1. Behavioral data

Due to failure to complete the task or to improper imaging data acquisition, two subjects were discarded from the analysis of the OBJECT paradigm, and one from that of the SPATIAL paradigm. The results presented here are therefore based on 8 subjects for the OBJECT paradigm and 9 subjects for the SPATIAL paradigm.

Behavioral performance as well as response times measured during the scanning session for these subjects are summarized in Figure D2. For the FAMILIAR condition, the subjects' performance did not differ significantly across paradigms [paired t -test $t(7) = -0.4$, $p = \text{n.s.}$], reaching 98.2 ± 0.7 percent correct responses in the OBJECT paradigm and 98.3 ± 0.6 percent correct responses in the SPATIAL paradigm. Response times for the FAMILIAR condition were, however, significantly shorter in the SPATIAL paradigm (656.1 ± 31.1 ms) than in the OBJECT paradigm (850.1 ± 36.8 ms) [paired t -test $t(7) = -3.2$, $p = 0.015$].

Likewise, in the Novel conditions, the subjects' performance did not differ significantly across paradigms [$F(1,7) = 2.4$, $p = 0.164$], although response times were again shorter for the SPATIAL paradigm [$F(1,7) = 17.3$, $p = 0.004$]. Paradigm * condition, 2*3 ANOVAs, with repeated measures for the latter factor, confirmed that, for both paradigms, performance did improve [$F(2,14) = 118.1$, $p < 0.0001$] and response times decreased [$F(2,14) = 5.9$, $p = 0.014$] over the three 12-trial blocks of learning (EARLY, MIDDLE, and LATE task conditions). Additional 2*2 ANOVAs indicated, however, that subjects were slightly, but significantly, less accurate during the LATE learning condition than during the FAMILIAR one [$F(1,7) = 7.4$, $p = 0.03$], reaching approximately 95 % correct responses at the end of both the SPATIAL and OBJECT learning instead of 98 % for the familiar conditions. Response times at the end of learning were also consistently longer than those observed for over-learned associations [$F(1,7) = 21.3$, $p = 0.002$]. Note that as observed in monkeys and PD patients, the novel associations were learned sequentially in both paradigms (see Figure D2-C).

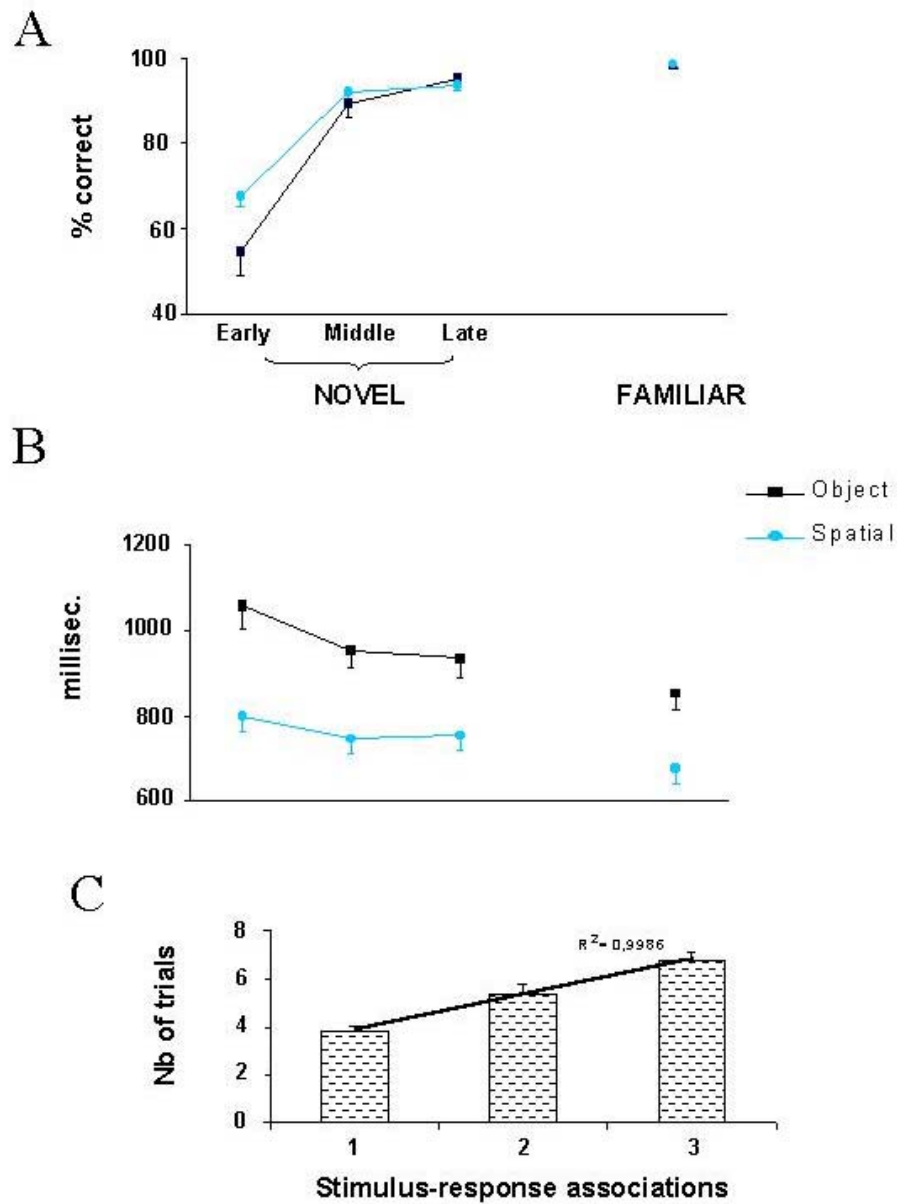


Figure D2. Percent correct responses (**A**) and reaction times (**B**) recorded during the scanning session over the three stages of learning novel associations (EARLY, MIDDLE, and LATE) and during execution of well-learned associations (FAMILIAR). Both behavioral measures improved with learning; yet, during the LATE stage of learning, subjects were slightly but significantly less accurate and less rapid than during execution of well-learned associations. **C.** Numbers of trials to achieve the learning criterion for each association in the Object paradigm. Note that the associations were learned sequentially. The best fitting curve is a linear curve ($R^2 = 0.989$).

2. fMRI activation data: Early learning of novel *versus* execution of familiar stimulus-response or location-response associations

Learning-related effects were first studied by contrasting the EARLY condition to the FAMILIAR one for each paradigm separately. The patterns of brain activation revealed by these comparisons are illustrated in Figures D3-A and D3-B, and detailed in Tables D1 and D2, for the OBJECT and SPATIAL paradigms, respectively.

For both paradigms, the EARLY – FAMILIAR contrast revealed a bilateral pattern of activation involving the medial and lateral surfaces of the frontal lobe, the parietal and temporal cortex, and the cerebellum. Direct statistical comparison of the two paradigms using a conjunction analysis confirmed the vast overlap between the networks engaged by object and spatial conditional learning. The results of this conjunction analysis are illustrated in Figure D4 and listed in Table D3. Within the medial wall of the frontal lobe, this overlap included a large focus of activation located rostral to the anterior commissure, and involving both the anterior cingulate cortex and the overlying presupplementary motor area (pre-SMA; Picard and Strick, 1996). The lateral premotor cortex also presented a site of activation common to both versions of the task. This site was located near the intersection between the superior frontal and precentral sulci, and was more extensive in the left than in the right hemisphere. Within the prefrontal cortex, both the dorsolateral (superior and middle frontal gyri) and the ventrolateral (inferior frontal gyrus) regions were recruited by the two paradigms. The clusters found in the anterior portion of the superior and middle frontal gyrus involved Brodmann's areas 9/46 and extended rostrally into polar area 10. Those found in the anterior extent of the inferior frontal gyrus involved Brodmann's area 47 and extended caudally into area 44. The other sites of activation common to the OBJECT and SPATIAL paradigms were located in the parietal cortex (intraparietal sulcus, bilaterally, and precuneus), the right inferior temporal gyrus, and the right and left cerebellum.

Based on the individual EARLY – FAMILIAR contrasts, some qualitative differences were noticeable between the two paradigms (compare Figures D3-A and D3-B). The lateral premotor site of activation was more extensive and more bilaterally symmetrical for the SPATIAL than for the OBJECT paradigm, whereas the reverse was true for the ventrolateral prefrontal site of activation. In addition, only the OBJECT paradigm yielded a significant subcortical activation within the thalamus. However, none of these differences was confirmed by the interaction analyses. These analyses identified only one significant difference across the two paradigms. Namely, the left focus lying over the intraparietal sulcus (Talairach

coordinates: -20, -63, 58) and extending into the precuneus (Talairach coordinates: -2, -77, 46) was found to be significantly more active during spatial than during object conditional learning.

3. fMRI activation data: Early *versus* late learning of novel stimulus-response or location-response associations

To further investigate the effect of learning on brain activation, the EARLY condition was contrasted with the LATE condition. Analyses performed for each paradigm separately suggested a nearly complete overlap of the patterns of activation yielded by object and spatial conditional learning. This overlap was confirmed by a conjunction analysis, which is illustrated in Figure D5 (interaction analyses again failed to identify any significant difference between the OBJECT and SPATIAL paradigms). The network outlined by this EARLY – LATE conjunction analysis was remarkably similar to that described above for the EARLY – FAMILIAR conjunction analysis (compare Figures D4 and D5). Namely, both networks involved the same medial premotor, lateral premotor, dorsolateral prefrontal, ventrolateral prefrontal, parietal, and cerebellar foci of activation. One major difference between the two comparisons, however, concerned the subcortical sites of activation. Unlike the EARLY – FAMILIAR comparisons, the EARLY – LATE comparisons revealed an engagement not only of the thalamus, but also of the striatum, in the early phases of both object and spatial conditional learning (Figure D6). These activation extended more anteriorly into the caudate nucleus in the OBJECT paradigm (Talairach coordinates, $y = +10$) as compared to the SPATIAL paradigm (Talairach coordinates, $y = -3$). Overall, in the OBJECT paradigm, the activation peak was centered on the caudate nucleus (Talairach coordinates: 16, 8, 8) and extended more posteriorly into the putamen as well as into the thalamic nuclei, including the mediodorsal nucleus. In the SPATIAL paradigm, the activation peak was more posterior (Talairach coordinates: $x = -10$, $y = -13$, $z = 8$), and centered on the lentiform nucleus (putamen/globus pallidus). As in the OBJECT paradigm, this activation extended posteriorly into the mediodorsal thalamic nucleus.

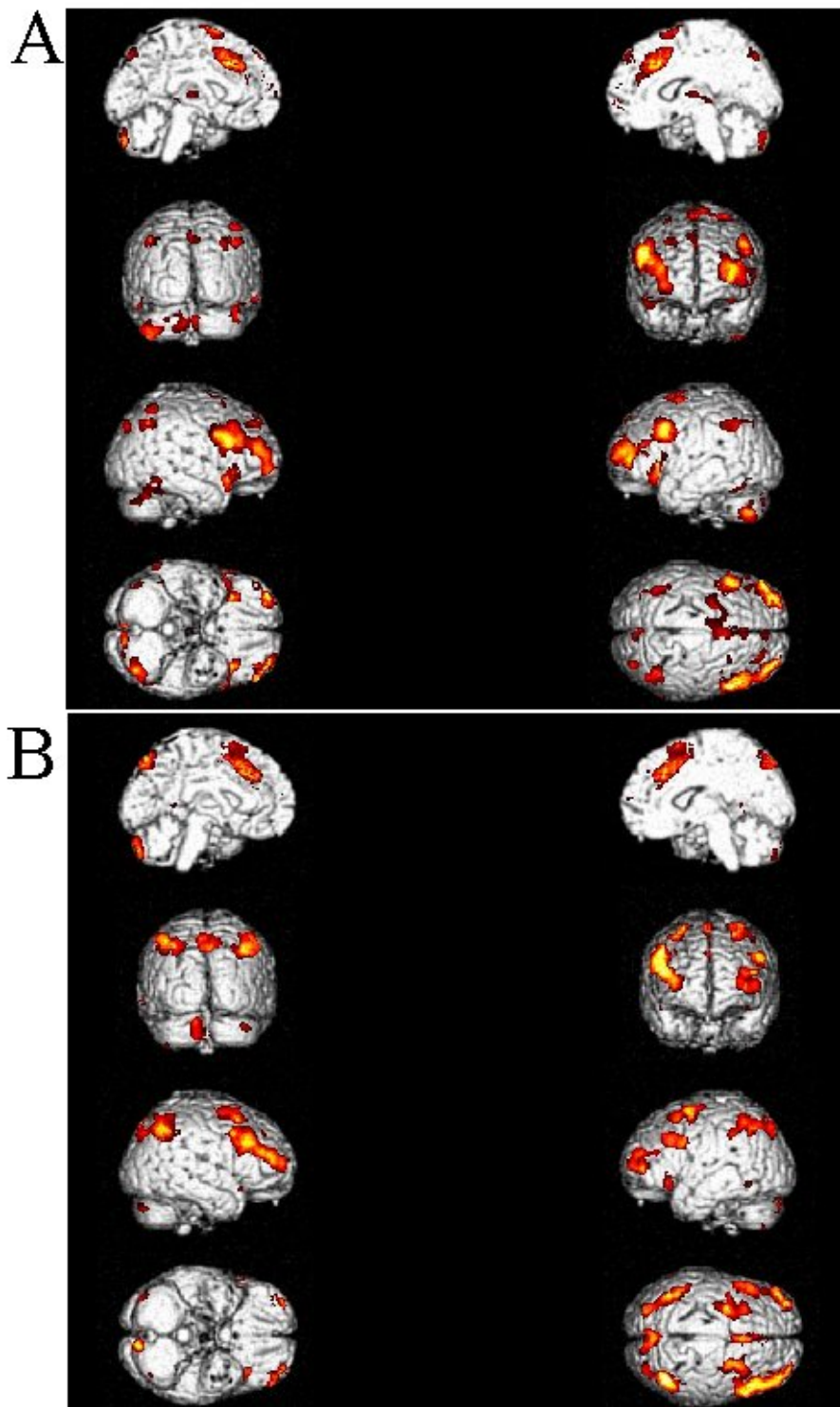


Figure D3. Activation patterns shown on medial, rostral, lateral, ventral and dorsal views of the MNI brain template, and obtained separately for the OBJECT (A) and SPATIAL (B) paradigms by contrasting the early phase of learning (EARLY) with the execution of well-learned associations (FAMILIAR).

TABLE D1. MAIN EFFECT : Brain activation related to learning conditional stimulus-response associations (OBJECT paradigm, EARLY minus FAMILIAR contrast)

		Talairach coordinates			t value	K		
Anatomical regions		x	y	Z				
<i>Anterior cingulate gyrus</i> <i>/ Pre-SMA</i>	R/L	2	23	36	12.76	1080		
		10	38	20	7.41			
<i>Prefrontal cortex</i>								
Superior frontal gyrus	R	4	51	42	7.79	40		
		26	47	38	7.94	71		
Middle frontal gyrus	R	40	51	18	11.73	2319		
		55	15	31	11.09			
	L	34	57	8	10.47	1064		
		-32	57	12	11.68			
Inferior frontal gyrus	L	-38	51	12	11.28	938		
		-44	47	9	10.47			
		-46	17	36	11.03			
	L	-36	23	-8	9.66	439		
		-50	19	1	7.35			
		-55	14	10	7.04			
R	-51	33	11	7.26	19			
	34	25	-3	10.16		434		
	48	15	-11	8.45				
		46	19	-18	8.09			
<i>Premotor cortex</i>								
Superior frontal gyrus	L	-28	1	63	9.15	358		
		R/L	2	11	62		8.74	
		-6	5	68	8.32			
Middle frontal gyrus	R	30	20	56	7.59	14		
	R							
<i>Parietal cortex</i>								
Intraparietal sulcus	L	-40	-50	39	9.02	255		
		-30	-70	46	6.83			
	R	46	-52	56	8.21	89		
		38	-52	43	8.11		195	
		46	-62	40	7.55			
Precuneus	R	34	-76	42	7.70	78		
	R/L	4	-73	44	7.04	70		
<i>Temporal cortex</i>								
Inferior temporal gyrus	R	65	-51	-9	8.63	50		
Fusiform gyrus	L	-49	-63	-14	6.89	53		
		-51	-53	-18	6.88			
		-48	-68	-7	6.44			
<i>Subcortical areas</i>								
Thalamus	R/L	6	-13	8	7.63	93		
		4	-29	3	7.30			
<i>Cerebellum</i>								
	R	47	-67	-25	8.57	154		
		46	-59	-17	8.11			
		50	-46	-18	7.32			
	L	-22	-83	-24	7.26	19		
		L	-34	-72	-35		9.79	389
		-44	-64	-34	8.32			
R/L	R	-42	-60	-41	6.75	313		
		4	-83	-24	8.75			
	-6	-81	-28	8.61				
	-10	-81	-20	6.97				

TABLE D2. MAIN EFFECT : Brain activation related to learning conditional stimulus-response associations (SPATIAL paradigm, EARLY minus FAMILIAR contrast)

		Talairach coordinates					
Anatomical regions		x	y	Z	t value	K	
Anterior cingulate gyrus / Pre-SMA	R/L	2	25	37	11.14	1064	
		0	8	49	8.67		
		2	16	58	8.60		
Prefrontal cortex							
Middle frontal gyrus	R	46	42	20	11.48	1687	
		48	27	34	10.94		
	L	-46	47	5	9.60		586
		-30	59	6	9.33		
		-38	51	16	9.18		
Inferior frontal gyrus	R	36	43	37	6.85	13	
		57	17	29	9.49		
	L	-46	23	32	8.79		529
		-49	11	31	8.22		
		-40	7	29	7.22		
	-34	23	-6	8.09	132		
Premotor cortex							
Superior frontal gyrus	L	-24	5	59	9.80	612	
		-28	20	52	8.13		
Precentral gyrus		-32	-7	63	8.04		
Middle frontal gyrus	R	36	20	52	10.08	455	
		30	3	59	10.04		
		20	19	60	7.43		
Parietal cortex							
Intraparietal sulcus	R	42	-60	44	9.55	1007	
		40	-52	38	9.15		
		42	-43	39	7.93		
	L	-44	-46	52	9.17		908
		-28	-73	46	8.36		
Precuneus	R/L	-38	-56	51	8.31	417	
		12	-79	50	8.87		
		0	-71	51	8.82		
Temporal cortex							
Inferior temporal gyrus	L	-63	-57	-6	7.90	21	
	R	46	17	-13	7.22	19	
Cerebellum							
	L/R	-8	-85	-21	9.11	322	
		2	-83	-36	7.61		
	R	42	-77	-25	8.56	40	
	L	-38	-72	-42	6.68	16	

Tables D1 and D2. For each cluster, the region showing the maximum t -value is listed first, followed by the other regions belonging to the cluster. x , y and z indicate respectively the left-right, rostro-caudal, and ventro-dorsal Talairach coordinates, and k is the number of voxels in the cluster. The statistical significance threshold for individual voxels was set at $p < .00001$ and k was set at 10.

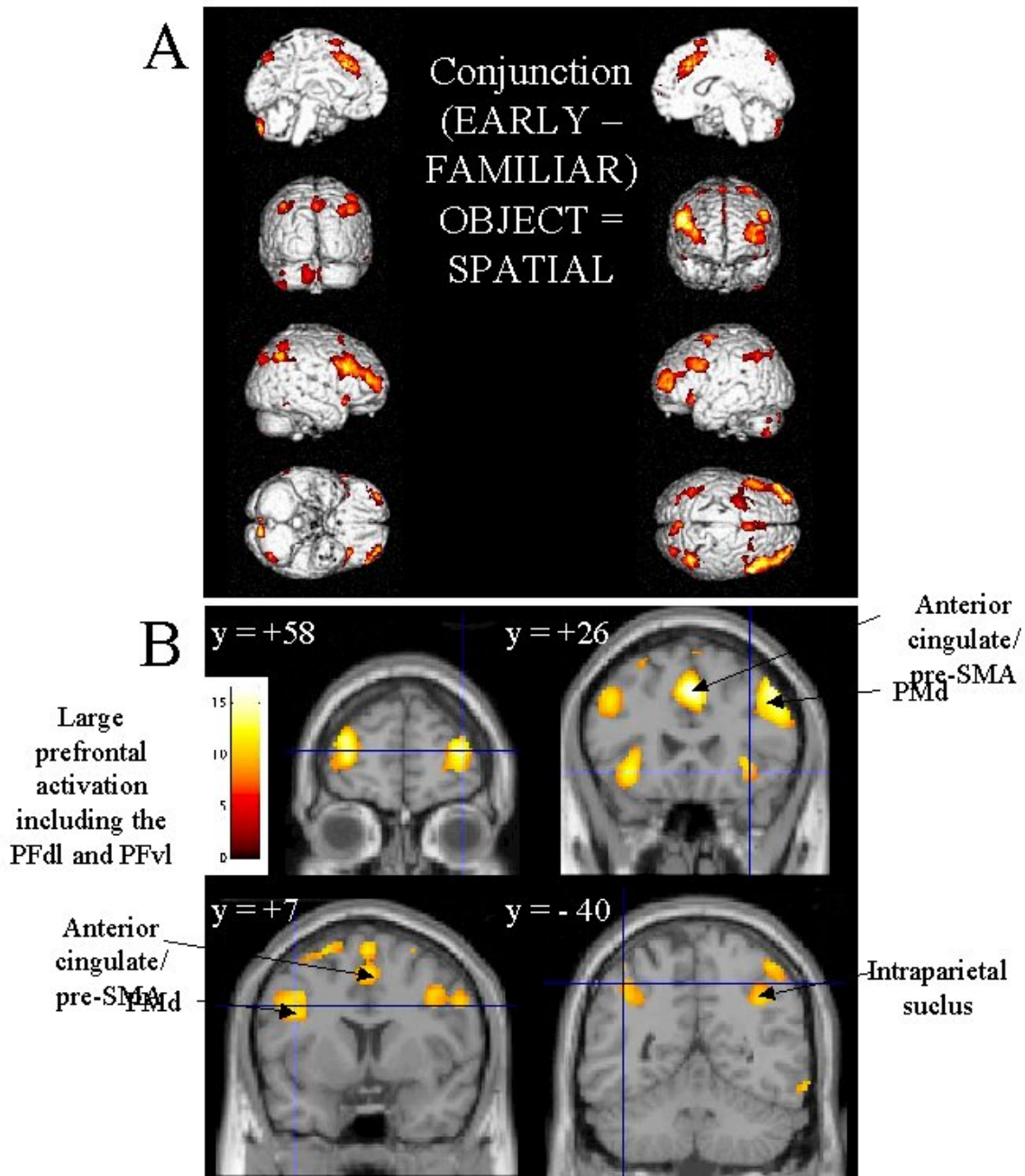


Figure D4. Brain regions equally engaged in object and spatial conditional learning (as revealed by the EARLY – FAMILIAR comparison) shown on the medial, rostral, lateral, ventral and dorsal views of the MNI brain template (A), and on a selection of coronal sections (B).

TABLE D3. CONJUNCTION ANALYSIS : brain regions equally engaged in the OBJECT and SPATIAL paradigms during learning. (EARLY minus FAMILIAR contrasts)

Anatomical regions		Talairach coordinates			t value	K
		x	y	Z		
Anterior cingulate gyrus / Pre-SMA	R/L	2	23	38	16.45	1152
		2	13	60	11.57	
		10	36	20	9.31	
Prefrontal cortex						
Middle frontal gyrus	R	40	51	16	15.00	1867
		48	27	34	14.56	
		34	59	8	14.21	
	L	-32	59	6	14.19	1548
		-32	57	14	13.95	
		-38	51	14	13.81	
Inferior frontal gyrus	L	-34	24	-8	12.38	253
		-54	20	-10	9.33	
Premotor cortex						
Superior frontal / Middle frontal gyri	L	-24	3	61	12.49	239
		-40	5	53	9.63	
		-28	20	56	9.04	
	R	30	18	56	11.18	37
		20	19	60	9.90	
Parietal cortex						
Intraparietal sulcus	R	44	-60	42	11.52	588
		40	-52	39	11.45	
		42	-56	54	11.12	
	L	-42	-43	41	11.23	401
		-28	-72	46	10.11	
		-38	-56	51	10.18	
Precuneus	R	32	-78	43	10.70	142
		R/L	2	-72	46	10.98
		12	-79	50	10.47	
Temporal cortex						
Inferior temporal gyrus	R	66	-52	-14	10.29	19
	R	48	17	-13	10.88	124
Cerebellum						
	L	-8	-81	-28	11.79	399
	R	2	-83	-36	10.15	
		-36	-70	-35	11.04	133
		-46	-68	-37	9.95	
		-40	-71	-25	9.07	29

Same convention as for Tables D1 and D2.

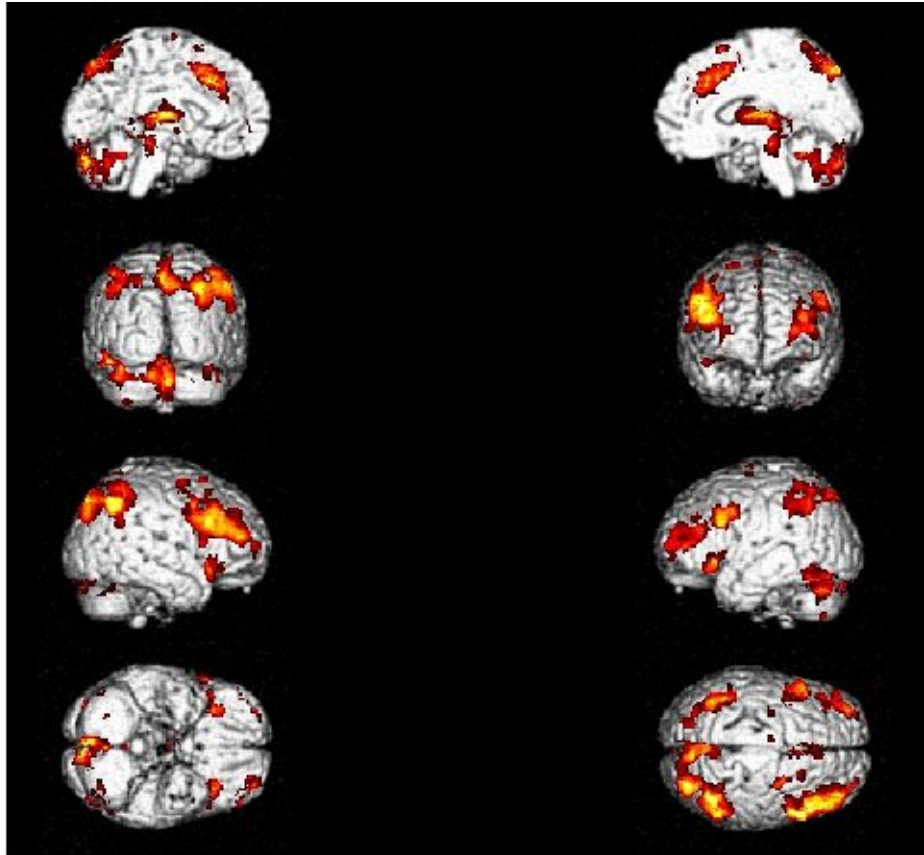


Figure D5. Brain regions equally engaged in object and spatial conditional learning (as revealed by the EARLY – LATE comparison) shown on the medial, rostral, lateral, ventral and dorsal views of the MNI brain template.

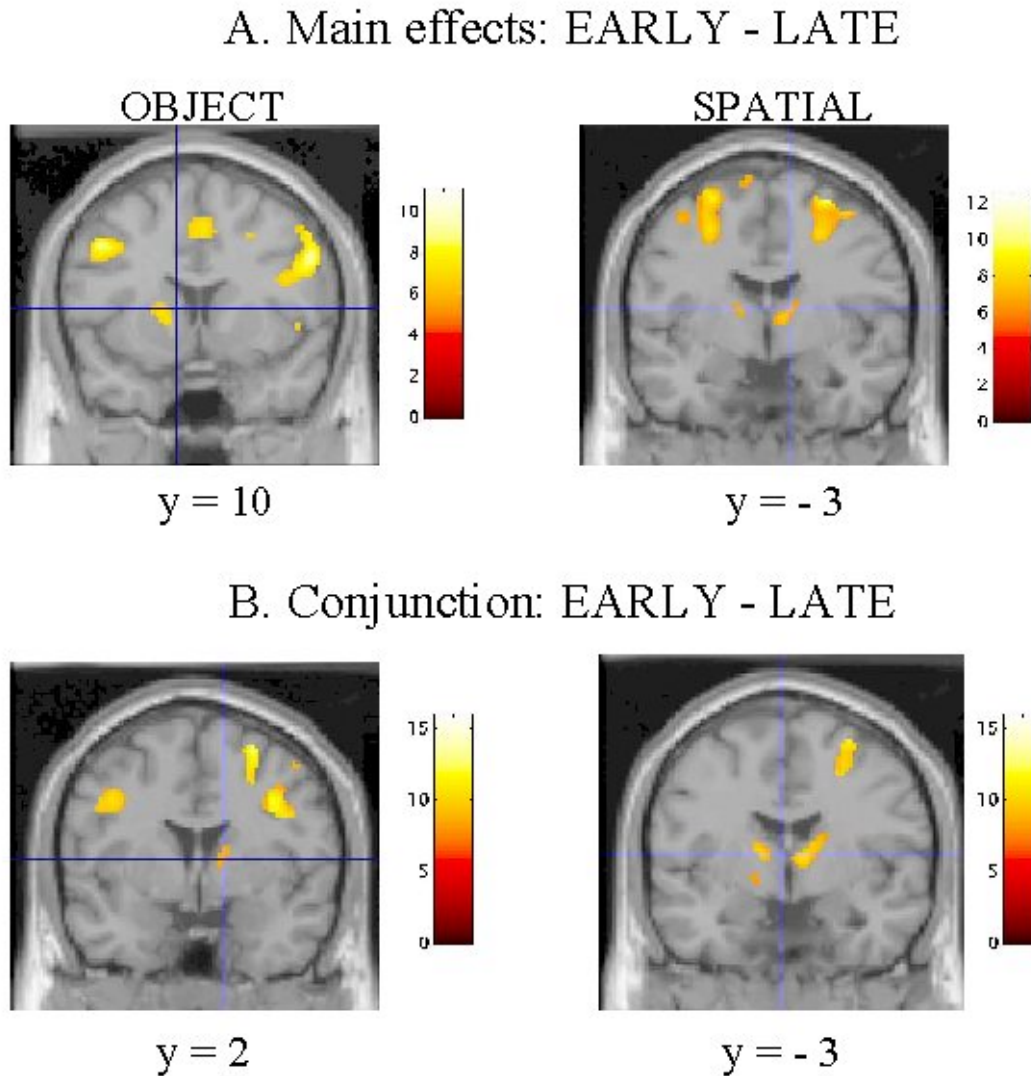


Figure D6. Coronal sections illustrating the activation sites identified in the striatum by the EARLY – LATE individual contrasts performed for the OBJECT and SPATIAL paradigms separately (A) and by a conjunction analysis (B, left and right caudate nuclei). Note that the activation site extended more anteriorly in the OBJECT than in the SPATIAL paradigm.

IV. DISCUSSION

In this study, we investigated brain activation changes during a visuo-motor conditional associative learning task in healthy subjects using fMRI. Subjects were required to learn by trial and error arbitrary associations between visual cues and finger movements, according to either the physical features of the stimulus (object) or its location (spatial). Learning-related changes were studied by comparing brain activation accompanying early stages of learning (EARLY) with those involved in subsequent stages (LATE versus FAMILIAR). For the FAMILIAR stage, subjects were overtrained across several days. Overall, comparing EARLY - FAMILIAR stages outlined a pattern of activation in the anterior cingulate cortex and overlying presupplementary motor area (pre-SMA; Picard and Strick, 1996), the lateral premotor cortex, the dorsolateral (Brodmann's areas 9/46 - 10) and ventrolateral (Brodmann's areas 47/44) prefrontal cortex, the parietal cortex (intraparietal sulcus, precuneus), the right inferior temporal gyrus, and the cerebellum. Interestingly, the contrast EARLY - LATE yielded an additional activation in the striatum and thalamus. These patterns of activation were obtained for both the object and spatial paradigms. Indeed, except for a preferential engagement of the parietal cortex in the spatial version of the task, little difference was observed across paradigms.

1. OBJECT *versus* SPATIAL paradigms

Performance of the subjects did not significantly vary across paradigms, confirming that the level of difficulty of the object and spatial versions of the task were equivalent, as intended. Subjects did respond more promptly in the spatial paradigm as compared to the object paradigm, indicating that they adequately focused on the location information during the SPATIAL paradigm, that is, they skipped the time-consuming identification of the physical features of the stimulus required by the OBJECT paradigm.

Regarding the cerebral activation elicited learning during both the OBJECT and SPATIAL paradigms, some qualitative differences were noticeable (compare Figures D3-A and D3-B). The PMd seemed to be more extensively recruited by the SPATIAL paradigm, whereas the reverse was true for the PFvl and the thalamus. However, none of these differences was confirmed by quantitative, interaction analyses. These analyses indicated that only the left intraparietal sulcus was significantly more active for spatial than for object conditional learning. It is now well established that the visual cortex contains two relatively

separate anatomical pathways, a dorsal occipito-parietal one and a ventral occipito-temporal one (Ungerleider & Mishkin, 1982) which have preferential (albeit overlapping) connections with the PFdl and PFvl, respectively. Each of these pathways is thought to convey specific visual information. The occipito-parietal pathway terminating in the PFdl, is thought to be specialised for the "where" (spatial) information, whereas the occipito-temporal pathway terminating in the PFvl, is thought to be specialised for the "what" (object) information. Although the foci of activation found in both paradigms tended to obey this dichotomy, statistical analyse failed to reach the significance level for the observed difference apart from this concerning the parietal cortex. However, it is important to note that in our study, even if the instruction given to the subjects varied according to the paradigm, in both cases, stimuli were presented at different locations, introducing a spatial component in both paradigm. In the SPATIAL paradigm, both the response times and the parietal activation indicate that the subjects ignore the physical properties of the stimulus. However, in the OBJECT paradigm, the absence of a selective temporal activation, could indicate that the subjects may not ignore the spatial information as efficiently as in they ignore the 'object' component in the spatial paradigm. This could explain the lack of significance in the interactions analysis.

2. Learning related changes

First, as compared to previous studies investigating brain activation underlying CAL (e.g. Toni et al., 2001a,b; Toni & Passingham, 1999, Toni et al., 2002; Deiber et al, 1997), and other forms of motor learning (e.g. Doyon et al., 2002; 2003; Jueptner et al., 1997a,b, Toni et al., 1998), brain activation in our study was more extensive. This difference may be due to the fact that, measurements were performed at 3 Tesla whereas in previous studies, measurements were performed either at 1.5 or 2T. Indeed, direct comparison using the same tasks, between fMRI data acquired at 1.5 and 3T fields did show that the latter yielded considerably larger activation especially in the prefrontal and parietal cortices (Krasnow et al., 2003). For example, in this study while subjects performed a 'n-back working' memory task, increases in activated voxels of 78 % and 59 % in the prefrontal and parietal cortices were found when data were acquired at 3T as compared to 1.5T.

Notwithstanding, the cerebral network activated in the present study resembles those previously described. This network includes the ventrolateral prefrontal cortex, the lateral and medial premotor cortices, the intraparietal sulcus and the cerebellum. All these structures are

thought to play distinct, complementary roles in CAL. The ventrolateral prefrontal cortex may be necessary for stimulus identification and working memory processes (Fuster et al., 2000; Murray et al., 2000; Passingham & Rushworth, 2000). Medial premotor areas activation could be related to the role of the anterior cingulate in error detection (see e.g. Dancause et al., 2002; Gehring & Fencsik, 2001; Paulus et al., 2002; Gehring & Willoughby, 2002, Bush et al., 2002), as neurons in this structure have been found to fire in relation to positive as well as negative feedback (Niki & Watanabe, 1979, Procyk & Joseph, 2001). Such structures, able to detect the consequences of a given action, appear to be of particular interest in learning processes. The parietal and most importantly the cerebellar activations are probably involved in the more direct sensori-motor transformations and parameters of movement execution (see for example Jenkins et al., 1994; Jueptner & Weiller, 1998). Activation of the cerebellum, but not the basal ganglia, have been found to be correlated to the force of movement (Dettmers et al., 1995).

Unlike previous studies, especially that of Toni et al. (2001b) who compared familiar *versus* novel conditional associations, our study revealed a significant activation in the PMd as well as in the dorsal prefrontal cortex. These differences could be due to the greater sensitivity of the magnet field used. Nonetheless, the activation found in the PMd is not surprising as electrophysiological recordings in monkeys found learning-dependent changes in these cortical areas in CAL (Mitz et al., 1991; Chen & Wise, 1995 a,b). This is also supported by lesion studies in humans (Halsband & Passingham, 1985) and animals (Kurata & Hoffmann, 1994). The activation found in the PFdl was however not expected. As previously mentioned, the specific role of the dorsal and ventral aspects of the lateral PF has been related to the type of information processed, such that PFdl is involved principally in spatial processing, whereas PFvl is involved in object processing ("domain specific" modularity, Goldman-Rakic, 1995). However, recent neuroimaging studies in humans (Haxby et al., 2000; Postle et al., 2000) and neurophysiology studies in monkeys (Rainer et al., 1998a,b; Rao et al., 1997) report an intermixing of "what" and "where" properties in the lateral PF cortex. Accordingly, Petrides and Owen have suggested that the dorsal and ventral regions mediate distinct processes ("process specific" modularity), rather than distinct sensory domains. In their view, PFvl is concerned with *'first order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long term memory'* [Petrides, 1996, page 1457] whereas PFdl is concerned with more demanding processes, such as the active manipulation and monitoring of series of information (Petrides, 1995). Two

interpretations could thus be proposed to explain the PFdl recruitment in our study. First, because in both paradigms, stimuli were presented in various locations, the activation of the PFdl could reflect the spatial component of the task ("domain specific" hypothesis). Second, it is possible that as compared to the previous study by Toni et al. (2001b), the stimuli used in our study were more complex. Indeed, in each learning set, stimuli from the same family were used (cf. Figure D1-A), making more difficult their manipulation in working memory, probably introducing 'organisational strategies' such as verbalisation and categorisation thereby leading to the recruitment of the PFdl (Frey & Petrides, 2000, "process specific" hypothesis). Our experiment does not allow us to favour one hypothesis.

3. Subcortical activation

Interestingly, the EARLY – LATE contrast, but not the EARLY - FAMILIAR one, yielded an activation in the striatum, in both paradigms. This seems to suggest that this structure was equally recruited in the EARLY and FAMILIAR stages, but less recruited during the LATE stages of learning. This is quite surprising as, according to previous studies, an antero-posterior gradient was found in the striatum concerning its recruitment along the different stages of learning. In this study, we failed to demonstrate such a gradient. This could be explained by spatial localisation limits inherent to imaging techniques (see for example, Brett et al., 2002) and the high voxel threshold used in our study as compared to others. Indeed, for example, in Toni et al.'s study a volume of interest and a less conservative statistical threshold ($p < 0.001$, uncorrected) have been especially applied to reveal basal ganglia activation. Such analysis will be performed in our study in order to provide more informative results about this key structure (in perspective). However, the quantitatively equal activation observed during the EARLY and FAMILIAR stages could in fact reflect 2 qualitatively different processes: an early recruitment of the striatum during the formation of novel stimulus-response associations on the one hand, and selection according to well-established stimulus-response associations on the other hand. Indeed, in early stages of learning, the striatum may participate to short-term maintenance in memory of the stimuli, the integration of feedback information whereas in late stages, it may contribute to the long term storage of arbitrary rules and the implementation of action selection. Although, the BOLD signal has been found to correlate more closely to the Local Field Potential (LFP) signal (e.g. Logothetis, 2003), our electrophysiological findings (see PART A, transient and long lasting changes during learning) tend to draw similar conclusions. Furthermore, the increase of

cortico-striatal effective connectivity during learning also supports this view (Toni et al., 2002). Interestingly, in this line, in early stages of learning, the subjects' performance in the SPATIAL paradigm tended to be better compared to the OBJECT paradigm, although this difference did not reach the significance level. When comparing brain activation elicited by both paradigms, OBJECT-related activation was more anterior in the striatum than SPATIAL activation. This difference could be correlated with the subjects' performance and could thus denote an anteroposterior gradient in the involvement of the striatum during learning as previously demonstrated.

Finally, the subcortical activation also included part of the thalamus. This activation was also found in the EARLY – FAMILIAR contrast in the object paradigm only. Accordingly, other studies have reported an involvement of the mediodorsal thalamic nucleus during new sequence learning but not during automatic execution (Jueptner et al., 1997). Indeed, this structure belongs to the basal ganglia thalamo-cortical loops and is heavily and reciprocally interconnected with the prefrontal cortex (Alexander et al., 1986).

4. Limits

Ten other subjects will be added to the sample presented here. Indeed, using 20 subjects, it will be possible to run more sensitive and accurate statistical approaches such as 'the random-effect' instead of a 'fixed-effect' analysis as been used in the present study. Indeed, the use of a 'random effect', but not the 'fixed effect' takes into account the variability across individual subjects of the localisation and weight of the activation foci ('fixed-effect analysis assume that each subject makes the same, fixed contribution to the observed activation and therefore discount random variations from subjects to subject', Friston et al., 1999, p. 386). In other words, a strong focus of activation found in only one subject could be misleadingly reported in the group analysis using a 'fixed-effect', but not a 'random-effect' analysis. However, in the present study, the number of subjects used did not allow us to run a random effect analysis. Nevertheless, the activation reported here were consistent across subject as been verified in each individual subjects contrast.

E - General Discussion

GENERAL DISCUSSION

Within the basal ganglia (BG), the striatum receives various signals including sensory, motor and motivational (feedback-related) signals, and its particular architecture is suitable for complex integration of these incoming information. Based on this observation, the present research was undertaken to investigate the role of the striatum in learning conditional visuo-motor associations. Three complementary approaches were combined: neurophysiology in behaving monkeys, functional neuroimaging (fMRI) in healthy humans, and neuropsychology in patients suffering from Parkinson's disease (a neurodegenerative pathology affecting the BG). The same type of task was used in all three experiments, where subjects had to learn associations or rules that linked a visual cue and a movement. These associations were arbitrary, and had to be learned by trial and error using the provided feedback.

Electrophysiological study : results and perspectives

Striatal activity was recorded in awake monkeys in two conditions: while the animals executed well-learned (familiar) associations, and during trial-and-error learning of novel associations. During learning, four associations were presented concurrently, instead of two, as in the only earlier previous study that has investigated striatal activity during associative learning (Tremblay et al., 1998). This allowed us to follow changes of neuronal activity over a long period of time and different stages of learning. In addition, our protocol was comparable to that used earlier to explore the changes of activity in the premotor cortex (Mitz et al., 1991). Thus, learning-induced changes in the striatum and premotor cortex, two critical nodes in the cortico-basal ganglia-thalamo-cortical loops, could be directly compared.

During the execution of familiar associations, the majority of the recorded cells exhibited selectivity for a particular association. This confirmed that striatal cells possess neural properties that can code specific stimulus-response bonds once they have become automatic, thereby differing from premotor cells whose activity during familiar associations is essentially movement-oriented (Boussaoud & Kermadi, 1997). During learning, striatal activity displayed significant changes. These changes were either transient, consisting in a time-limited increase in activity (above the level recorded in the familiar condition) during early learning stages, or long-lasting, consisting in a gradual increment of activity over the entire course of the learning session, up to the level of activity characteristic of the familiar

condition. These learning-related changes closely resemble, both in their nature and their temporal dynamics, those recorded in premotor cortical areas with tasks comparable to that used in the present study (Mitz et al. 1989; Chen & Wise, 1995a, b). Interestingly, similar transient and long-lasting changes have also been observed in both the orbital and lateral portions of the prefrontal cortex with different visuo-motor conditional tasks (Assad et al., 1998; Tremblay & Schultz, 2000), as well as in the hippocampus during learning of visuo-visual (location-scene) associations. These two types of learning-related changes could therefore represent rather ubiquitous brain plasticity mechanisms whose functional meaning depends on the specific structure in which they occur. Within the basal ganglia, we proposed that they reflect different processes necessary for the establishment of arbitrary visuo-motor rules. Transient changes could mediate monitoring of competing information in short-term (working) memory, and/or the development of strategies aimed at diminishing the working memory load. These time-limited changes could be related to the phasic response of dopamine neurons (Schultz, 2002). By contrast, long-lasting changes may mediate the slow, incremental establishment of stimulus-response bonds preceding the automatization of arbitrary associations. These durable changes may be related to the tonic dopaminergic influence on striatal functions (Schultz, 2002).

In the future, the testing of the animals involved in the first experiment will be pursued in order to address two questions that remain to be answered. First, in our initial working hypothesis (see Part A), we had surmised that neuronal changes in the striatum would occur earlier during learning than those observed in the PMd, suggesting a possible causal relationship, in the sense that premotor changes would result partly from those taking place in the striatum. To date, our electrophysiological data do not confirm this prediction. Therefore, to dissect the respective contributions of the striatum and premotor cortex, we are planning to: 1) record simultaneously the activity in the two structures, and 2) reversibly inactivate the striatum and follow the resulting changes in the activity of PMd cells. Second, it is still unclear how the integration of different types of information takes place in the striatum. To shed some light on this issue, we are planning to analyze the synchronization of activity at the level of population of neurons using simultaneous recordings of both multiple single-cell responses (see Aosoaki et al., 1994; Raz et al., 1996; and Kimura et al., 2003) and local field potentials in the striatum.

Functional imaging study : results and perspectives

We investigated the global network involved in different stages of conditional associative learning using fMRI. The early stage of learning yielded selective activation in several brain regions, including the premotor areas, the prefrontal cortex, the parietal cortex, the inferior temporal cortex, and the cerebellum. The striatum was found to be equally recruited during the early learning stage and execution of well-established associations. By contrast, it was relatively less engaged during the late stage of learning.

We observed no antero-posterior functional segregation within the striatum during learning, unlike previous imaging studies (e.g. Jueptner et al., 1997) which reported that the anterior and posterior striatal regions participated in the acquisition and consolidation phases, respectively. Our perspective is therefore to re-analyze our data using a finer analysis (based on a region-of-interest design) to improve spatial resolution and determine whether this observation also holds true for conditional associative learning. We are also planning to study the brain activation underlying the intermediate stage of learning and to examine the temporal evolution of the signal along the process of learning. Finally, we will also investigate the cerebral activation underlying the execution of well-learned association by studying the activation elicited by the following contrasts: FAMILIAR - EARLY (or MIDDLE or LATE) as well as LATE - EARLY (or MIDDLE or LATE) and FAMILIAR - LATE.

Neuropsychological study : results and perspectives

The ability of advanced Parkinson patients to perform a visuo-motor conditional associative learning task was investigated both with and without L-Dopa treatment. OFF medication, we found that, within a relatively homogeneous group of nine patients, learning was significantly retarded in six patients, whereas it appeared normal in the remaining three. When it did occur, the learning impairment was accompanied by an excessive number of repetitions of the same incorrect associations, which suggested inadequate monitoring of competing items in working memory or inhibition of spontaneous preferences. We have hypothesized that this deficit was in fact present in all patients, and that the inter-individual variability evoked above simply reflects whether or not the patient was able to devise a compensatory strategy in order to circumvent it. The development and/or use of such a strategy seemed to be dependent upon the dopaminergic system. Of particular interest, in light

of the data obtained in the other two experiments, is the fact that retention of newly learned associations was mildly disrupted in all patients alike, indicating that disruption of the retention phase was present whether or not an impairment was detectable during the acquisition phase. This dissociation again suggests an implication of the striatum in at least two processes, one required only during the early stages of learning, and one necessary at later stages for long-term storage of newly acquired associations.

Relative to previous reports on the ability of Parkinson patients to learn conditional associations, we demonstrated a complex pattern of deficits and the use of a dopaminergic-dependent compensatory strategy. In order to study the underlying processes accompanying the deficits observed and the development of the compensatory mechanism, it would be interesting to use Positron Emission Tomography, with a marker of the dopaminergic system such as the [¹⁸F]-6-fluoro-L-Dopa.

What does conditional associative learning tell us about basal ganglia functions ?

The research presented here combines three different, albeit complementary approaches. Results from all three approaches converge to indicate that the striatum plays a key role in the learning of arbitrary visuo-motor associations, as measured by conditional learning tasks. These tasks require to concurrently learn, by trial and error, several associations, each linking a specific visual stimulus with a particular motor response. They therefore tax at least two different types of processes, short-term (working memory) processes necessary to guide performance during the acquisition phase, and long-term (habit memory) processes to ensure the slow and incremental formation of each individual stimulus-response bond. Interestingly, all three studies argue for a role of the striatum in both types of processes. In the electrophysiological study, transient learning-related changes may reflect the monitoring of previously tried associations in working memory, and/or the development of a particular strategy. By contrast, the long-lasting changes may mediate the long-term storage of each newly learned associations, and lead to the striatal properties found in the familiar conditions. In the fMRI study, the equal recruitment of the striatum in the early learning of novel associations and the execution of well-learned ones could be related to the data obtained in the electrophysiological study, although the BOLD signal may be more linked to local field potentials than to single-cell responses (Logothetis, 2003). Finally, the deficits found in advanced Parkinson patients are also compatible with the idea that the basal ganglia are

involved in the acquisition as well as in the retention phase of conditional associative learning.

In summary, the basal ganglia have long been seen as a motor center. More recently, they have been involved in various cognitive functions. However, to date, the exact non-motor functions of these structures remain obscure. Numerous authors have postulated a role in habit memory (e.g. Mishkin et al., 1984; Jog et al., 1999), whereas a few others have proposed a direct implication in working memory (e.g. Levy et al., 1997). Here, by using complementary approaches and by dissecting the different processes underlying a single behavioral task, we have provided evidence that the basal ganglia is involved in both of these functional domains.

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