Cognition and the Basal Ganglia: A Possible Substrate for Procedural Knowledge

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ABSTRACT: Disruption of neural activity within the basal ganglia of experimental animals causes selective learning deficits in tasks requiring switching between response strategies. These data along with reports of both general and specific intellectual impairment in patients with neurodegenerative disorders such as Parkinson's disease, appear to support the theory of cognitive functions of the basal ganglia. Recent studies have failed to confirm general cognitive or memory deficits in parkinsonian patients, but have identified deficiencies in devising and executing certain cognitive strategies. Following the lead of theorists such as Squire and Mishkin, this brief review emphasizes the distinction between procedural and declarative knowledge and examines the possible role of the basal ganglia in the acquisition and retention of procedural knowledge.

RÉSUMÉ: La cognition et les noyaux gris centraux: un substrat possible pour la connaissance procédurale. Une perturbation de l'activité neuronale à l'intérieur des noyaux gris centraux chez des animaux de laboratoire provoque des déficits sélectifs de l'apprentissage pour des tâches exigeant de passer d'une stratégie de réaction à une autre. Ces observations ainsi que le compte rendu d'une atteinte générale et spécifique des fonctions intellectuelles chez les patients atteints de maladies neurogénératives, telle la maladie de Parkinson, semblent supporter la théorie selon laquelle les noyaux gris centraux auraient des fonctions cognitives. Des études récentes n'ont pas mis en évidence de déficit général des fonctions cognitives ou de la mémoire chez les parkinsoniens, mais ont plutôt identifié des déficits dans la conception et l'exécution de certaines stratégies cognitives. A la suite des théoristes tels que Squire et Mishkin, cette brève revue fait ressortir la distinction entre la connaissance procédurale et la connaissance déclarative et examine le rôle possible des noyaux gris centraux dans l'acquisition et la rétention de la connaissance.

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The role of the basal ganglia in the neural control of movement is indisputable, but there is still considerable debate as to whether movement is the sole function controlled by this important region of the brain. In part, the relative size of the basal ganglia and their strategic location within the forebrain vis-a-vis the cortex, thalamus and limbic system, have prompted a number of theorists to suggest the participation of the basal ganglia in a variety of cognitive processes.[1,2,3] It must be noted however that this concept is not without its detractors.[4]

Recent developments in cognitive neuroscience emphasize the distinction between two different forms of knowledge, one subserving the acquisition and retention of new skills (procedural knowledge) the other concerned with factual information (declarative knowledge); each subserved by anatomically distinct systems in the brain.[5,6,7] The present review will re-examine evidence from selected studies with experimental animals and patients with the neurodegenerative disorder Parkinson's disease from this new perspective, in an attempt to clarify the role of the basal ganglia in cognitive function.

Two Categories of Knowledge

By definition, amnesia in humans is characterized by profound deficits in the establishment of new memories and the retrieval of certain older memories encoded before the onset of amnesia.[5,6] However, it is now well established that a number of important forms of learning and memory are preserved in amnesia.[6] For example, amnesic patients can acquire and perform (a) pattern-analyzing skills necessary for mirror reading, (b) sensory-motor skills required for rotary pursuit and bimanual tracking or mirror tracing tasks, and (c) cognitive skills that lead to the optimal solution of The Tower of Hanoi puzzle.[6] It must be emphasized that these new skills are learned and remembered despite complete memory loss for both the general and specific details associated with the original learning trials. This profound distinction between preserved and diminished capacities for learning and memory in amnesia had led to the resurrection of earlier suggestions that knowledge exists in two fundamentally different forms:[5,6,7] one subserving the

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acquisition of specific facts, data, or personal experience (i.e., declarative knowledge; memory with record), the other concerned with the development of new sensory-motor and cognitive skills (i.e., procedural knowledge; memory without record). The factual information that characterizes declarative knowledge appears to be generated and stored by structures in the medial temporal and diencephalic regions of the brain, areas that are damaged specifically in amnesic patients. Clearly, the preserved capacity for procedural learning must reside in anatomically and functionally distinct neural systems; those that undergo modification during the acquisition of the procedures required for successful processing of new skills.

In a recent consideration of this issue, Mishkin and his colleagues[7] utilized the terms "memories" and "habits", with the former referring to the record of prior stimulus associations and the latter to stimulus-response connections favoured by the behaviorists. These authors attributed habit formation to activity within the cortico-striatal system. In the final analysis, the concept of "habits" may prove to be too restrictive, in view of the evidence that skill learning is a general phenomenon that encompasses not only perceptual-motor processes but also cognitive strategies necessary for problem solving.[5,6] Nevertheless, the general hypothesis that the basal ganglia play an essential role in processing procedural knowledge may help to resolve the debate concerning the participation of the basal ganglia in cognitive function.

Cognitive Deficits Following Manipulation of Basal Ganglia in Animals

Much of the initial evidence for cognitive mechanisms within the basal ganglia was derived from experiments in which specific forms of learning and memory were disrupted by lesions or electrical stimulation of these brain regions in a variety of species (Table 1). In an excellent review of this extensive literature, Öberg and Divac[2] have placed these deficits into several categories including delayed response tasks, which require correct choice of direction, as distinct from choices of when to initiate or withhold specific responses (avoidance conditioning, differential responding or discrimination learning). In general these deficits may be categorized as impairments in the ability to switch between different behavioral strategies[2] and an inability to acquire new motor skills necessary for the successful initiation of approach or avoidance behavior.[17] Superficially, these impairments resemble deficits in procedural learning. It must be emphasized that complete reciprocity between basal ganglia dysfunction and deficits in procedural knowledge, also requires the preservation of declarative knowledge. Reports of specific memory deficits following electrical stimulation of the striatum would appear to be inconsistent with this prerequisite.[15,20,23] However, most studies suggesting a role for the striatum in memory formation have failed to control for either state dependency or the stimulus properties of brain-stimulation. When these factors are controlled for it is clear that many of these apparent memory deficits are artifacts.[24] Therefore it remains a distinct possibility that manipulation of basal ganglia function in animals may lead to selective deficits in procedural learning while leaving declarative knowledge intact.

Although there is a paucity of data linking the basal ganglia to procedural as distinct from declarative knowledge, one recent study by our group provides direct evidence for such a dissociation.[25] Many studies have confirmed that neurotoxic lesions of the nigrostriatal dopamine pathway[17] or pharmacological blockade of dopamine receptors[25] can block the acquisition

Table 1: Representative Examples of Learning and Memory Deficits Produced by Lesions or Electrical Stimulation of the Basal Ganglia in Rat and Monkey

Deficit	Neural Manipulation	Species	
Delayed Response Tasks			
a) Alternation	Lesion	Rat	Gross *et al*, 1965[8]
	Kainic Acid Lesion	Rat	Divac *et al*, 1978[9]
	Lesion	Monkey	Rosvold *et al*, 1958[10]
b) Spacial reversal	Lesion	Rat	Kolb, 1977[11]
c) Successive discrimination	Electrical Stimulation	Rat	Livesey and Muter, 1977[12]
Avoidance Conditioning			
a) Passive avoidance	Lesion	Rat	Mitcham and Thomas, 1972[13]
	Kainic Acid Lesion	Rat	Sanberg *et al*, 1978[14]
	Electrical Stimulation	Rat	Fibiger and Phillips, 1976[15]
b) 1-way active avoidance	Lesion	Rat	Winocur, 1975[16]
	6-OHDA Lesion SNC	Rat	Fibiger *et al*, 1974[17]
c) 2-way active avoidance	Lesion	Rat	Neill and Grossman, 1970[18]
	6-OHDA Lesion	Rat	Neill *et al*, 1974[19]
Differential Responding			
Appetitive	Lesion	Rat	Kolb, 1977[11]
	Electrical Stimulation	Rat	Herz *et al*, 1974[20]
	Lesion	Monkey	Butters and Rosvold, 1968[21]
Discrimination Learning			
Patterns	Lesion	Monkey	Divac *et al*, 1967[22]
	Electrical Stimulation	Monkey	Cohen, 1972[23]

Unless otherwise stated, neural manipulation was in the striatum.
SNC = substantia nigra pars compacta.

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of 1-way active avoidance behavior by rats. This deficit cannot be attributed to motor impairment, because escape behavior is left intact as is an overtrained avoidance response. In the experiment in question, rats treated with pimozide failed to acquire the avoidance response although they escaped readily when shock was presented after a 10 sec tone stimulus (Figure 1A). The same rats then received several sessions of food reinforced lever pressing in a different apparatus, without drug treatment. Subsequent presentation of the tone that had signalled shock in the avoidance test, caused a significant attenuation of lever pressing for food (Figure 1B). These results provide conclusive evidence that pimozide-treated rats, although failing to acquire the avoidance response in the shuttle box, had learned and remembered the association between the tone and shock. In the context of the present discussion it may be claimed

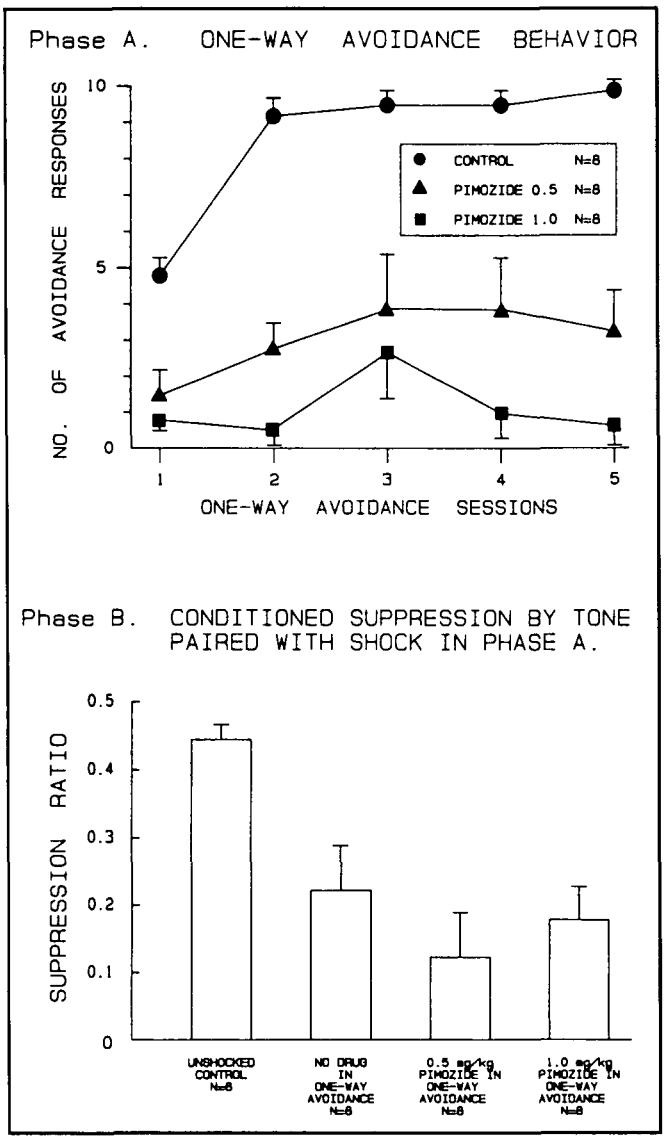

Figure 1 — Pimozide blocks the acquisition of a 1-way active avoidance response in a procedure in which a tone signals impending footshock after a 10 sec interval (Phase A). In a subsequent procedure (Phase B), the same groups are tested in an undrugged state and the tone paired previously with footshock elicits a conditioned emotional response, thereby confirming the prior establishment of an association between these two stimuli in Phase A. Adapted from Beninger et al (1980).[25]

that disruption of the basal ganglia by blockade of dopamine function led to a deficit in procedural learning, while sparing the acquisition of declarative knowledge concerning the predictive relationship between tone and shock.

Cognitive Deficits Associated with Parkinson's Disease

As noted above, disruption of the normal neural functioning of the basal ganglia in animals is accompanied by a disturbance in higher order perceptual processing and problem solving. Given that such deficiencies are not accompanied by general motor, sensory, or homeostatic deficits, it would seem appropriate to ascribe a degree of cognitive function to the basal ganglia.[2] The difficulty arises when one moves from this general case to the more specific one of cognitive dysfunction associated with neurodegenerative diseases of the basal ganglia, such as Parkinson's disease. Although several investigators have reported pervasive intellectual impairment in the parkinsonian population,[26,27,28] a great many carefully designed and well controlled studies have failed to confirm this condition as a general feature of the disease, but they have noted a variety of specific cognitive deficits (Table 2). Furthermore, nondemented parkinsonian patients do not appear to have significant deficits in immediate or long-term memory for factual information.

The most compelling evidence for cognitive disorder in Parkinson's disease is derived from neuropsychological tests such as the Wisconsin Card Sort Test (WCST) in which sorting categories are changed without notice and the subject must deduce the correct new category by error feedback. Parkinsonian subjects fare poorly on this test[33,34,38] as they do on related tests.[37,39] Accordingly, the nature of the cognitive impairment is described as "an inability to generate plans for task achievement internally";[33] "difficulty in shifting conceptual sets";[38] impaired "organization of actions at a higher level, . . . in the decision making or planning level of skills".[39] These deficiencies are symptomatic of frontal cortical damage and the functional contribution of striatal projections to the frontal lobe is now emphasized.[33,34,39] For heuristic purposes, it may be appropriate to consider these impairments as deficits in the capacity to modify internal operations or procedures necessary for efficient switching between cognitive sets or categories. In the context of the earlier discussion, this would constitute a deficit in procedural learning.

Additional support for a procedural learning deficit in Parkinson's disease may be found in studies of pursuit tracking tasks in which parkinsonians failed to learn a tracking response[40] although normal tracking was observed when the subjects were informed of the repetitive nature of the task.[41] It may be argued that these patients were unable to acquire this perceptual-motor skill (procedural knowledge) unless provided with an external mnemonic (declarative knowledge). Squire and Cohen[6] maintain that developing the skills to solve the Tower of Hanoi is an important example of procedural knowledge requiring cognitive skill learning. Therefore it is highly significant that patients with Parkinson's disease and Huntington's disease recently have been shown to be impaired in solving this puzzle efficiently.[42] Complimentary studies are underway in our laboratory (Carr, Phillips and Calne, in preparation) to confirm these results with the Tower of Hanoi, and to extend them to other exemplars of procedural learning, including mirror tracing and priming. Priming refers to a situation in which prior exposure to words or pictures greatly enhances their subse-

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Table 2: Cognitive Deficits Associated with Parkinson's Disease

Deficit	Neuropsychological Test	
General Intellectual Impairment	Wechsler Adult Intelligence Scale (WAIS) Wechsler Memory Scale (WMS)	Reitan and Boll, 1971[26] Loranger *et al*, 1972[27] Pirozzolo *et al*, 1982[28]
Visuospatial Tasks	Route-walking Tracing degraded patterns	Bowen *et al*, 1972[29] Stern *et al*, 1983[30]
Memory Processes		
a) temporal sequencing of long term memory	Dating of public events	Sagar *et al*, 1985[31]
b) immediate recall	Logical passages (WMS)	Riklan *et al*, 1976[32] Taylor *et al*, 1986[33]
c) recognition of supraspan word list	Rey Auditory Verbal Learning Test (RAVLT)	Taylor *et al*, 1986[33] Taylor *et al*, 1987[34]
Concept Formation	Wisconsin Card Sort (WCST) WAIS — performance scale	Bowen, 1976[35] Matthews and Haaland, 1979[36]
Shifting Capacity	Word production, Block sorting, Animal sorting	Cools *et al*, 1984[37]
Executive Functions —		
defined as subjective generation of task specific categories	WCST WCST, RAVLT Bead-Tapper, Delayed Response task (spacial)	Lees and Smith, 1983[38] Taylor *et al*, 1986[33]
Instability of Cognitive Set	Odd-Man-Out test	Flowers and Robertson, 1985[39]

quent use in completion of word or picture fragments in free association tests, a capacity that is preserved in amnesia.[5] If patients with degenerative disorders of the basal ganglia can be shown to be deficient in the acquisition of procedural knowledge, while having preserved capacity for declarative learning and memory, this would provide further confirmation of the distinction between these two classes of knowledge; while at the same time locating the neural substrates for procedural knowledge in a system comprised of the striatum and its afferent projections to the frontal cortex.

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