Memory in Neurodegenerative Disease

Biological, Cognitive, and Clinical Perspectives

Edited by
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Memory in neurodegenerative disease

Cognitive impairment in late life is a growing clinical and public health problem, with Alzheimer's disease the most prevalent of the progressive dementias. Memory disorders are the commonest and most disabling feature of neurodegenerative disease, and this book is the first to review in depth the neurobiological and clinical characteristics of memory and its disorders in this group of patients. In addition to Alzheimer's disease it presents current information about memory disorders in Huntington's and Parkinson's diseases and in other neurological conditions such as progressive supranuclear palsy, Creutzfeldt – Jakob disease and HIV-associated dementia.

The contributors are among the most distinguished working in this field. They present the neuroanatomical and neurochemical basis of memory disorders in neurodegenerative disease, and review the contribution of neuroradiology and neuropathology to the understanding of memory and amnesia. Different types of memory are differently affected in these conditions, and the clinical and neuropsychological implications are thoroughly explored. Diagnosis, assessment and treatment issues are discussed, as are ethical and legal considerations and topics of emerging interest such as the early detection of dementia, preserved cognitive functions and neurosurgical interventions. The book is in three parts, each with an integrative summary from a leading authority.

Bringing together biological, cognitive and clinical information, this book will be an essential reference for neuropsychologists, neurologists and psychiatrists, experimental psychologists and other neuroscientists. As memory disorders are so fundamental to neurodegenerative disease, it also serves as an authoritative and up-to-date overview of the dementias and the prospects for treating them.

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Preface

Many volumes are dedicated to studies of memory, which might be considered the essence of the rich tapestry of life. Some volumes describe normal memory, others disordered memory. This book is designed to fill a gap by focusing specifically on memory in neurodegenerative conditions. The explosion of neuroscience research dealing with this topic has left many seeking a single source which might familiarize them with the basics of research outside their own area of expertise. Although no book can be everything to everyone, and cover every relevant topic, this book attempts to bring together biological, cognitive and clinical perspectives, so that neuropsychologists, neurologists, psychiatrists and neuroscientists can familiarize themselves with allied research outside their immediate area of expertise. An effort is made to present research of recent and emerging interest, for example, preclinical detection of dementia, the description of prospective memory and the renaissance of surgery for movement disorders due to neurodegenerative processes. Often neglected topics, such as ethical and legal issues, are also addressed.

I thank my wife, Kristy Straits-Tröster, for her immense patience and understanding while bearing countless solitary hours during the completion of this project. My parents, Guy and Christine Tröster, continue to understand that work load sometimes necessitates putting up with an 'alien' son, and their understanding and inspiration is, as always, greatly appreciated.

The invaluable assistance of Julie Fields in the completion of this volume is most gratefully acknowledged, as is the encouragement and support of Dr Richard Barling, Director of Medical Publishing at Cambridge University Press, who demonstrated great faith in taking on this project. Tremendous gratitude also goes to the editorial and production staff at Cambridge University Press, and especially to Mr Joe Mottershead, without whose professionalism and arduous effort this volume might still be in press several years from now. I also extend my thanks and deep appreciation to the authors contributing to this book. Not only did they all deliver superb chapters in a short time frame, but they patiently endured my editorial whims and rewrites. A final word of gratitude goes to William Bartholome, MD, and Mr Don Lambert, who familiarized me with 'Grandma' Layton's inspiring art.

To my family

For their love, support, patience, and above all, encouragement

To the many thousand individuals participating in the research that is the subject of this book

For giving selflessly of themselves in the hope of helping others

PART I

Biological perspectives

1 Nonhuman primate models of memory dysfunction in neurodegenerative disease: contributions from comparative neuropsychology

MARLENE OSCAR-BERMAN
AND FIONA BARDENHAGEN

INTRODUCTION

Results of nonhuman animal research can provide new information that human experimentation does not allow, usually for ethical considerations or because of limited control over complex environmental influences. The new knowledge can then be used to help understand human disorders. In the present chapter, we review the application of behavioral methods – developed in nonhuman animal laboratories and modified for human use – toward clarifying memory dysfunction in human neurodegenerative disease. Implicit in nonhuman research models of human brain functioning is the assumption of homologous structural-functional relationships among the species (Riley and Langley 1993; Wasserman 1993). Research on brain mechanisms underlying behaviors across species, contributes to the discovery of common and divergent principles of brain-behavior relationships, ultimately to understand how the brain functions. With understanding comes the potential for assessment and treatment of human neurobehavioral disorders.

One approach to understanding interspecies brain functions, comparative neuropsychology, involves the direct evaluation of human clinical populations by employing experimental paradigms originally developed for nonhuman animals (Weiskrantz 1978; Oscar-Berman 1984, 1994; Roberts and Sahakian 1993). Over many decades of animal research, the paradigms were perfected to study the effects of well-defined brain lesions on specific behaviors and many of the paradigms still are used widely to link specific deficits with localized areas of neuropathology (for reviews, see Medin 1977; Deutsch 1983; Arnold 1984; Stuss and Benson 1986; Meador et al. 1987; Mitchell and Erwin 1987; Fuster 1989; Sahgal 1993). The comparative neuropsychological approach employs simple tasks that can be mastered without relying upon language skills. Precisely because these simple paradigms do not require linguistic strategies for solution, they are especially useful for working with patients whose language skills are compromised, or whose cognitive skills may be minimal (Oscar-Berman 1991, 1994; Oscar-Berman et al. 1991). Comparative neuropsychology contrasts with the traditional approach of using tasks that rely upon linguistic skills, and that were designed to study human cognition (Walsh 1987; Vallar and Shallice 1990; Lezak 1995). As important ambiguities about its heuristic value had not been addressed empirically, only recently has comparative neuropsychology become popular for implementation with brain-damaged patients (for reviews see Oscar-Berman 1994; Squire 1992; Roberts and Sahakian 1993; Seidman et al. 1995). Within the past decade it has had prevalent use as a framework for comparing and contrasting the performances of disparate neurobehavioral populations on similar tasks.

An historical context provides the necessary forum for presenting current-day examples of the usefulness of the approach; therefore, we provide a brief history of comparative neuropsychology, beginning with the early experiments of E.L. Thorndike (1911) in the context of the Darwinian thinking of the time. Next, we review evidence

showing that human and nonhuman primates do solve many so called animal tasks in similar ways. Moreover, results of numerous research studies already have clearly demonstrated that the tasks – despite their apparent simplicity – are sensitive to specific cognitive impairments after brain damage in humans and nonhumans alike. Performances of patients with various forms of neurodegenerative disease on comparative neuropsychological tasks are reviewed, and the implications of these findings are discussed in terms of comparative neuropsychological models of working memory and declarative memory.

HISTORICAL CONTEXT

During the first half of this century, neuropsychology was not a separate subdiscipline as we know it today; rather, neuropsychology was subsumed under physiological psychology, the study of the relationship between the brain and behavior. Research in physiological psychology relied mainly on animal subjects. Until the 1950s, only a handful of behavioral laboratories were conducting research with human neurological patients. The research was led by the following investigators, to mention a few: Wechsler (1944), Hebb (1949), Teuber (1955), Penfield (1958), Pribram (1958), Reitan (1962) and Milner (1964) in North America; Russell (1959) and Whitty and Zangwill (1966) in the United Kingdom; and Luria (1966) in Russia. Around that same time, Frank Beach was the editor of the *Journal of Comparative and Physiological Psychology*, a journal devoted to research on the biological underpinnings of behavior. Beach was intrigued by the observation that most studies appearing in the journal relied upon data collected on one laboratory species, the rat. Consequently, he reviewed all of the articles published in the *Journal of Comparative and Physiological Psychology* since its inception in the 1930s (Beach 1960) and discovered that approximately 60% of the papers used laboratory rats, 10% used submammalian vertebrates or invertebrates and 30% employed other mammals (mostly nonhuman primates). In other words, until at least the 1950s, inferences about brain–behavior relationships in people were based principally upon studies of nonhuman species, especially the rat. To understand how the emphasis on rat research occurred, it is important to go back further in time (for additional historical information see also Bitterman 1960, 1975; Masterton et al. 1976).

Darwinian influence and Thorndikian connectionism

In 1871, Darwin published *The Descent of Man and Selection in Relation to Sex*. In addition to morphological continuity along the phylogenetic scale, Darwin also considered behavioral continuity. For Darwin, continuity was not compatible with novelty. Darwin tried to demonstrate that seemingly unique characteristics of animals were not really unique at all; rather, . . . 'some hint or promise of it always could be discovered at an earlier point in the series' (Bitterman 1960, p. 704). According to Darwin, then, phylogenetic differences were more quantitative than qualitative.

Psychologists at the end of the nineteenth century were reluctant to accept Darwin's ideas, not because they questioned his conclusions, but because they had little faith in his data. Darwin relied mainly on anecdotal reports from naturalists and zookeepers instead of controlled laboratory experimentation. In the 1890s, one of these skeptics was a doctoral student, E.L. Thorndike, who wanted to explore the derivation of human intelligence. Thorndike was critical of the anecdotal approach, and to collect data for his doctoral dissertation, he built experimental equipment in which to quantify animal behavior. The equipment included puzzle boxes or problem boxes. The animals could see food outside the boxes, and they could escape to retrieve the food by performing simple actions such as pulling a loop, pressing a lever or stepping on a treadle. Thorndike recorded the time it took animals to escape and retrieve the food on each of a series of trials, and he observed that time decreased over trials. In addition, there was transfer, or facilitation, from one experimental situation to another. The terms *learning set* and *learning to learn* (Harlow 1949; Jarrard 1971) later were used to describe gradual improvement over similar problems. Today, terms such as *procedural memory* and *implicit learning* (Tulving 1985; Roediger and Craik 1989; Squire 1992) are applied to the same general phenomenon.

Thorndike's methods had the following advantages over anecdotal reports: objectivity and quantification of the measure (time across trials); reproducibility; flexibility in the experimenter's control over the complexity of the task; and efficiency, because observations could be made on many subjects. Furthermore, using Thorndike's

methods, researchers could observe a wide variety of species, with each species relying on its own unique sensory, motor, and motivational characteristics to solve the problems.

In addition to problem boxes, Thorndike used mazes and other experimental devices to study discrimination learning (i.e. the ability to consistently choose one of two or more stimuli presented together over trials). By the early 1900s, numerous investigators interested in measuring animal intelligence, were studying many species of animals in a variety of Thorndikian situations. No matter what the experimental situations, different species behaved similarly: they all gradually increased the speed and number of correct responses, and they all gradually decreased incorrect responding. Figure 1.1 shows a maze designed for measuring animal intelligence, along with learning curves from three different species obtained by three different investigators. The curves show decreases in errors with each run through the maze, expressed as a proportion of the number of errors that were made on the first run. One curve is for a rat (Small 1901); one curve is for a sparrow (Porter 1904); and one curve is for a monkey (Kinnaman 1902). All showed a gradual increase in correct responding, and a gradual decrease in errors.

As more species were tested in a variety of experimental situations, the resultant learning curves suggested that Darwin's ideas about phylogenetic continuity might apply to learning. There were no major differences in the ways different animal species solved the problems, only the rapidity with which task solution was acquired. In 1911, Thorndike published *Animal Intelligence: Experimental Studies*, in which he described the behavior of many different species, and he summarized his theoretical ideas. Thorndike concluded that the principles of learning are the same throughout the phylogenetic scale, and that because of differences in their sensory capacity, motor agility and motivation, animals differ only in the speed of learning, and in the type of learnable material. Thorndike wrote: 'If my analysis is true, the evolution of behavior is a rather simple matter. Formally, the crab, fish, turtle, dog, cat, monkey, and baby have very similar intellects and characters. All are systems of connections subject to change by the laws of exercise and effect' (1911, pp. 280–281). The Law of Exercise states that every response in the presence of a stimulus tends to increase the strength of the tendency for the stimulus to evoke the response; learning is gradual and incremental. The Law of Effect states that the strength of the stimulus–response bond is increased by pleasant consequences and decreased by unpleasant consequences; in other words, learning depends on reinforcement.

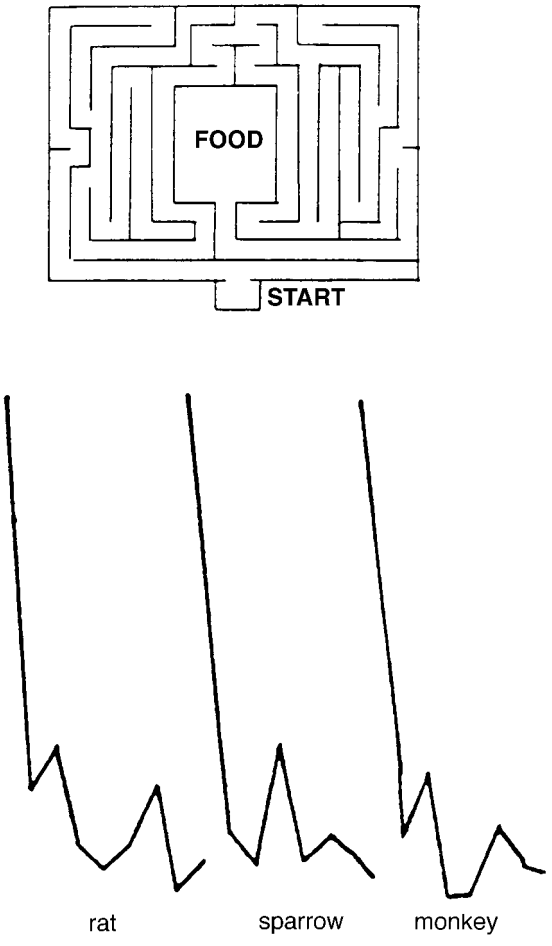

Figure 1.1. A maze designed by Small (1901) for measuring animal intelligence, along with learning curves from three different species trained in the maze. The curves show decreases in errors with each run through the maze, expressed as a proportion of the number of errors that were made on the first run. One curve is for a rat (Small 1901); one curve is for a sparrow (Porter 1904); and one curve is for a monkey (Kinnaman 1902). From Bitterman, M.E. In *Animal Learning*, ed. M.E. Bitterman et al., 1979, pp. 1–23, Plenum Press, with permission.

As years went by, Thorndike's Stimulus–Response (or S–R) Reinforcement principle became popular, with men like Clark Hull, Kenneth Spence and B.F. Skinner being

among its most vocal supporters (Hilgard and Bower 1975). Others viewed S–R Reinforcement theory with skepticism, and they provided alternative theories (Hilgard and Bower 1975; Oscar-Berman 1991). Although the theorists disagreed on which law of learning might be the universal one, there was overall agreement that the same principles would apply to all species. Consequently, the laboratory rat – an inexpensive and convenient research subject – was commonly used as a representative animal model.

Reversal learning and probability learning: control by systematic variation

From the 1950s to the 1970s, investigators tested the idea that the same laws of learning would apply to all species. One of these investigators was M.E. Bitterman, a comparative psychologist in Pennsylvania. As it was impossible to arrange a set of conditions that made the same sensory, motor and motivational demands for all species, Bitterman (1960) introduced another approach: *Control by systematic variation*. Thus, Bitterman and his colleagues developed a range of standardized testing situations to accommodate the specific sensory and motor capacities of different species of animals, and testing took place under a range of drive states (Bitterman et al. 1979). Standard situations used by Bitterman and his colleagues were *reversal learning* and *probability learning* paradigms. Reversal learning requires subjects first to learn to choose one of two stimuli consistently (e.g. to go *left* when given a choice of responding to two identical stimuli located on the left and the right sides, or to pick *black* when given a choice between a black and a white stimulus). After making the correct choice, the subjects next must learn to switch, or reverse, their choice to the previously unrewarded stimulus (go *right* instead of left, or pick *white* instead of black). The subjects are given a series of such reversals.

Probability learning situations present subjects with choices that differ in amount of payoff. For example, in a 70:30 probability learning condition, 70% of the time the right side (or a black stimulus) will be correct, and 30% of the time the left side (or a white stimulus) will be rewarded. The distribution of reward is reliable but random, such that the subject can not know when a reward will be given for a response to either choice. When one alternative is rewarded more than the other (e.g. 70:30), it is most efficient to maximize the choice of the higher of two payoffs, but many animals, including humans commonly match their responses to the reinforcement distributions in a systematic way.

In reversal tasks and probability learning paradigms, using spatial cues or visual cues, rats could be tested in a T-maze (running response), or in a Skinner box (pressing levers). Similarly, fish could be tested in a water maze, or by swimming against one of two switches. The motivation level or drive state of each species was varied systematically in terms of percentage body weight. Bitterman and his colleagues reasoned that if, under conditions of control by systematic variation, a specific behavioral pattern appeared in one species but not in another, interspecies differences in underlying neural mechanisms of learning would be a tenable explanation; artifacts based on sensory–motor abilities and hunger would be ruled out (Bitterman 1960, 1975; Bitterman et al. 1979).

Using this approach, different species were ordered hierarchically according to learning abilities (see Table 1.1). Bitterman concluded that rats, monkeys and people are subject to the same laws of learning on these tasks. Differences in learning ability by other species begin to appear as neocortical tissue decreases in size.

OTHER BEHAVIORAL PARADIGMS IN COMPARATIVE PSYCHOLOGY

By the 1970s, behaviorists were employing a wide variety of experimental paradigms to assess animal cognition, and monkeys were more commonly being studied than in earlier times. Among the many paradigms popular at the time were learning set tasks, delayed reaction tasks, and delayed conditional discrimination tasks.[1] Each of these classes of tasks will be described in turn.

Learning set paradigms

Harry Harlow (1949, 1951; Harlow et al. 1971) and his colleagues at the University of Wisconsin developed paradigms to compare learning and memory abilities across primate species (Jarrard 1971). Comparisons among primate groups is facilitated by species similarities in sensory systems, as well as the ability to respond with the hands and fingers. Common testing situations used by Harlow

[1] For further information about a variety of learning and memory paradigms used in comparative psychology and comparative neuropsychology, see Masterton et al. 1976; Medin 1977; Arnold 1984; Meador et al. 1987; Sahgal 1993.

Table 1.1. *Bitterman's comparative scheme*

	Spatial tasks		Visual tasks	
Animal	Successive reversals	Probability learning	Successive reversals	Probability learning
Human	Yes	M	Yes	M
Monkey	Yes	M	Yes	M
Rat	Yes	M	Yes	M
Pigeon	Yes	M	Yes	Random
Turtle	Yes	M	No	Random
Decorticated Rat	Yes	M	No	Random
Fish	No	Random	No	Random
Cockroach	No	Random	?	?
Earthworm	No	?	?	?

Notes:
'Yes' represents progressive improvement in performance over successive reversals and 'no' represents absence of progressive improvement. 'M' stands for matching of responses to reinforcement distributions in a systematic way, or maximizing the choice of the higher of two payoffs; 'random' refers to matching with no defined strategy. No data were obtained in cases where the '?' appears.
Source: Bitterman 1960, 1975.

and his colleagues were *learning sets*, i.e. series of simple problems where the stimuli or response requirements change from problem to problem, but the principle to be learned remains the same. For example, in visual object learning sets, two distinctly different stimulus items are presented on the left and right sides of a stimulus tray in a Wisconsin General Test Apparatus (Figure 1.2). The objects cover reinforcement wells, only one of which contains a reward, e.g. a piece of food or a coin. To obtain the reward, the subject must learn a *win-stay, lose-shift* strategy, i.e. to choose the object consistently being rewarded, and to avoid the other object. Incorrect strategies include choosing only one side, e.g. the left; alternating sides; alternating objects; choosing randomly; etc. With practice, different species of primates, including children, were observed to show precipitous improvement, as though they had learned to learn the problems (illustrated in Figure 1.3). Investigators ranked species in terms of numbers of problems required to achieve the win-stay, lose-shift strategy, such that only one information trial was needed to solve a problem. The rankings paralleled the phylogenetic scale, again supporting the idea that similar laws of learning apply to all animals.

Learning-to-learn is the formation of learning sets; the principles to be acquired are not limited to the simple win-stay, lose-shift strategy. In some experiments, the principle to be learned may be *win-shift, lose-stay* (i.e., reversal learning). Other principles are *matching to sample* (MTS) and *nonmatching to sample* (NMTS) (discussed in **Delayed conditional discrimination tasks**); here subjects must choose one of two stimuli that is the same (or different from) a sample stimulus in an array of three stimuli. Another principle requires subjects to alternate responding between two stimuli (as in *object alternation* or OA), while ignoring the irrelevant left-right spatial positions of the stimuli.

Delayed reaction tasks

Delayed reaction tasks (Figure 1.2), such as *delayed response* (DR) and *delayed alternation* (DA), are spatial tasks (usually relying upon visual input) that measure a subject's ability to bridge a time gap (Goldman-Rakic 1987; Fuster 1989; Oscar-Berman et al. 1991). This ability has been termed working memory, which is a transient form of memory (Goldman-Rakic 1987). Working memory is multimodal in nature, and it serves to keep newly-incoming information available on-line; it acts much like a mental clip-board for use in problem solving, planning, etc. In the classical DR task, the experimenter places a piece of food (or some other reward) into a reinforcement-well under one of two identical stimuli. The subject is able to see the experimenter put a reward there, but can not reach it. After the experimenter covers the food-wells with the stimuli, she/he lowers a screen, obscuring the stimulus tray. After a delay period, usually between 0 and 60 s, the experimenter raises the screen to allow the subject to make a choice. The subject then pushes one of the stimuli away and, with a correct choice, takes the reward; attentional and spatial memory skills are needed to do this.

DA shares important features with DR. Both are spatial tasks, and both have a delay between stimulus-presentation and the opportunity to make a response. In DA, however, subjects must learn to alternate responding from left to right. On each trial, the side not previously chosen is rewarded, and a brief delay (usually 5 s) is interposed between trials. Instead of having to notice and remember the location of a reward placed there by the experimenter

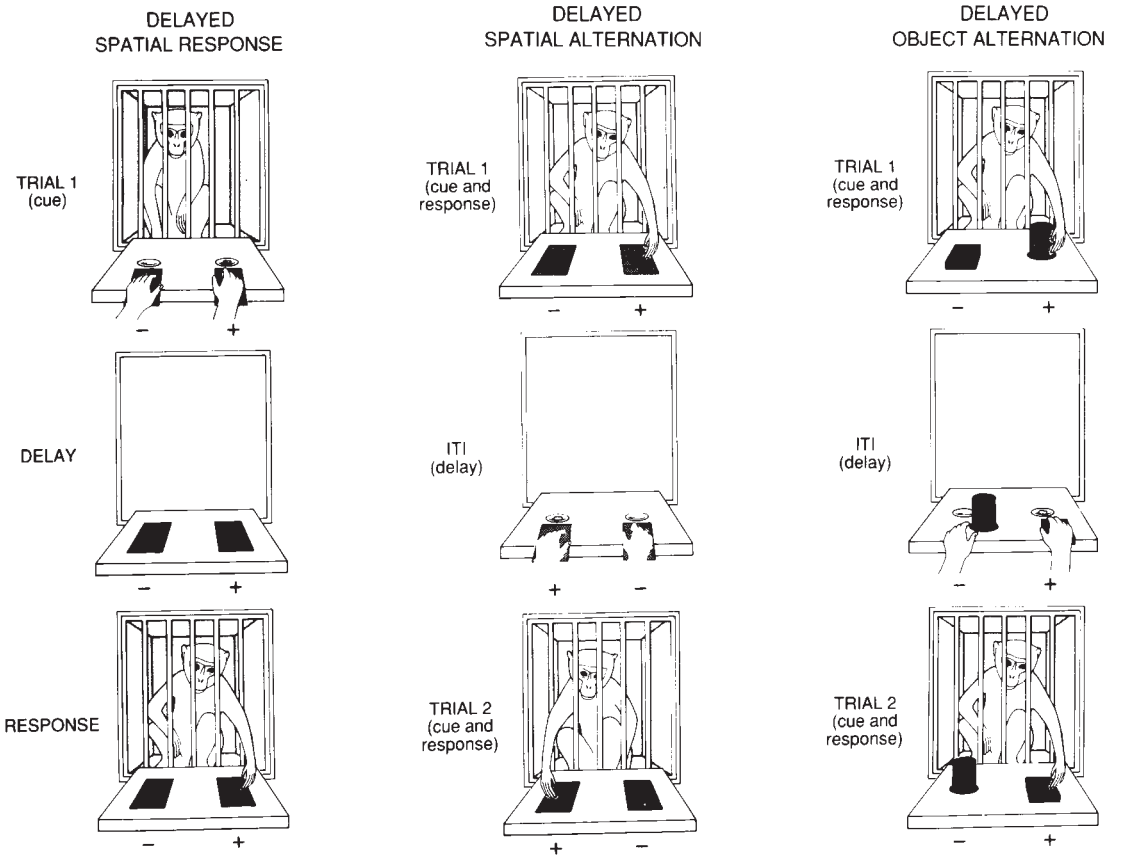

Figure 1.2. Three different tasks presented to Rhesus monkeys in a Wisconsin General Test Apparatus. The tasks illustrated can test working memory skills. The delayed reaction tasks, delayed response (DR) and delayed alternation (DA), rely heavily on spatial memory. The object alternation (OA) task is highly sensitive to perseverative responding. From H.R. Friedman and P.S. Goldman-Rakic, 1988, *Journal of Neuroscience*. 8: 4693–4706, Society for Neuroscience, with permission.

(in DR), subjects must remember the side last chosen, and whether or not a reward had been available. Subjects must also learn to inhibit, on each trial, the previously rewarded response (i.e. they must not perseverate with consecutive responses to one side only). Rankings of the performance levels of a wide range of mammals, including children, on delayed reaction tasks have been reported to parallel the phylogenetic scale (Jarrard 1971; Masterton et al. 1976).

Neuroanatomical systems in delayed reaction task performance.

Delayed reaction tasks have a unique characteristic: they are very sensitive to damage of prefrontal cortical-subcortical brain systems. For over half a century, researchers have observed that monkeys with bilateral lesions of the prefrontal cortex perform poorly on DR and DA, even with very short delays (Warren and Akert 1964; Arnold 1984; Goldman-Rakic 1987; Fuster 1989; Oscar-Berman et al. 1991). In monkeys, two large subdivisions of the prefrontal cortex have been recognized to be important in normal performance on delayed reaction tasks: the dorsolateral surface of the prefrontal cortex (especially area 46 in the principal sulcus), and the ventral prefrontal region including the orbitofrontal surface and inferior convexity. A schematic representation of the two systems is reproduced in Figure 1.4, where it can be seen that, from top to bottom, their connections run through different regions of virtually the same brain structures.

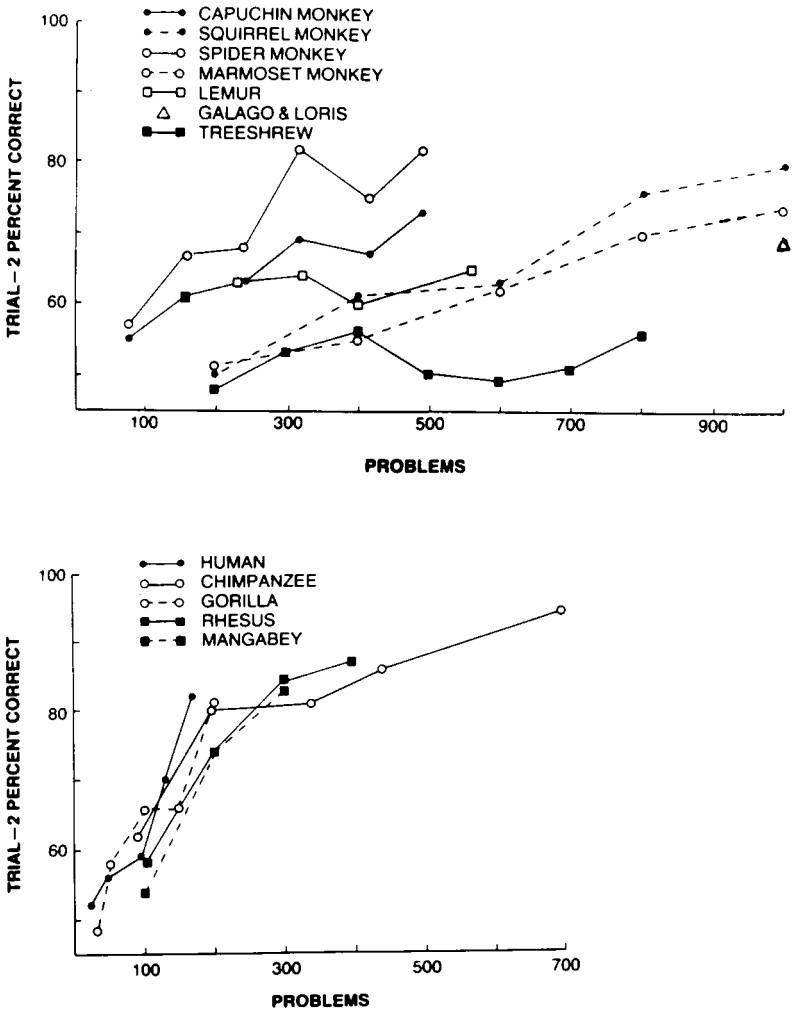

Figure 1.3. Performance by different species of primates, including children, on two-choice object learning-set problems. The curves illustrate precipitous improvement or learning-to-learn the win-stay, lose-shift strategy. From J.L. Fobes and J.E. King, 1982, In *Primate Behavior*, ed. J.L. Fobes and J.E. King pp. 289–326, Academic Press, with permission.

The dorsolateral and ventral subdivisions of prefrontal cortex have correspondingly different cytoarchitectonics, neurochemical sensitivities and connections with the rest of the brain (Warren and Akert 1964; Arnold 1984; Goldman-Rakic 1987; Fuster 1989; Oscar-Berman et al. 1991). The dorsolateral system maintains more intimate connections with other neocortical sites than the ventral system. The dorsolateral system's connections with limbic sites are less striking than the orbitofrontal system's. Visuospatial memory and attentional functions are thought to be compromised with dorsolateral lesions. Although the classical DR and DA paradigms overlap in sensitivity to deficits in spatial working memory, DR is more sensitive than DA to visuospatial attentional deficits (Oscar-Berman and Hutner 1993). By contrast, functions involved in response inhibition have been linked to orbitofrontal cortex. The ventral frontal system, of which the orbitofrontal cortex is a part, is intimately connected with basal forebrain and limbic structures, but its connections with other neocortical regions are not as extensive as the dorsolateral system's, and, like the dorsolateral system, the ventral system supports successful performance on DA and DR, but it is especially important for DA performance. DA is more sensitive than DR to abnormal perseverative responding (Oscar-Berman and Hutner 1993).

We noted in a previous section that OA, like DA, is an alternation task. OA uses a simple object reversal

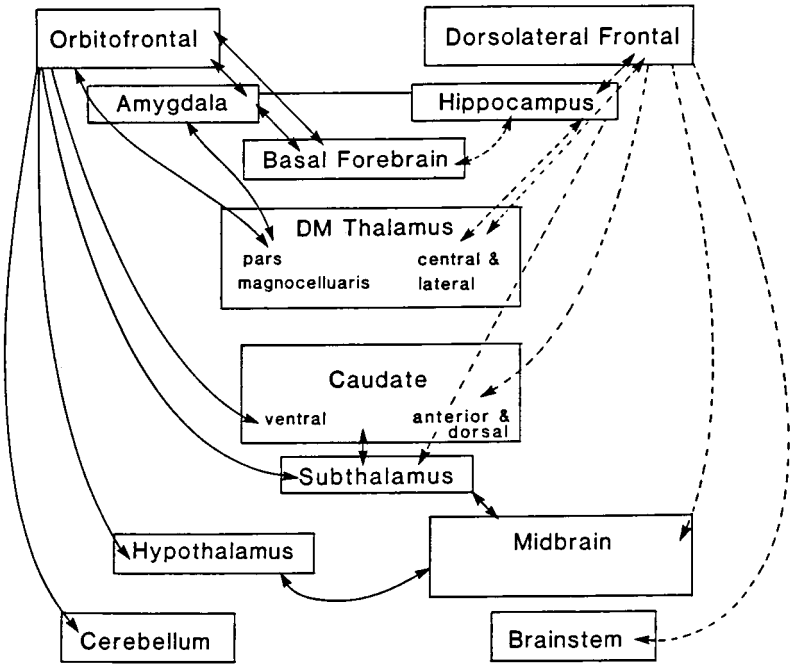

Figure 1.4. Schematic representation of two frontal lobe brain systems, illustrating the pathways that run through different regions of many of the same structures. From M. Oscar–Berman et al. 1991, In *Frontal Lobe Function and Injury*, ed. H.S. Levin, H.M. Eisenberg and A.L. Benton, pp. 120–138, Oxford University Press, with permission. Copyright (c) 1991 by H.S. Levin et al.

procedure which, like DA, requires memory for the previous response, response inhibition, and rule learning, but in OA, unlike DA, irrelevant spatial cues must be ignored. As it turns out, it has been shown that OA is even more sensitive than DA to perseveration, and OA is highly sensitive to prefrontal brain damage (Oscar-Berman and Hutner 1993; Freedman et al. 1998).

To test the sensitivity of DR, DA and OA tasks to bilateral prefrontal damage in humans, we administered these tasks to patient groups with bilateral frontal lobe lesions (Freedman and Oscar-Berman 1986a; Freedman et al. 1998). We found significant abnormalities in patients with focal prefrontal lesions documented with computed tomography (CT) scans. In addition, we and other investigators tested patients with a variety of disorders affecting frontal brain systems, and many of the patient groups were impaired on DR, DA and/or OA (Pribram et al. 1964; Chorover and Cole 1966; Park and Holzman 1992; Weinberger et al. 1992; Seidman et al. 1995; Gansler et al. 1996; Partiot et al. 1996; Postle et al. 1997). In these studies (which are reviewed later) the resultant profiles of the deficits across the patient populations differed. The different profiles were interpreted to reflect damage to distinct frontal systems (for reviews, see Olton et al. 1985; Overstreet and Russell 1991; Squire 1992; Oscar-Berman and Hutner 1993; Wasserman 1993; Albert and Moss 1996).

Delayed conditional discrimination tasks

Human amnesic patients have been tested on other tasks designed to measure memory in monkeys, and researchers have found that the tasks are sensitive to human memory dysfunction. These tasks include *concurrent discrimination learning* (CL), *delayed matching to sample* (DMTS), and *delayed nonmatching to sample* (DNMTS). In CL, subjects are rewarded for choosing an arbitrarily designated correct item from a set of two stimuli. Several pairs of different stimuli are presented to the subjects, and after the first presentation of the list and a delay interval, the list is presented again. Subjects are rewarded for choosing the previously correct stimulus from each pair. The list is repeated several times to allow subjects to learn to identify the correct stimuli. CL therefore relies on a win-stay, lose-shift strategy, requires memory for stimuli over time, and is reinforced through stimulus–reward associations. Like monkeys with limbic system lesions, amnesic patients perform poorly on this task (Kessler et al. 1986; Aggleton et al. 1988, 1992; Gaffan et al. 1990).

In DMTS, the subject views a stimulus, and then after a delay, must choose that same stimulus from a test pair

comprised of the familiar stimulus and a novel one. DNMTS differs from DMTS only in the response required: in DNMTS, subjects must choose the novel stimulus when presented with the test pair. In humans, several studies have shown that performance on DMTS and DNMTS deteriorates when the duration of stimulus exposure is shortened, or when stimulus complexity, or delay-to-test intervals are increased (Mishkin 1982; Oscar-Berman and Bonner 1985, 1989; Squire et al. 1988). These findings show that memory for specific target stimuli over a temporal delay is an important component of DMTS and DNMTS (Oscar-Berman and Bonner 1989).

DMTS, DNMTS and CL are different from delayed reaction tasks in a number of ways. They require memory for specific and multiple stimulus characteristics, often over long delays, and the tasks are sensitive to lesions in the limbic system. The type of memory they involve has been called declarative – or explicit – memory (Tulving 1985; Squire 1992). Declarative memory differs from working memory in that the former is archival in nature; declarative memory can be demonstrated by tasks that require free recall, stimulus recognition or familiarity judgments (Mishkin 1982; Squire et al. 1988; Olton et al. 1992; Squire 1992).

Neuroanatomical systems in delayed conditional discrimination task performance

Nonhuman animal research using DMTS, DNMTS and CL tasks has contributed to our understanding of the structures involved in new learning. It is widely accepted that a limbic brain system, comprised of regions within the temporal lobes, diencephalon and basal forebrain, is necessary for the formation of declarative memories (Mishkin and Appenzeller 1987; Squire 1992; Zola-Morgan and Squire 1993). Mishkin and others have proposed that a combined interruption of two memory-related pathways is necessary for amnesia. One pathway travels the fornix from the hippocampus to the mammillary bodies, then progresses along the mamillothalamic tract to the anterior nucleus of the thalamus, and possibly to the cingulate cortex, before returning to the hippocampus. The other pathway connects the amygdala and medial thalamic nuclei (e.g. the magnocellular portion of the dorsomedial thalamic nucleus), possibly linking with the orbitofrontal cortex, and from there, feeding back to the amygdala (Mayes et al. 1988). Recent evidence shows that the amygdala is not critical in the formation of declarative memories, but it plays a significant role in forming stimulus–reward and cross-modal associations (for reviews, see Dudai 1989; Zola-Morgan and Squire 1993).

Unlike tests of working memory (or of other prefrontal functions), tests of declarative memory are not reliably sensitive to damage of different subregions of the limbic system. Impaired performance on DMTS, DNMTS and CL, therefore, can indicate disruption anywhere in the two aforementioned limbic-memory pathways, or possibly in connected prefrontal sites as well. The limbic system, however, does seem to be necessary for the consolidation and retrieval of more enduring representations of uni-, poly- and supramodal information (Dudai 1989). Hence the distinction between (1) declarative or archival memories mediated by the limbic system, and (2) the short-term manipulation of memories in prefrontal working memory.

PATIENTS WITH NEURODEGENERATIVE DISEASES OR OTHER NEUROBEHAVIORAL CONDITIONS

The original work on behavioral and neuroanatomical systems involved in comparative neuropsychological tests was based upon nonhuman models. More recently, researchers studying human neurobehavioral disorders have used comparative neuropsychological tests to clarify the functional significance of human prefrontal cortex and limbic system structures. Tasks such as those described earlier have been used with patients because of the sensitivity to prefrontal and limbic system dysfunction in monkeys. Most often, DA, DR and OA have been used in human disorders where frontal system damage is known or suspected. Delayed conditional discrimination learning tasks such as DMTS, DNMTS and CL generally have been used in patient groups with limbic dysfunction and declarative memory impairments. Table 1.2 lists groups tested on behavioral paradigms from comparative neuropsychology.

In humans, evidence regarding functional brain specificity is not as clear as with monkeys. One reason for this relates to the diffuse involvement of several brain systems in many human neurological diseases, in sharp contrast to the precise lesions induced in animal research. Although many of the disorders listed in Table 1.2 involve overlapping pathology of the dorsolateral and the ventral

Table 1.2. *Performance by patient groups*

Tasks							
Prefrontal			Limbic			Neurobehavioral	
DR	DA	OA	DMTS	DNMTS	CL	Disorders	References
++	++	++	++	?	?	Alzheimer's disease	Freedman and Oscar-Berman 1986b; Freedman 1990; Sahgal et al. 1992.
−−	++	?	?	?	++	Huntington's disease	Oscar-Berman and Zola-Morgan 1980; Oscar-Berman et al. 1982.
++	±	++	?	?	?	Parkinson's disease with dementia	Freedman and Oscar-Berman 1986b; Freedman 1990; Partiot et al. 1996.
−−	−−	++	?	?	?	Parkinson's disease without dementia	Freedman and Oscar-Berman 1986b; Canavan et al. 1990; Freedman 1990.
++	++	?	?	?	?	Progressive supranuclear palsy	Partiot et al. 1996.
−−	++	?	?	?	?	Olivopontocerebellar atrophy	El-Awar et al. 1991.
?	?	?	++	?	?	Senile dementia of the Lewy body type	Sahgal et al. 1992.
++	++	++	?	?	?	Bilateral frontal lobe lesions	Pribram et al. 1964; Freedman and Oscar-Berman 1986a; Freedman et al. 1998.
−−	++	++	?	?	?	Closed head injury	Gansler et al. 1996.
−−	±	?	?	?	?	Anterior communicating artery disease	Freedman and Oscar-Berman 1986a.
±	±	?	?	?	±	Nonfrontal lesions, and unilateral frontal lesions	Chorover and Cole 1966; Oscar-Berman et al. 1982; Canavan et al. 1990; Verin et al. 1993.
?	?	?	++	?	++	Encephalitis	Aggleton et al. 1992.
±	++	?	++	++	++	Alcoholic Korsakoff's syndrome	Oscar-Berman and Zola-Morgan 1980; Oscar-Berman et al. 1982, 1992; Oscar-Berman and Bonner 1985, 1989; Freedman and Oscar-Berman 1986a; Kessler et al. 1986; Aggleton et al. 1988; Squire et al. 1988; Gaffan et al. 1990
−−	−−	−−	±	±	±	Alcoholism (without Korsakoff's syndrome)	Oscar-Berman et al. 1982, 1992; Oscar-Berman and Bonner 1985, 1989; Freedman and Oscar-Berman, 1986a; Aggleton et al. 1988, 1992; Bowden et al. 1992; Bardenhagen and Bowden 1995.
±	++	++	?	?	?	Schizophrenia	Park and Holzman 1992; Weinberger et al. 1992; Seidman et al. 1995.
−−	++	−−	?	?	?	Depression	Freedman 1994.
++	−−	++	++	++	?	Post-traumatic stress disorder	Koenen et al. 1997.

Notes:

Delayed Response (DR), Delayed Alternation (DA), Object Alternation (OA), Delayed Matching-to-Sample (DMTS), Delayed Nonmatching-to-Sample (DNMTS), and Concurrent Learning (CL) tasks.

++ = Impairment; −− = No impairment; ± = Impairment in some patients; ? = Not tested.

prefrontal systems, for example, findings from individual studies suggest that some groups are more heavily influenced by dorsolateral than by ventral prefrontal dysfunction (e.g. patients with Parkinson's disease and dementia: Freedman and Oscar-Berman 1986b, 1987; Freedman 1990), while other groups appear to be more heavily influenced by ventral than by dorsolateral dysfunction (e.g. patients with olivopontocerebellar atrophy or late-stage Huntington's disease: El-Awar et al. 1991; Oscar-Berman et al. 1982). Other patients performed poorly on all of the prefrontal tasks (i.e. Alzheimer's disease patients: Freedman and Oscar-Berman 1986b; Freedman 1990); in these patients, there is damage to both systems. It is important to note that the dichotomy is not strict; it is used to emphasize quantitatively different degrees of dysfunction and damage.

Fewer patient groups have been studied using declarative memory tests than working memory tests, but the results shown in Table 1.2 are consistent with predictions based on the neuropathology of these conditions. Amnesic patients with alcoholic Korsakoff's syndrome (involving diencephalic, limbic, basal forebrain and cortical damage: Harper and Kril 1990; Hunt and Nixon 1993) or herpes simplex encephalitis (thought to involve temporal lobe damage: Aggleton et al. 1992) perform poorly on both DMTS and CL. An interesting finding is that of impaired DMTS and CL performance in some groups of non-Korsakoff alcoholics (Aggleton et al. 1988; Bowden et al. 1992). This shows that DMTS and CL are more sensitive to subtle changes in memory functioning than conventional neuropsychological measures, and may signal the presence of undiagnosed neuropathology involving limbic system sites in nonamnesic alcoholics (Bowden 1990; Bowden et al. 1992). We expect that impairments on DMTS, DNMTS and CL tasks would also be apparent in other neurodegenerative conditions where gross or subtle memory impairments are noted.

DMTS deficits also have been recorded in patients with dementia of the Alzheimer type (Sahgal et al. 1992), and senile dementia of the Lewy body type (characterized by senile plaque formation and variable limbic, neocortical and subcortical Lewy body formation; Sahgal et al. 1992). Several of the neurobehavioral disorders represented in Table 1.2 involve overlapping pathology of prefrontal and limbic systems. Findings of deficits on tasks sensitive to both prefrontal and limbic dysfunction can be interpreted as reflecting underlying involvement of both systems in the disorder in question, but possible interactions between prefrontal and limbic regions in memory functioning should also be considered.

Research is needed to determine whether there is a dissociation between impairments on tasks sensitive to prefrontal and limbic damage, respectively, in patients with discrete prefrontal or limbic lesions. Indeed, although the sensitivity of comparative neuropsychological tests to brain lesions is well established, few well-controlled studies have set out to determine the neuroanatomical specificity of these tasks in humans. Important control factors are homogeneity of the lesion site within patient groups (Freedman and Oscar-Berman 1986a); the delay between occurrence of the lesion and testing (Verin et al. 1993); and methodological consistency (Bardenhagen and Bowden 1998). It is possible that a number of comparative neuropsychological tasks will prove to be sensitive, but not specific, to prefrontal or limbic lesions in human subjects. Until the specificity of these tests in humans is demonstrated definitively, it is important to interpret research findings cautiously, in terms of patterns of impairment and damage within functional systems.

COMPARATIVE NEUROPSYCHOLOGY AND MODELS OF MEMORY

Comparative neuropsychological research has provided a framework that is helpful for understanding memory dysfunction in neurodegenerative disorders. In some neurodegenerative diseases (e.g. Parkinson's disease and progressive supranuclear palsy), patients may have working-memory and attentional impairments resulting from prefrontal system damage (Freedman and Oscar-Berman 1986b; Partiot et al. 1996; Postle et al. 1997). In other disorders (e.g. herpes encephalopathy), there may be new learning impairments suggestive of disruptions in declarative memory and limbic system damage (Aggleton et al. 1992). Models of working memory and of declarative memory recognize the complexity of neuroanatomical and neurochemical systems underlying behavior, and they can be used to explain the heterogeneity of neurobehavioral symptoms observed within and between neurodegenerative diseases (Wickelgren 1997).

Goldman-Rakic's (1987) model of prefrontal working memory postulates that prefrontal cortex receives sensory and mnemonic representations of reality as well as

symbolic representations (e.g. concepts, plans) which have been elaborated in other cerebral areas. This sensory and mnemonic information is maintained by the prefrontal cortex in representational memory until a decision or operation is required, when it is used to modulate behavior. Responses are initiated as a motor command. Prefrontal working memory is thus thought to regulate behavior through the manipulation of representational knowledge. This model explains why so-called frontal lobe symptoms can be seen in patients with lesions in non-frontal parts of the brain. The sensory and mnemonic information that comprises representational memory is gained from other cortical areas; therefore, disruptions in transmission of information from those areas may lead to a breakdown in the frontal lobe's use of representational memory in modulating complex behaviors.

Goldman-Rakic (1990) has noted that the prefrontal cortex is part of a larger network of cortical areas, and that the heterogeneity of frontal lobe symptoms might be due to disruptions in different parts of the network. In addition, others have argued against viewing the functions of different areas of the prefrontal cortex separately, stating that they should be considered as parts of the integrative functions of the circuits in which they are involved (Groenewegen et al. 1990). These views are echoed by Berman and Weinberger (1990, p. 522), who have stated that 'disruption anywhere along the complex circuitry connecting prefrontal cortex with other brain areas can cause a clinically significant syndrome of abnormal behavior suggestive of prefrontal lobe dysfunction'. Given the extensive anatomical connections of prefrontal and limbic circuits, it has also been suggested that prefrontal lesions may cause impairments on tasks thought to represent limbic system dysfunction (Dudai 1989).

Declarative memory impairments resulting from limbic system damage have been demonstrated in neurobehavioral disorders characterized by amnesia. Although much is known about the neuroanatomy of declarative (or explicit) memory, less is known about the structures subserving procedural (or implicit) memory (Tulving 1985; Saint-Cyr and Taylor 1992; Squire 1992). Procedural memory (described earlier in the discussion of Learning Sets) applies to learning of rules, habits, and skills. Procedural memory is more robust than declarative memory in classical amnesic disorders (Oscar-Berman and Zola-Morgan 1980; Squire 1992); however, it may be impaired in conditions involving the basal ganglia, such as Parkinson's and Huntington's diseases (for a review, see Saint-Cyr and Taylor 1992). For example, Verin et al. (1993) suggested that the striatum, which is considered to be the substrate of pre-elaborated motor programs, could also be viewed as the anatomic substrate of pre-elaborated routine behavioral programs. Two types of behavioral organizations involving the prefronto–striato–pallido–thalamo–prefrontal loop were proposed. The first requires elaboration of new behavioral schemata by a learning process, permitting adaptation of the subject to new environmental situations. The second is independent of the environment, concerns routine and stereotyped behaviors and is generated by subcortical structures that are normally repressed by prefrontal cortex. Lesions in prefrontal cortex may, therefore, release control of these stereotyped behaviors. This is consistent with the suggestion that basal ganglia (striatal)–frontal lobe circuitry contributes to procedural memory functions (Saint-Cyr and Taylor 1992). The striatum is thought to be a procedural memory buffer, necessary to mobilize new procedures and to select among known procedures; it is designed to function intuitively and nonconsciously. Prefrontal working memory oversees the use of this mechanism, and intervenes when opportunities for solutions are apparent. Breakdowns in the cooperative interaction between striatal procedural memory functions and prefrontal explicit working memory processes may be responsible for intrusive errors of motor sequences seen in Huntington's disease, and also the bradyphrenia and bradykinesia of Parkinson's disease (Saint-Cyr and Taylor 1992).

Comparison of working memory tasks and declarative memory tasks

Differences between declarative and working memory tasks are illustrated by research conducted with human subjects in Australia (alcoholics and nonalcoholic controls; Bardenhagen and Bowden 1995; Bardenhagen and Bowden 1998). In this research, we manipulated knowledge of the response rules in DMTS and OA. The response rule in DMTS is a simple matter of choosing the familiar stimulus. Provision of this rule, prior to and during testing on DMTS, had a small effect on performance of the subjects, but the major determinant of performance was the length of the list to be remembered. All subjects performed very well on lists of one item, but there was a significant decrease in correct responding as list length increased to two and four items, and all subjects

performed near chance on lists of eight items. The results indicated that memory for stimuli over time, not rule knowledge, was crucial to task performance (Bardenhagen and Bowden 1995).

In contrast to DMTS where provision of the response rule had only a minor effect on performance, instruction in the response rule had a major effect on OA performance. There are two response rules in OA: the alternation rule (the reward alternates between objects on successive trials) and the correction rule (a trial is not over until the correct object is chosen). Performance is measured in terms of perseverative and nonperseverative errors. By definition, the first error on any trial is nonperseverative; subsequent errors on that trial are perseverative. Results with OA tasks are summarized in Figure 1.5. Subjects who were provided with the alternation rule performed almost without errors, which suggests that knowledge of the alternation rule is a major requirement for task success. Subjects who were provided with the correction rule made no perseverative errors, but made the same number of nonperseverative errors as subjects who were given neither rule. These results indicate that the ability to induce rules was a necessary precondition to success on OA and suggest that a proportion of perseverative errors may be due to a lack of knowledge of the response rules (Bardenhagen and Bowden 1998).

The results of these two studies emphasize the differences in mnemonic requirements of declarative and working memory tests: declarative tests rely heavily on memory for stimuli over temporal intervals in order to recognize or recall the target stimuli, and working memory tasks rely upon manipulation of representational memories to solve problems, or induce rules. Our data also highlight the need for intact working memory skills in DMTS performance, as provision of the response rule was helpful to some subjects. Thus, it is likely that people (and monkeys) induce the response rule in DMTS, DNMTS and CL tasks. The response rule in declarative memory tasks requires a simple stimulus–reward association, hence the lesser effect of knowledge of the DMTS response rule on task performance. At this point it should be noted that most tasks draw on procedural memory processes for access to previously acquired behavioral programs and knowledge of the response rule. For example, in DMTS subjects learn to choose the familiar stimulus and in OA they learn to alternate correctly.

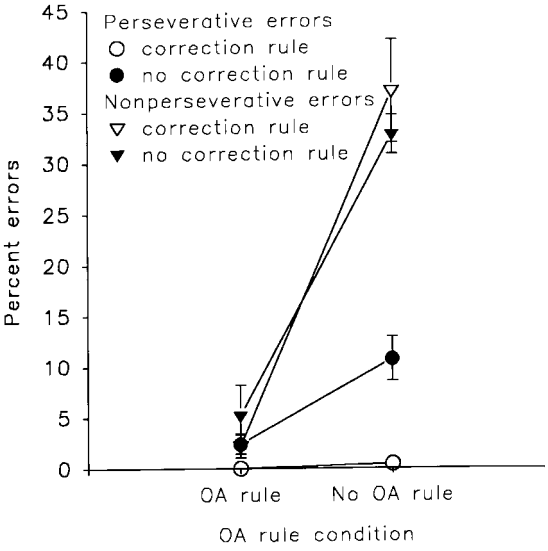

Figure 1.5. Performance on an object alternation (OA) task by four groups (five subjects per group of combined alcohol-dependent and non alcoholic controls). Points represent mean perseverative or nonperseverative errors (mean errors expressed as a percentage of trials completed), and bars depict standard errors of the means. Adapted from Bardenhagen and Bowden 1998.

CONCLUSIONS AND IMPLICATIONS

Comparative neuropsychological tests are much the same today as in earlier versions of the tasks used to investigate learning in the context of Darwin's ideas about phylogenetic continuity. Research with nonhuman animals demonstrated that the same laws of learning apply to rats, monkeys and humans, but the methods of comparative neuropsychology have been applied to human neurobehavioral disorders only recently. Some modifications have been made to the tests to facilitate the transfer to testing human subjects, generally involving changing the reward from food to money. The standard administration of the tasks in humans still involves minimal instructions, thus necessitating a degree of procedural learning in humans, as in nonhuman animals.

Findings from research with human neurobehavioral disorders has supported the models of memory hypothesized from experiments with nonhuman animals. These different forms of memory are tied to different functional systems of the brain. Disruptions to structures or tracts involved in the limbic system, a complex circuit of

diencephalic, medial temporal and basal forebrain structures, is known to result in impaired new learning, recall and recognition of information. This form of memory is often called declarative memory. Declarative memory is contrasted with procedural memory, which involves acquisition of habits, skills and other information not available for conscious recall or recognition (and thought to involve circuitry of prefrontal cortex and basal ganglia). Damage to prefrontal brain systems results in impairments on tasks requiring the integration of memories, plans and ideas over short temporal intervals; this form of memory has accordingly been named prefrontal working memory. Disruptions to the neuroanatomical or neurochemical systems in the limbic and frontal networks may result in impairments in declarative, procedural or working memory abilities.

When neurodegenerative conditions have a localized onset, memory impairments related to the area affected will be apparent; therefore, in groups with putative medial-temporal or diencephalic pathology (e.g. herpes encephalitis), declarative memory impairments might be evident. These would manifest as forgetfulness, anterograde or retrograde amnesia, or poor performance on DMTS or CL. In cases with suspected frontal lobe involvement (e.g. closed head injury), impairments in working memory may be seen as deficits in planning or integration of information, and abnormal perseverative responding, for example. Deficits in delayed reaction tasks also are expected. Diseases involving the basal ganglia (e.g. Huntington's disease, Parkinson's disease, progressive supranuclear palsy) might result in problems with routine or stereotyped behaviors, i.e. impairments in a form of procedural memory. As neurodegenerative diseases are often diffuse in their effects, either early or late in the clinical course, impairments in any of these three memory systems may be apparent. This would apply to the later stages of the diseases mentioned above, but also to earlier stages of conditions like vascular dementias, demyelinating conditions, Creutzfeldt–Jakob disease, mitochondrial disorders and other metabolic conditions, and schizophrenia. Ideally, research with memory disordered populations would employ tasks sensitive to prefrontal and limbic system damage to help identify impairments of the different types of memory in these disorders. This information could, in turn, be used to help devise rehabilitation and treatment strategies for people with memory disorders.

In summary, behavioral paradigms from comparative neuropsychology have provided sensitive tools for assessing declarative and working memory impairments, but further research needs to be conducted to determine the specificity of these tools. Experimental manipulations are a promising way of further understanding the cognitive and theoretical aspects of the tests, and to help further understanding of normal memory processes. Despite the unknown specificity of the tests in humans, the sensitivity of comparative neuropsychological tests ensures their utility in examining performance in a wide range of neurobehavioral disorders. As we begin to learn about performance profiles of patients with different neurobehavioral disorders on these tasks, about behavioral patterns on different forms of the tests, and about the neuroanatomical systems involved in memory, an integrative approach to understanding human brain functioning emerges. An integrative approach recognizes the interconnectivity of the different functional systems, and it accounts for the heterogeneity of neuropsychological symptoms between and within different neurobehavioral disorders.

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2 Nonprimate animal models of motor and cognitive dysfunction associated with Huntington's disease

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INTRODUCTION

The purpose of this chapter is to present the neuropathological, neurochemical and neuroanatomical substrates of Huntington's disease (HD) followed by a discussion of the extant animal models aimed at mimicking the neuropathological, neurochemical and neuroanatomical characteristics of this disease. Then, the neurological, behavioral and cognitive dysfunctions of HD are reviewed, and this review is followed by a discussion of possible parallel functions associated with models of caudate dysfunction aimed at mimicking the neurological, behavioral and cognitive characteristics of HD. Unfortunately, there is a paucity of studies that have examined cognitive dysfunction in the best models of HD. Thus, in order to determine whether the caudate in animals, especially the rat, mediates motor and cognitive functions that parallel similar caudate mediated functions in humans, the patterns of motor and cognitive deficits in animals with caudate dysfunction induced by multiple means will be described. To the extent that there are caudate mediated parallels in motor and cognitive functions between animals and humans, there would be a greater impetus to study in more detail the cognitive dysfunctions of animal models of HD.

NEUROPATHOLOGICAL FEATURES OF HUNTINGTON'S DISEASE

At a macroscopic level, the primary area of pathology in HD is the head of the caudate nucleus and, to a lesser extent, the putamen (see also Chapter 3). In a large scale postmortem study, Vonsattel et al. (1985) found that the dorsomedial aspects of the caudate appear to be the locus of greatest cell loss in this structure with the ventrolateral aspects of this nucleus becoming more affected as the disease progresses. Other brain regions also appear to be affected in HD but, again, the brunt of the pathology occurs in the striatum. De La Monte et al. (1988) examined standardized coronal slices of 30 HD patients and found a volumetric reduction of over one-half in the caudate nucleus and putamen, whereas the cerebral cortex, white matter and thalamus only experienced a reduction of approximately one-fourth their normal volumes. In vivo examination of HD patients' brains using computed tomography (CT) and magnetic resonance imaging (MRI) often reveals normal volumetric indices in the early course of the disease and the hallmark caudate atrophy in the later courses of the disease (Cala et al. 1990). Positron emission tomography (PET) studies, however, have identified striatal hypometabolism in HD even in the absence of structural changes (Kuhl et al. 1982; Chapter 6), which suggests that abnormal metabolic activity may be a precursor to the later morphological changes. From a gross anatomical perspective, the brains of HD patients can often exhibit cortical atrophy (i.e. sulcal widening and gyral atrophy), particularly in the frontal regions (Forno and Jose 1973; Cummings and Benson 1992).

Several other neuropathological hallmarks of HD can be observed at the microscopic level. Although there appear to be at least six types of cells within the striatum, HD tends to have a predilection for the smaller neurons. In particular, the medium-sized spiny neurons tend to be most affected in this disease, whereas aspiny and larger neurons are not as affected (Graveland et al. 1985; Ferrante et al. 1987; Kowall et al. 1987). Once the medium-sized spiny neurons have deteriorated in the striatum, they

appear to be replaced by astrocytes (Vonsattel et al. 1985). The medium-sized spiny neurons contain gamma-aminobutyric acid (GABA) and the death of these cells leads to a substantial depletion (approximately 80%) of this neurotransmitter in the basal ganglia of patients with HD (Bird et al. 1973; McGeer et al. 1973; Stahl and Swanson 1974; Perry and Hansen 1990), although other neurochemicals also appear to be decreased in this disease, including choline acetyl transferase, enkephalin, dynorphin and substance P (Stahl and Swanson 1974; Wu et al. 1979; Beal et al. 1988a,b). Increases in some neurochemicals, such as somatostatin and neuropeptide Y, have also been reported (Beal et al. 1988b).

Given the fact that HD results in characteristic changes at both the macro- and microscopic level, Vonsattel et al. (1985) have developed a pathological severity scale for HD which takes into account changes at both the morphological and neuronal levels. An examination of this scale is instructive because it provides a description of the neuropathological progression of the disease. The scale uses a rating system with five grades (0–4). Grade 0 reflects no macro- or microscopic abnormalities despite the clear presence of HD symptomatology in vivo. Grade 1 brains demonstrate normal striatums at the macroscopic level, whereas at a microscopic level, astrocytosis is readily apparent in the medial aspects of the caudate. Grade 2 reflects macroscopic atrophy of the head of the caudate with microscopic neuronal loss and astrocytosis in the head, body and tail of the caudate. Grade 3 is indicative of severe striatal atrophy at the macroscopic level with early involvement of the nucleus accumbens and globus pallidus, and the microscopic changes include astrocytosis in all aspects of the caudate, mild astrocytosis in the dorsal putamen and relative sparing of the nucleus accumbens. The final grade, Grade 4, reflects almost complete obliteration of the caudate at both macroscopic and microscopic levels, and with the nucleus accumbens demonstrating moderate astrocytosis.

There are several important issues related to the neuropathology of HD which should be taken into consideration when attempting to develop an animal model of this disease. First, the neuropathology associated with HD varies as a function of the stage of the disease. For example, it appears that the head of the caudate nucleus is the brain region most affected in this disease, despite the fact that other parts of the caudate may be affected earlier in the course of the disorder. Thus, researchers attempting to develop an animal model of HD must take into consideration which stage of the disease they are attempting to mimic. The use of the rating system developed by Vonsattel et al. (1985) could help in gauging the degree of pathology which is attempted to be mimicked by any given animal model. Second, there are both macro- and microscopic pathological features that are hallmarks of this disease, and therefore the level at which the model is being developed must be taken into consideration. It is not enough to simply reproduce the neuropathology at a macroscopic level (e.g. introducing lesions into the head of the caudate); a good model of this disease must also mimic the disorder at a micro-anatomical level. Third, not all patients with HD demonstrate the same behavioral manifestations of the disease, which suggests that there may be patient-to-patient variation in the neuropathological features of this disease. This latter point argues for the notion that a single model of HD may not be viable and several models may need to be developed, each specific to the particular subtypes of this disease.

DEVELOPMENT OF ANIMAL MODELS OF HUNTINGTON'S DISEASE

In order to generate an animal model of HD, it is very important to mimic the pattern of cell loss and subsequent changes in neurotransmitter function observed in the caudate-putamen. The earliest and still most important animal models of HD are based on the assumption that overproduction of glutamate in cortical connections to the caudate results in excitotoxic damage to caudate neurons. The first rat model was based on intracranial injections of kainic acid into the caudate of rats resulting in the destruction of intrinsic striatal neurons and spared axons of afferent origin (Coyle and Schwarcz 1976; McGeer and McGeer 1976). There are, however, a few serious problems with the kainic acid model, in that kainate, probably due to its convulsive properties, produces severe extrastriatal damage which includes the limbic system. Furthermore, damage includes the small, aspiny interneurons containing somatostatin and neuropeptide Y as well the enzyme dihydronicotinamide adenine dinucleotide phosphate diaphorase (NADPH). These neurons do not degenerate in HD (Beal 1994). Finally, the slow progressive disorder of HD cannot be triggered by a single injection of kainic acid.

The second, and currently the best animal (rat) model of HD, results from an intracranial injection of quinolinic acid (QUIN; 2,3-pyridine decarboxylic acid), an NMDA antagonist, into the caudate of rats resulting in intrastriatal neuronal loss and sparing of afferent axons (Schwarcz et al. 1983). In this model QUIN first produces swelling of dendrites and, later, degeneration of postsynaptic processes followed by gliosis. The area of neuronal degeneration is spherical and remains confined to the area of injection. Thus, in contrast to kainic acid injections, the lesions induced by QUIN do not extend beyond the caudate nucleus. QUIN produces neurochemical changes that are similar to those observed in the caudate of HD patients. For example, there is depletion of neurochemical markers of spiny neurons including GABA and substance P, an increase in neurochemical markers of aspiny neurons including somatostatin and neuropeptide Y, but no change in the enzyme NADPH (Beal et al. 1986). It should be noted that Davies and Roberts (1987) did not find selective sparing of somatostatin and NADPH containing striatal neurons following QUIN injections. There are increases in serotonin levels and neurotensin immunoreactivity, decreases in choline acetyltransferase activity levels, but no changes in dopamine levels (Beal 1994). QUIN induced lesions result in marked depletion of NMDA receptors similar to that observed in HD patients (Greenamyre and Young 1989). It is important to note that QUIN, which is an endogenous tryptophan metabolite, is present in rats and human brains (Wolfensberger et al. 1983) and 3HAO, the enzyme responsible for the biosynthesis of QUIN, is enhanced in the caudate–putamen complex of the brain of HD patients (Schwarcz et al. 1987). Finally, the observation that a single injection of QUIN into the caudate leads to a slow progressive reduction in the size of the caudate nucleus proceeding outward from the lesion zone (Beal et al. 1986), coupled with the observation that QUIN is not very toxic in the developing rat striatum (Foster et al. 1983), suggests that QUIN induced lesions might mimic the pathology of late onset HD. Other animal models emphasize an impairment in energy metabolism within the caudate–putamen complex which is characteristic of HD patients (Beal 1994). More work is needed to determine whether the anatomical and biochemical changes in this model match the pattern observed in HD patients.

COGNITIVE AND BEHAVIORAL CHANGES IN HUNTINGTON'S DISEASE AND ITS ANIMAL MODELS

Over the past 20 years our understanding of the nature and pattern of neuropsychological deficits in HD has become increasingly clear. From a global standpoint, the overall pattern of cognitive deficits observed in this disease appears to be very different from that observed in patients with primarily cortical dementias, such as Alzheimer's disease (AD) (Chapters 8, 10, 11, 12 and 18). In general, patients with AD display a marked anomia, a rapid rate of forgetting and constructional apraxia. In contrast, patients with HD do not demonstrate an anomia, and their memory impairment is characterized by deficient retrieval processes. Patients with HD dementia exhibit deficits in problem solving, abstract reasoning, information processing speed and certain components of attention (McHugh and Folstein 1975; Mendez 1994; Morris 1995).

Although HD typically results in global cognitive deterioration (i.e. dementia), only some cognitive functions are affected early in the course of the disease. An understanding of which specific areas of cognition are affected in patients with HD is important, because the goal of any animal model of this disease should be to recreate very similar behavioral abnormalities. The following sections provide brief reviews of the specific cognitive deficits observed in patients with HD, and of behavioral deficits in rats with damage to the caudate.

Motor functioning

Choreiform movements, which are involuntary jerking movements, are the unmistakable hallmark of HD. Initially evident in the hands and face, they progress to eventually involve the rest of the body. Huntington's disease also affects voluntary movements. For example, HD patients often demonstrate akinesia (an impairment in initiating voluntary movement) and bradykinesia (slowness in voluntary movement once initiated). Several studies have examined the specific nature of the voluntary movement abnormalities observed in HD. For example, Bradshaw et al. (1992) found that HD patients were impaired in the initiation of sequential movements, and that this deficit was even more pronounced in the absence of preparatory cues. These investigators also found that the time HD patients take to carry out a motor sequence (i.e. movement time) was not aided by the use of preparatory cues, whereas

normal controls were able to utilize this information to reduce their movement time. Interestingly, HD patients' deficits in movement initiation and speed were associated with the degree of their functional incapacity, a finding which suggests that impairments in voluntary movements may be a good predictor of everyday functioning (Girotti et al. 1988).

A similar pattern of voluntary movement abnormalities has been observed in rats with caudate lesions. For example, ibotenic or QUIN lesions of the lateral caudate result in significant impairments in movement initiation and reaching movements of the tongue and forelimbs, in the use and accuracy of forelimb movement, in swimming speed, in changes in the frequency and duration of a variety of motor movements, and in reversal of limb preference (Whishaw et al. 1986; Pisa 1988; Sanberg et al. 1989; Pisa and Cyr 1990; Block et al. 1993). These changes in movement initiation, programming, frequency, duration and amplitude parallel the motor problems observed in HD patients.

There is also evidence of important regional specificity in the behavioral changes produced by caudate lesions. Ibotenic or QUIN lesions of the medial caudate, in contrast to the lateral caudate, do not produce any, or only mild, changes in motor activity (Pisa 1988; Pisa and Cyr 1990; Furtado and Mazurek 1996).

Declarative learning and memory in Huntington's disease

The ability to consciously recollect information is among the most widely studied phenomena in HD. Several studies have demonstrated that HD patients are impaired on standardized measures of memory, and that their profile of memory deficits differs from that in other memory impaired patients. For example, in contrast to patients with damage primarily to the medial temporal lobes (e.g. AD patients) or dorsomedial nucleus of the thalamus (e.g. Korsakoff's patients), patients with HD tend to commit a higher number of perseverative errors, recall more words from the recency portion of a word list, demonstrate relatively better recognition than free recall and have a relatively normal rate of forgetting (Butters et al. 1988; Massman et al. 1990; Delis et al. 1991; Tröster et al. 1993). HD patients have also been shown to be impaired on tasks that require learning of associations among stimuli (Sprengelmeyer et al. 1995a). Together, these results suggest that HD is associated with mildly deficient encoding, intact storage but markedly deficient initiation of systematic retrieval strategies (Butters et al. 1985, 1986).

In addition to their deficits in learning new information (i.e. anterograde amnesia), HD patients have difficulty with tasks that require recall of information learned in the past (i.e. retrograde amnesia). For example, HD patients are deficient in recalling famous faces and historical information (Albert et al. 1981; Beatty et al. 1988); however, the pattern of their retrograde memory impairment is qualitatively different than that observed in patients with AD or Korsakoff's disease. Patients with HD are equally impaired in recalling information from all past decades, whereas AD and Korsakoff's patients are differentially impaired in recalling more recent memories (Albert et al. 1981; Beatty et al. 1988).

Nondeclarative memory and learning in Huntington's disease

There is accumulating evidence that patients with HD also are impaired on a broad range of tasks that require the acquisition and retention of novel skills or procedures, but do not require the conscious recollection of previously encountered information. For example, Martone et al. (1984) found that HD patients were deficient in improving their performance across multiple trials of a mirror-reading task. Similarly, Paulsen et al. (1993) observed that HD patients neither adapted to viewing a spatial target through prisms that shifted central fixation 20 degrees to the right or left, nor demonstrated the normal after effects of prism adaptation after removing the viewing apparatus. Patients with HD are also impaired in learning the pursuit-rotor test, a task which requires subjects to maintain continuous contact between a rod and a point on a moving turntable (Heindel et al. 1989). Using a serial reaction time task, Knopman and Nissen (1991) demonstrated that, compared to normal controls, patients with HD were deficient in decreasing their reaction times over multiple trials when pressing four buttons in a set sequence. HD patients also demonstrate a deficit in developing a sensory–motor bias. Specifically, Heindel et al. (1991) administered a weight-biasing task to a group of HD patients in which subjects were asked to rate the perceived weight of a set of test weights after having been previously exposed (i.e. biased) to a heavier or lighter set of weights. The normal controls in this study rated the set of test weights as being heavier if they had been biased with the lighter weights, but as lighter if they had been biased with heavier weights. In

contrast, moderately demented HD patients did not demonstrate this biasing effect, which suggests that they were unable to adapt to the sensory–motor feedback provided by the biasing weight set.

The deficits of HD patients on these various tasks of skill or procedural learning are in marked contrast to their relatively intact performances on other tasks that do not require the learning of a novel skill or procedure (i.e. tasks that have limited motor requirements), but nevertheless also require the unconscious recollection of previously experienced material. For example, HD patients have been shown to be relatively unimpaired on priming tasks that require lexical processes, semantic processes or visuoperceptual processes (Shimamura et al. 1987; Salmon et al. 1988; Heindel et al. 1989, 1990), and there is some evidence to suggest that these types of memories in HD patients are relatively stable over extended periods of time (Bylsma et al. 1991). Thus, it appears that HD patients' deficits on tasks that do not require the conscious recollection of information are somewhat specific to the motor domain. This has lead Heindel et al. (1993) to argue for the notion that dysfunction of the striatum in HD patients leads to a deficit in the establishment of motor programs, a view which is consistent with that of other investigators (e.g. Saint-Cyr and Taylor 1992).

At first glance it might appear that HD patients' deficits in motor-based learning and memory are due to the motor impairments observed in this disease; however, several studies have indicated that the patients' poor performances on these tasks are not associated with the degree of their motor symptoms, but rather with their overall level of cognitive status (Heindel et al. 1991; Paulsen et al. 1993). This suggests that the motor impairment of HD cannot completely account for the deficient motor-based learning and memory in this disease.

Learning and memory in animals with caudate lesions

Based on research with animals it has been assumed that the basal ganglia, including the caudate nucleus, mediate procedural learning as exemplified by the learning of stimulus–response associations or habits (Mishkin and Petri, 1984; Phillips and Carr 1987). Support for this idea comes from the findings that visual pattern discrimination and concurrent visual object discrimination are disrupted in monkeys with lesions of either the putamen or the tail of the caudate, but not in monkeys with lesions of the hippocampus (Mishkin 1982; Wang et al. 1990). It should be noted, however, that monkeys with lesions in the tail of the caudate have difficulty only in remembering new visual object discriminations, not previously acquired ones.

It has been suggested that in rats the caudate mediates the sensory–motor integration involved in learning of stimulus–response associations as required by tasks in which a particular motor response is reinforced in the presence of a single cue, or by tasks that require a consistent choice of direction, or a consistent choice to initiate or withhold responding (Phillips and Carr 1987; McDonald and White 1993). Support for this idea comes from a large number of studies indicating that damage to the dorsal caudate impairs brightness discrimination (Schwartzbaum and Donovick 1968), tactile discrimination (Colombo et al. 1989), conditional visual discrimination (Reading et al. 1991), right/left maze discrimination (Cook and Kesner 1988), runway learning (Kirkby et al. 1981), eight-arm maze learning (Colombo et al. 1989; Packard and White 1990), cued radial arm or Morris water maze learning (Whishaw et al. 1987; Packard and White 1990). In this latter task, only an approach response to the correct visual cue location is required. Furthermore, lesions of the caudate have resulted in inappropriate selection of fixed-interval schedules (Hansing et al. 1967). It should be noted that rats with hippocampal lesions are not impaired on the above mentioned tasks (McDonald and White 1993). As lesions of the caudate in rabbits impair classical conditioning of an eye-blink response, but not heart rate conditioning (Powell et al. 1978), it is likely that the caudate is involved only in stimulus-somatic motor response associations.

There is some evidence for regional specificity in caudate lesions' effects on behavior. In a conditional visual discrimination (fast versus slow frequency of light flashes) task requiring a choice bar press response, only ibotenic acid lesions of the lateral, but not the medial caudate, result in task acquisition impairments. A similar impairment in learning a stimulus–response association (entering an arm of an eight-arm maze if cued by a light) following lateral caudate lesions was also reported by McDonald and White (1993). These findings suggest that the lateral caudate is necessary for the acquisition of response rules to perform accurately on conditional visual discrimination tasks (Reading et al. 1991).

The major problem in interpreting the exact involvement of the caudate in stimulus–response association

learning derives from the difficulty in determining whether the impairment is due to a failure in detecting the sensory stimulus, a deficiency in learning stimulus–reward associations or a defect in shifting attentional set. With respect to visual information, it can be shown that caudate lesioned rats are not impaired in recognizing visual stimuli, learning stimulus–reward associations or in shifting attention (Kesner et al. 1993; McDonald and White 1993; Ward and Brown 1996). Furthermore, it is possible to demonstrate that increased firing of single cells within the caudate, associated with a learned head movement in response to an auditory cue, is context dependent. In other words, caudate cells respond only when the auditory cue elicits a head movement (Gardiner and Kitai 1992). In general, there is overwhelming support that the caudate, and more specifically the lateral caudate, mediates procedural learning, as exemplified by stimulus–response learning, in nonprimates. Even though there are no data on stimulus-response learning in rats following QUIN lesions of the caudate, the above mentioned animal studies suggest a parallel between HD patients' and caudate lesioned rats' procedural memory impairments.

Executive and attentional functions

Patients with HD also demonstrate deficits outside the memory domain. 'Executive function' deficits have long been reported in this disease (Caine et al. 1978; Fedio et al. 1979). In particular, patients with HD consistently perform poorly on tasks that emphasize novel problem solving, planning and concept formation (Brandt and Butters 1986; Lange et al. 1995), e.g. the Wisconsin Card Sorting Test. This test requires subjects to sort cards so that the cards match one of four stimulus cards on one of three predetermined dimensions (the dimension is not explicitly revealed to the subject). The subject must thus deduce from the examiner's feedback about the correctness of each response, the dimension along which cards are to be matched. After a predetermined number of correct sorts, the sorting rule is changed (without explicit instruction to the subject). The subject must shift response strategy based on the examiner's verbal feedback about the correctness of the previous response. On this test, HD patients are often impaired in switching to a new rule once they have established a sorting principle (i.e. they perseverate; Josiassen et al. 1983). Other studies have also demonstrated that HD patients are impaired on tests that place a heavy emphasis on switching between cognitive sets (Starkstein et al. 1988).

Different components of attention also appear to be affected in patients with HD. For example, these patients often demonstrate impairments on tasks that require mental tracking and manipulation of information, such as serial sevens, mental arithmetic and backward digit span (Folstein et al. 1990; Pillon et al. 1991). HD patients also demonstrate impairments on tasks requiring them to maintain vigilance over extended periods of time, or to divide their attention between different stimuli (Sprengelmeyer et al. 1995b). Certain attentional inhibitory mechanisms are also impaired in this disease (Sprengelmeyer et al. 1995b; Swerdlow et al. 1995). For example, using a task that has been employed extensively in animals, Swerdlow et al. (1995) demonstrated that patients with HD do not show the normal pattern of decreased acoustic or tactile startle response following a prepulse, suggesting that these patients are impaired in sensory–motor gating. Patients with HD do not appear to be impaired in their ability to shift attention between spatial locations, such as on the Posner task (Tsai et al. 1995) or between different levels of visual hierarchical stimuli (Filoteo et al. 1995).

HD patients also show impairments on working-memory tasks (Chapter 8) which require subjects to recall motor-based responses. In a preliminary study, Duncan-Davis et al. (1996) administered tests of spatial and motor working-memory to a small group of HD patients. During the study phase of the spatial memory task, subjects were shown a subset of six stimulus locations (X's) randomly selected from a set of 16 and presented in a sequential manner. In the test phase immediately following the study phase, two stimulus locations (X's) were presented simultaneously. The subject was asked to indicate which location they had seen during the study phase. During the study phase of the motor working-memory task, subjects were shown sequential presentations of six hand positions randomly selected from a set of 16, and they were asked to imitate the hand position. During the test phase, subjects were shown two pictures of different hand positions and were asked to determine which one they had seen in the study phase. The preliminary results of this study are shown in Figure 2. 1. Relative to normal controls, the HD patients were differentially impaired in the motor memory task. Interestingly, a recent study by Pasquier et al. (1994) demonstrated that HD patients were impaired on a task

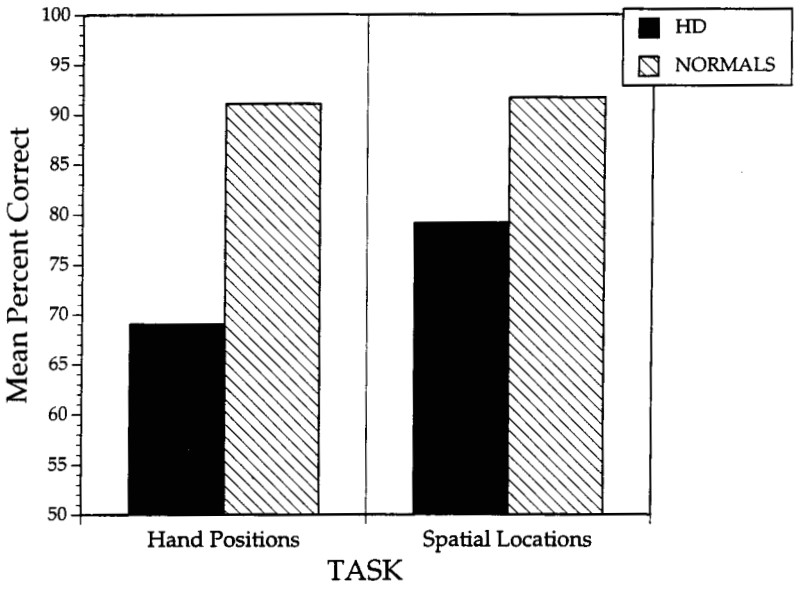

Figure 2.1. Mean percentage correct for Huntington's disease (HD) patients and control subjects based on working memory tests for hand positions and spatial locations.

requiring them to recall the spatial displacement of a handle on the apparatus. The results of that study, along with our preliminary findings, suggest that patients with HD are impaired on working-memory tasks, particularly when the task places a heavy demand on motor processes.

Similar patterns of working-memory deficits have also been demonstrated in rats with caudate lesions. For example, electrolytic lesions in the medial caudate impair rats' memory for a specific motor response (right-left turn), but not memory for a visual object or for a spatial location (Kesner et al. 1993). The performances of control and caudate lesioned rats on motor and spatial delayed matching to sample procedures (using short delays (1–4 s) between the study and test phases), are illustrated in Figure 2.2. Caudate lesioned rats were impaired only on the motor delayed matching to sample task. Medial caudate lesions also do not disrupt working memory for eight spatial locations on an eight-arm maze (Cook and Kesner 1988; Colombo et al. 1989). The pattern of greater impairment on motor than spatial working memory tasks in caudate lesioned rats closely parallels that observed by Duncan-Davis et al. (1996) in HD patients.

With respect to the ability to switch strategies, it has been shown that rats with ibotenate lesions of the medial caudate have difficulty in selecting alternative strategies in cue and place water navigation tasks (Whishaw et al. 1987) and in spatial reversal learning (Kolb 1977). These results, too, are consistent with observed deficits in HD patients (Caine et al. 1978).

To evaluate covert attention in caudate lesioned rats, rats were tested with a Posner paradigm involving the presentation of valid and invalid spatial cues following unilateral, large 6-OHDA lesions of the caudate. The results indicated that these lesions only increased mean reaction times contralateral to the side of the lesion, but the reaction times did not change differentially as a function of the requirements to disengage, maintain or shift attention. Rats following caudate lesions thus appear not to have any deficits in directing attention. Instead, the deficit on the Posner paradigm is probably due to an impairment in motor activity (Ward and Brown 1996). This lack of effect of caudate lesions on rats' covert attention is similar to that reported for HD patients (Filoteo et al. 1995).

In general then, it appears that the medial caudate mediates 'executive' functions as indicated by its involvement in working memory for motor responses and in the selection of alternate strategies. The medial caudate does not, however, mediate covert attentional processes.

Spatial orientation

Patients with HD are also impaired on visual tasks, even when such tasks do not place heavy emphasis on motor responding. For example, patients with HD demonstrate deficits on tests of visual confrontation naming; however,