PART I

Biological perspectives

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1

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

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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

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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 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

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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.

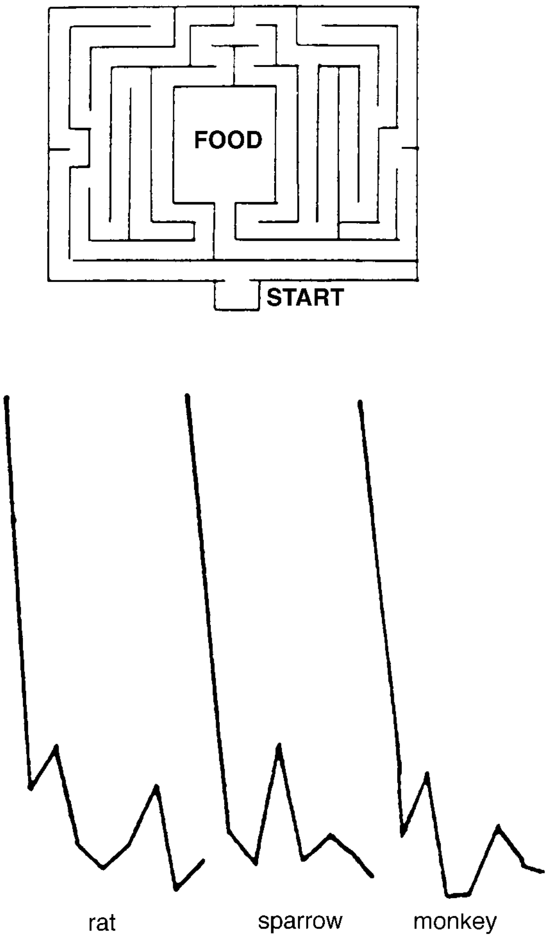

Figure 1.1. A maze designed by Small (1901) for measuring animal intelligence, along with learning curves from three different species trained in the maze. The curves show decreases in errors with each run through the maze, expressed as a proportion of the number of errors that were made on the first 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

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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

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[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

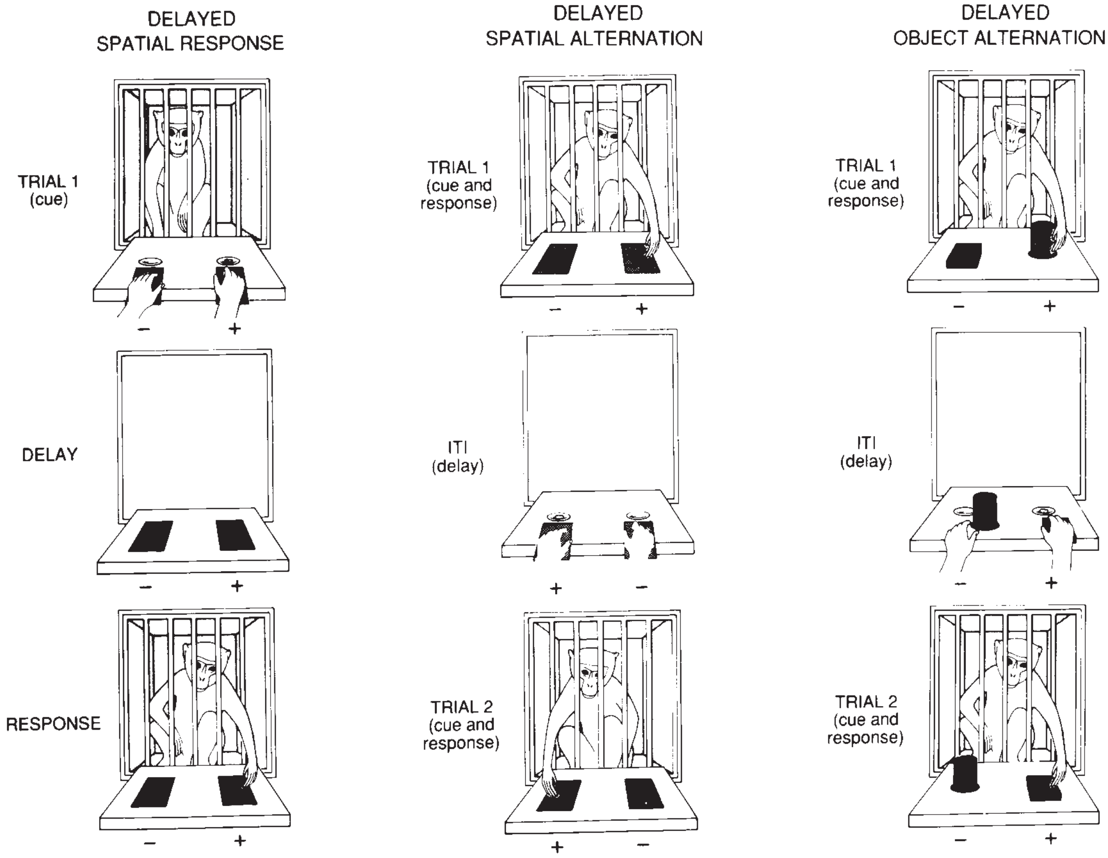

Figure 1.2. Three different tasks presented to Rhesus monkeys in a Wisconsin General Test Apparatus. The tasks illustrated can test working memory skills. The delayed reaction tasks, delayed response (DR) and delayed alternation (DA), rely heavily on spatial memory. The object alternation (OA) task is 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.

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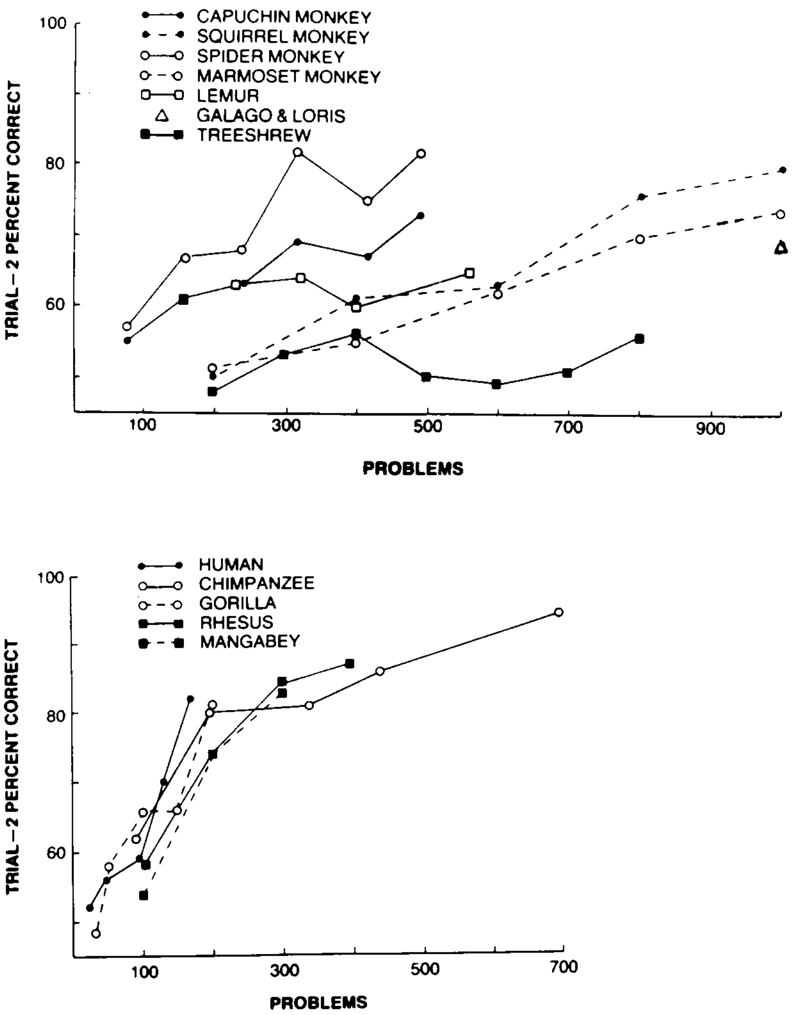

Figure 1.3. Performance by different species of primates, including children, on two-choice object learning-set problems. The curves illustrate precipitous improvement or learning-to-learn the win-stay, lose-shift strategy. From J.L. Fobes and J.E. King, 1982, In *Primate Behavior*, ed. J.L. Fobes and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

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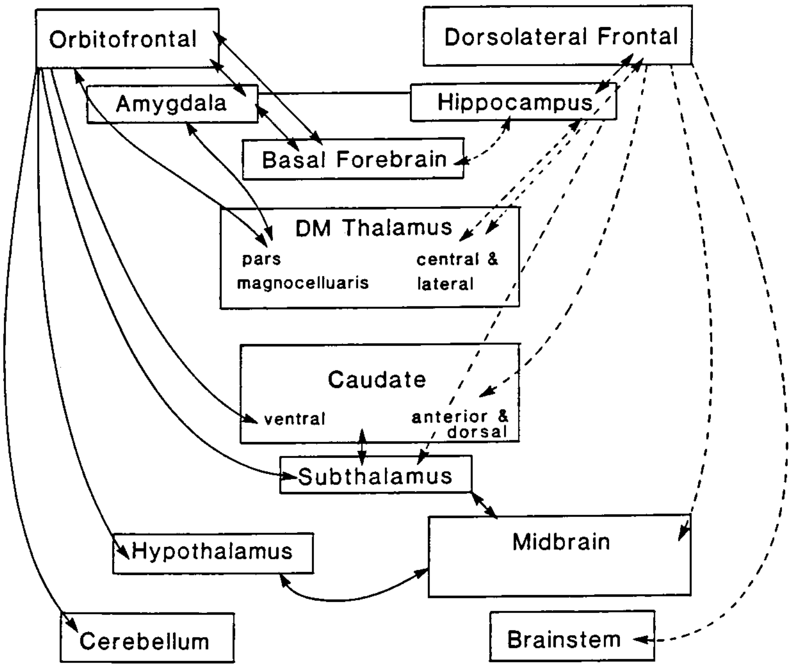

Figure 1.4. Schematic representation of two frontal lobe brain systems, illustrating the pathways that run through different regions of many of the same structures. From M. Oscar–Berman et al. 1991, In *Frontal Lobe Function and Injury*, ed. H.S. Levin, H.M. Eisenberg and A.L. Benton, pp. 120–138, Oxford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

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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