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THE USE OF ANIMAL MODELS TO STUDY THE EFFECTS OF AGING ON COGNITION

Michela Gallagher

Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

Peter R. Rapp

Center for Behavioral Neuroscience, State University of New York at Stony Brook, Stony Brook, New York 11794

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ABSTRACT

This review addresses the importance of animal models for understanding the effects of normal aging on the brain and cognitive functions. First, studies of laboratory animals can help to distinguish between healthy aging and pathological conditions that may contribute to cognitive decline late in life. Second, research on individual differences in aging, a theme of interest in studies of elderly human beings, can be advanced by the experimental control afforded in the use of animal models. The review offers a neuropsychological framework to compare the effects of aging in human beings, monkeys, and rodents. We consider aging in relation to the role of the medial temporal lobe in memory, the information processing functions of the prefrontal cortex in the strategic use of memory, and the regulation of attention by distributed neural circuitry. We also provide an overview of the neurobiological effects of aging that may account for alterations in psychological functions.

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INTRODUCTION

From a life-span perspective, the study of aging seeks to understand the changing capacities of the elderly as a normal developmental process. Within this framework, the biology of aging is an important determinant. Just as functions and adaptive capacities depend on the biological development of the young child or adolescent, later life provides a distinctive biological setting in which familiar tasks are performed and new challenges are met. In addition, environmental factors late in life combine with many decades of a person's history to influence the capacities of an individual. We offer the view that important insights into aging as a developmental process can be provided by the study of animal models. The review covers areas of research that illustrate and support this premise.

NORMAL AGING AND ANIMAL MODELS

A major challenge in the study of aging is to define the boundaries of normal change as distinct from pathological conditions. Such boundaries are recognized for development in early life. For example, landmarks are defined for physical growth and cognitive functions; departure from the norm is identified by a failure to manifest certain changes that are expected in the usual course of development. The boundaries of normal aging, as distinct from pathological conditions, are less clearly defined because certain expected changes in cognition during aging do not differ from the earliest manifestations of age-related pathological conditions. For example, the incidence of Alzheimer's disease (AD) increases with advancing age. Although the occurrence of AD is relatively rare before the age of 60, it becomes increasingly prevalent in the decades that follow. Impaired memory, which is the hallmark symptom of AD in its earliest stages, is also one of the most common cognitive features of nondemented elderly individuals (Craik & Jennings 1992, Crook et al 1986). Currently no definitive test can diagnose AD in its earliest stages so that

memory impairment associated with this pathological condition can be separated from memory decline that might be attributable to nonpathological aging.

Age-related neurodegenerative diseases such as Alzheimer's have a slow progressive course. If such diseases remain undetected for many years before a clinically significant phase of decline, relatively subtle changes in presumably healthy older individuals that are ascribed to normal aging might, at least in part, be due to occult pathological processes. Effects of Alzheimer's disease on the brain, such as plaques and neurofibrillary tangles, that meet neuropathological criteria for diagnosis have been detected in autopsy material from individuals not judged to have been impaired by clinical assessment before death (Crystal et al 1988, Morris et al 1991). On this basis, it is likely that studies of elderly human subjects will include some individuals with unrecognized neurological disease.

Additional findings from neurological assessments combined with functional testing support this conjecture. Elderly individuals who have radiological evidence of medial temporal lobe atrophy in the brain along with mild cognitive impairment determined by clinical screening were found to be at high risk for developing dementia (de Leon et al 1993). At follow-up four years after the original assessment, 25 of 86 such subjects had received a diagnosis of AD. Brain atrophic changes are also found in some elderly individuals who show no evidence of cognitive impairment in clinical assessments. In a sample of approximately 150 elderly subjects (ages 55–88 years, mean 70.0 years) who were presumed to be healthy, Golomb et al (1993) found atrophy of the medial temporal lobe in certain individuals. Although no participants in this study showed evidence of cognitive impairment in clinical assessments, differences between the subjects with and without medial temporal lobe atrophy were evident in more sensitive tests of cognitive function. Subjects with atrophy performed more poorly on tests of recent memory than the neurologically normal individuals. Much current interest is also focused on a biological marker, the e4 allele of apolipoprotein E, associated with higher risk for dementia (Corder et al 1993). Recent reports indicate that presumably healthy individuals bearing this marker perform less well on assessments of memory than their aged cohorts (Bondi et al 1995, Helkala et al 1996). Such findings raise the question of whether even mild memory impairment might represent a very early indicator of a pathological process.

Notwithstanding the findings discussed above, other evidence indicates that cognitive alterations in aging occur apart from degenerative neurological disease. Age-associated memory impairment (AAMI) was defined a decade ago (Crook et al 1986) to identify elderly individuals who complain of memory impairment by self-report and have memory test performance at least one

standard deviation below the mean established for young adults. According to these criteria it is estimated that the occurrence of AAMI substantially exceeds what would be expected based on the prevalence and incidence of probable Alzheimer's disease (prevalence and incidence of AAMI about 35% and 6.6% per year compared with 13% and 3% per year for probable AD) (Lane & Snowdon 1989). Furthermore, Youngjohn & Crook (1993) reported that AAMI is stable in elderly individuals based on follow-up assessment four years later. These investigators concluded that AAMI is a relatively benign condition that does not follow a progressive course. Several limitations of this study, however, are worth noting. First, a considerable number of participants that did not return for follow-up testing might have had greater decline than those that did, a phenomenon that is problematic for research of this type. Second, the subjects in this study, who were on average in their early sixties at the first assessment, were followed for a relatively brief interval of four years when the incidence of Alzheimer's disease continues to be low. Further examination of such individuals into later decades might be needed to provide a better indication of the course of AAMI.

A related issue in the definition of normal aging concerns the observation of individual differences in the elderly population. As indicated above, cognitive decline is evident in some individuals in the elderly population (e.g. AAMI), whereas function is better preserved in other aged individuals. In contrast with the usual individual differences that exist at earlier points in development, variability is often described as markedly increased with advancing age. In accordance with this description, a recent survey of published data found greater variability (coefficients of variation) among the elderly compared with young adults on a number of measures widely reported to be sensitive to aging, e.g. reaction time, memory, and fluid intelligence (Morse 1993). Although this phenomenon is often observed, the origin of increased variability in aging is not well defined. Perhaps variability in aging reflects differences that are expressed only in the later decades of life. Alternatively, individual differences might become magnified late in life because of the cumulative impact of different biological and experiential backgrounds over many decades. More information about factors underlying individual differences will be important for understanding normal aging.

The discussion above provides a background for considering the usefulness of animal models in the study of aging. The likelihood that the same pathological processes in human disease occur and are manifest in identical ways across several species could be considered quite low. Many progressive neurological diseases such as Alzheimer's do not afflict species commonly used in laboratory research on aging, e.g. rats, mice, monkeys. However, it is reasonable to expect that at least some features that characterize biological aging of the

mammalian brain would be evident in different species. Thus, commonalities across species might help to identify normal neurobiological aging, as distinct from pathological conditions, and those psychological functions most affected by aging.

The use of laboratory animals can address other aspects of human aging that have proven difficult to study in a systematic way. If normal aging is characterized by increased variability, this phenomenon of individual differences might be evident in other species. Because cohorts of laboratory animals can be maintained under relatively controlled conditions it should also be possible to isolate factors contributing to such individual differences.

The relevance of research with laboratory animals for an understanding of human aging, however, depends on whether the specific functions and biological systems targeted for study are appropriate models for human aging. Scientific advances over the past few decades have provided a foundation for developing useful animal models of aging. We outline a framework currently employed for investigating the neurobiological basis of functional changes in aging. The approach is built on a background of research in neuropsychology, cognitive psychology, and neuroscience.

The field of neuropsychology originally led to clinical descriptions and psychometric profiles for certain types of brain damage as an aid to diagnosis. Because the consequences of certain forms of damage were remarkably selective, neuropsychological studies also came to serve as a basis for making inferences about the normal function of specific brain regions. Alongside developments that came from neuropsychological research, cognitive psychology has greatly contributed to our understanding of psychological processes. Cognitive psychology studies the components and organization of functions such as memory within the framework of information processing and representation. As a related burgeoning field, cognitive neuroscience is building on advances in psychology using new technologies, such as functional neuroimaging and methods for recording the ensemble encoding of information by neurons, to study information processing in the brain. Research derived from these traditions of neuropsychology and cognitive neuroscience has contributed to the development of animal models in the study of aging, as exemplified by the areas covered in the following sections.

MEDIAL TEMPORAL LOBE SYSTEM

Psychological Functions of the Medial Temporal Lobe

Patients with medial temporal lobe damage have circumscribed deficits in memory; the syndrome includes an anterograde amnesia and spares remote memory and general intellectual capacities (Corkin 1984, Scoville & Milner 1957). Anterograde amnesia refers to the inability to remember new informa-

tion and episodes of life that occur after medial temporal lobe damage. The anterograde memory impairment is considered to represent a defect in mechanisms that allow long-term retention of new material. In support of this concept many domains of information processing and immediate memory (e.g. digit span) are preserved in these amnesic patients. Moreover, the recognition that patients with such amnesia have areas of preserved memory, e.g. priming and skill learning, advanced the concept that the brain possesses multiple memory systems (Cohen & Squire 1980). The domain of memory in medial temporal lobe amnesia is variously described as declarative or explicit memory, referring to representations in memory that provide a basis for the conscious recollection of facts and events.

Research using animal models has sought to define the components of the medial temporal lobe that contribute to the amnesic syndrome. Considerable evidence for deficits in declarative memory has been obtained in other species, but agreement has not yet been achieved about the underlying structures subserving memory within the medial temporal system. The most widely used animal model under study in this area of research is a recognition memory task performed by rhesus (or cynomolgous) monkeys (Squire & Zola-Morgan 1991). In this delayed nonmatch-to-sample task, monkeys are presented with an object on an information trial. After a variable delay, the original object is presented with a novel object, and selection of the novel object is rewarded. Considerable consensus surrounds the observation that damage to cortical regions of the medial temporal lobe (perirhinal, entorhinal, parahippocampal cortex) produces a significant delay-dependent deficit in this object-recognition task (Meunier et al 1993, Suzuki et al 1993). Less consensus has been achieved concerning the effects of damage confined to the hippocampus (Murray 1996). However, it is clear that damage to the hippocampus alone produces less severe impairment than damage restricted to the cortical regions of the medial temporal lobe. It is interesting to note that relatively similar findings have been reported in studies of rodents designed to parallel the delayed nonmatch-to-sample task used with monkeys. Damage to cortical structures associated with the hippocampal formation produces delay-dependent impairments that are not observed after selective damage to the hippocampus (Otto & Eichenbaum 1992, Wilner et al 1993).

Different perspectives are offered to account for findings in this line of research. By one view, a common function in memory is served by the component medial temporal lobe cortical regions and the hippocampus, with more severe impairment resulting from more extensive damage to this system (Squire & Zola-Morgan 1991). Another view is that the components of this system may serve somewhat different functions in declarative memory. For example, the relative insensitivity of delayed nonmatch-to-sample tasks to

damage of the hippocampus alone may indicate that the medial temporal cortical regions can subserve memory representation for individual items independent of the hippocampus, while the hippocampus is essential for the formation of more complex representations in memory (Eichenbaum et al 1994). In agreement with this distinction, certain representations that provide a basis for the flexible use of information in memory appear to be highly sensitive to selective hippocampal damage in laboratory animals. For example, it has been argued that spatial information is an exemplar of this type of representation, and it is well documented that severe deficits in spatial tasks are observed after lesions of the hippocampus. Another instance of memory representation sensitive to disruption of the hippocampus comes from a study using probes for memory after animals were trained on a set of nonspatial stimulus-stimulus associations. Normal rats demonstrated two forms of flexible memory that were not shown by rats with selective hippocampal lesions, i.e. transitivity, reflected in the ability to compare across stimulus pairs that share a common element, and symmetry, referring to the ability to associate paired elements presented in the reverse of the training order (Bunsey & Eichenbaum 1996).

Additional research is needed to establish more firmly whether the brain regions that comprise the medial temporal lobe are functionally heterogeneous with respect to their roles in declarative memory. Further advances in this area of cognitive neuroscience will continue to provide an important background for understanding the neurobiological basis of altered memory processes in the elderly.

Psychological Functions of the Medial Temporal Lobe in Normal Aging: Human Beings

The characteristics of memory impairment in presumably healthy elderly adults appear to parallel the general features of medial temporal lobe amnesia (Craik & Jennings 1992). Remote memory and immediate memory (e.g. digit span) are spared. Elderly subjects, however, perform more poorly on typical tests of declarative memory (e.g. paired associates, delayed paragraph recall). Such deficits point to involvement of medial temporal lobe structures. Evidence that alterations in the medial temporal lobe may underlie age-associated memory impairment is noted above; Golomb et al (1993) found that elderly individuals with hippocampal atrophy performed less well on tests of delayed recall.

Functional neuroimaging studies are now providing new information about the relative activation of this system in young and elderly individuals during performance of memory tasks. Grady et al (1995) measured cerebral blood flow during encoding and recognition of faces. They reported that poorer memory performance in healthy elderly individuals relative to young individuals was associated with a reduction in hippocampal and prefrontal cortical

activation during encoding. In the context of this observation, it is noteworthy that hypoactivity in the medial temporal lobe is not invariably observed in the brains of elderly subjects. In contrast with the results of Grady et al, another recent study found comparable medial temporal lobe activation in young and elderly subjects during successful recall (Schacter et al 1996). In that experiment, a word-stem completion task was administered to produce either high or low recall of study words. When neuroimaging was done during retrieval tests, equivalent hippocampal activation in young and aged groups was observed during successful recollection (high recall versus either low recall or baseline), which indicates that an age-related deficiency localized to the medial temporal lobe does not occur in all conditions where hippocampal activation is observed. These results also suggest that memory deficits in the elderly are not due to deficient medial temporal function during the retrieval of information. Rather, deficits may be attributable, at least in part, to a functional impairment in medial temporal lobe processing of new information, i.e. encoding, that serves as a basis for later recognition or recall.

Before turning to the examination of memory performance in aged laboratory animals, we reiterate that age-associated memory impairment is not evident in all individuals in the elderly human population. Thus, it is of interest in studies of laboratory animals to assess whether similarities can be found in the effects of aging on memory that resemble those features encountered in human beings and to determine whether individual differences also exist in other species over the course of aging.

Psychological Functions of the Medial Temporal Lobe in Normal Aging: Animal Models

The delayed nonmatching-to-sample task used to assess recognition memory in young monkeys with medial temporal lobe damage has also been used to test aged monkeys (Moss et al 1988, Presty et al 1987, Rapp & Amaral 1989). Although aged monkeys have difficulty in learning this task with a very brief retention interval, given sufficient training virtually all older subjects are able to reach a criterion equivalent to young monkeys. When the memory demands are then manipulated by increasing delays, monkeys approximately 25 years or older are impaired. Individual differences in recognition memory among aged monkeys are also observed, with an impairment in a subset of aged monkeys that qualitatively resembles the effect of medial temporal lobe damage in young monkeys (Rapp & Amaral 1991). Furthermore, aged monkeys with such deficits also perform more poorly on rapidly learned two-choice object discrimination problems, another assessment that is sensitive to medial temporal lobe damage (Rapp 1993). An additional parallel in the pattern of impairment across aged monkeys and young monkeys with medial temporal lobe damage is found in a task that increases the load of information in memory.

Subjects are tested for identification of each new item added to an array of previously presented items (Killiany et al 1995). Thus, studies of nonhuman primates have demonstrated memory impairments on tests sensitive to the integrity of the medial temporal lobe. Moreover, the presence and/or severity of such deficits varies considerably in the aged population. Because the neural substrate within the medial temporal lobe system for the most commonly used task in this research, delayed nonmatching-to-sample, is not clearly defined, age-related impairment on this assessment might reflect alterations in medial temporal lobe cortical systems either alone or together with alterations in the hippocampus.

Other evidence for alterations in the hippocampus in aged monkeys comes from a report of impairment in the flexible use of information in memory. As noted in the prior section, a test for the use of information in memory that is sensitive to selective damage of the hippocampus has recently been demonstrated by probes for transitive inference in rodents. After learning a set of stimulus-stimulus associations, young intact rats infer relations among the items, an ability that is lacking in rats with lesions confined to the hippocampus (Bunsey & Eichenbaum 1996). In a recent study, monkeys that learned a hierarchy of object-object discriminations were tested for their use of information in memory. The performance of aged monkeys during probes failed to show response latency effects that are taken to reflect the relational processing of information that underlies transitive inference (Rapp et al 1996).

Deficits that are widely studied in aged rodents in spatial tasks may also reflect a declarative memory impairment. Aged rats, like young rats with damage to the hippocampus, have deficits in a variety of spatial tasks (for an overview, see Gallagher et al 1995). Moreover, impaired spatial learning in aged rats or in young rats with hippocampal damage can be demonstrated to occur independent of decline in sensorimotor/motivational functions and in learning that is guided by a stimulus or object used as a local cue (Gage et al 1989, Gallagher et al 1993). In addition, individual differences have been particularly well documented in this line of research. Among certain strains of rats, a proportion of aged animals exhibit highly preserved performance on such tasks, while other aged cohorts perform entirely outside the range of young rats (Gallagher et al 1993).

With respect to the neurological basis for impairments of aged rodents on spatial tasks, note that these tests do not provide an entirely selective assessment of the function of the hippocampus (Gage et al 1984). For example, young rats with lesions of cortical systems interconnected with hippocampus, e.g. entorhinal/perirhinal cortex, also exhibit deficits in spatial tasks (Nagahara et al 1995). Thus additional assessment is needed to distinguish between impairment that may have a basis in the altered status of the hippocampus

versus these cortical regions. As noted earlier, a version of delayed nonmatch-to-sample developed for studies of rodents has revealed a sensitivity to entorhinal/perirhinal cortex damage that was not seen after selective damage to the hippocampus in young rats (Otto & Eichenbaum 1992). A recent study reported that aged rats that learned this task at short retention intervals performed no differently than young rats when increasing delays were introduced (Zyzak et al 1995). The same rats used in this assessment were also evaluated in a spatial task where an age-related deficit was observed. Thus, aged rats that are impaired in a spatial task that is sensitive to the integrity of the hippocampus can display intact performance on an assessment that is more selectively sensitive to the integrity of related cortical regions in the temporal lobe. Such results support the concept that impairment in spatial tasks reflects an effect of aging on the hippocampus.

Behavioral studies demonstrating a decline in functions associated with medial temporal lobe structures in laboratory animals provide evidence for age-associated memory impairment independent of pathological conditions that affect the elderly human population. Moreover, individual differences in aging are often documented in studies of nonhuman primates and rodents, which provides an additional parallel with observations in human beings.

Neurobiology of Aging in the Medial Temporal Lobe

Much current research in laboratory animals is directed at the neurobiological basis of decline in cognitive functions associated with the medial temporal lobe. Two concepts about the basis for this decline in aging, which have prevailed for several decades, have recently come under new scrutiny. In the first case, neurodegeneration within the hippocampus had been thought to play a significant role (Meaney et al 1988). A second influential concept held that degeneration in the basal forebrain cholinergic system, a component of which innervates the hippocampus and related cortical structures, provides a basis for memory deficits in aging (Bartus et al 1982). In each case, recent studies indicate that these long-standing concepts may be incorrect. After discussing the research dealing with those topics, we consider other potential substrates for age-related loss of function in the medial temporal lobe system.

The conclusion that neuron loss occurs in the aged hippocampus was reached in earlier studies of human, nonhuman primate, and rodent brains (Brizzee et al 1980, Dam 1979, Issa et al 1990, Meaney et al 1988). In some of these reports, the concept that neurodegeneration causes age-related cognitive decline was further bolstered by evidence that the presence and severity of behavioral impairment were correlated with loss of principal neurons in the hippocampus (Issa et al 1990). It is important to note, however, that studies of neurodegeneration were originally based on methods for estimating neuron density. Neurodegeneration is now being studied using new methods that are

unbiased for many factors that could influence measures of neuron density, such as the size of neurons and the size or composition of nonneural cells, and so forth. Recent results using these new methods for measuring the total number of neurons in a brain structure indicate that no neuron loss appears to occur in the hippocampus during normal aging across a variety of species.

Studies of aging in human, nonhuman primate, and rat brain have now shown equivalent numbers of the principal neurons (Figure 1) in the hippocampus (Rapp & Gallagher 1996, Rasmussen et al 1996, West 1993, West et al 1993). Moreover, the recent anatomical studies of rats showed that even aged animals with substantial deficits indicating hippocampal dysfunction exhibited no loss of neurons in this structure. For example, Rapp & Gallagher (1996) observed a wide range of spatial ability in the aged rats included in their study but relatively little variability in numbers of hippocampal neurons and no suggestion of a decline in neuron number associated with age or behavioral impairment.

Additional evidence indicates that neuron number is preserved in the hippocampal formation of aged nonhuman primates, including those monkeys with identified memory impairment (West et al 1993). In addition to comparable numbers of principal neurons in the hippocampus proper, this study found no significant loss of neurons in cortical regions associated with the hippocampal formation (e.g. entorhinal cortex and subiculum). This finding is particularly noteworthy because a subset of the aged monkeys had deficits in recognition memory assessed in delayed nonmatch-to-sample, a task that is sensitive to the integrity of cortical areas in the medial temporal lobe.

Neurodegeneration in the hippocampus was formerly viewed as an inevitable consequence of normal aging. Reports that the principal neurons of the hippocampus are preserved across a variety of species, even in the presence of substantial behavioral impairment, may prompt a shift in the view that neuronal loss in this structure serves as a basis for age-related cognitive decline. Neurodegeneration in the hippocampus also appears to distinguish certain pathological conditions from normal aging. In contrast with normal aging, stereological methods detect significant reductions in the number of principal neurons in the hippocampus in individuals with diagnosed Alzheimer's disease (West et al 1994).

A second long-standing concept about the neurobiological basis of cognitive decline in aging has focused on the basal forebrain cholinergic system (Bartus et al 1982). Cholinergic neurons within this system that are located in the medial septum and vertical limb of the diagonal band (MS/vDB) provide innervation of the hippocampus and related medial temporal cortex (Koliatsos et al 1990). Atrophy and degeneration of these neurons is detected in aged brains (Fischer et al 1989, Smith & Booze 1995, Stroessner-Johnson et al 1992), and marked pathology affects this system in Alzheimer's disease

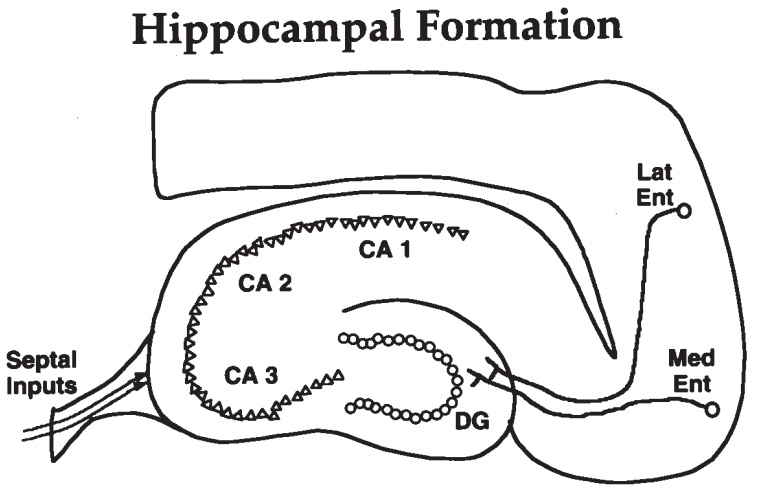

Figure 1 The schematic shows the principal neurons of the hippocampal formation, the granule cells of the dentate gyrus (DG), and the pyramidal neurons of the hippocampus proper (areas CA1–CA3). Two major input pathways to the hippocampal formation are illustrated. Input from the lateral and medial entorhinal cortex (Lat Ent and Med Ent) provides highly processed information and terminates primarily on the dendrites of the granule cells in the dentate gyrus. A subcortical pathway (Septal Inputs) enters through another route and provides widespread innervation of the hippocampal formation. This latter input includes the cholinergic innervation of the hippocampal formation. A trisynaptic circuit through the hippocampus (not shown) begins with the synapses formed by the entorhinal cortex projection onto the dentate granule cells. Those cells in turn project to the CA3 area. The CA3 pyramidal neurons form a third set of synapses within this structure, projecting onto the pyramidal cells in the CA1 area.

(Coyle et al 1983, Davies & Maloney 1976). It is further noteworthy that the number and size of these neurons are affected by age across a variety of species, including rats, monkeys, and human beings. The possibility that neurodegeneration within this population of neurons contributes to functional impairment has found support in numerous studies showing that the amount of cholinergic neuron deterioration is related to the severity of behavioral deficit in aged subjects (for an overview, see Gallagher et al 1995). Note that the vast majority of these correlational studies have used rat performance on spatial tasks as the behavioral assessment. Recent evidence, however, challenges the conclusion that deterioration of cholinergic neurons can account for age-related impairments in spatial tasks (Gallagher & Colombo 1995). At issue in this line of research is not whether degeneration occurs within the basal forebrain cholinergic system, but whether that effect of aging causes behavioral decline.

One way to assess the contribution of the septohippocampal cholinergic system to age-related impairments is to examine whether removing these

neurons in young animals reproduces the deficits observed in aging. A newly developed immunotoxin 192 IgG-saporin can be used to target selectively basal forebrain cholinergic neurons. After injection of the immunotoxin into the MS/vDB, a nearly complete removal of the cholinergic innervation of the hippocampus can be achieved. It has come as a surprise, given the cholinergic hypothesis of age-related impairment, that immunotoxin-induced lesions of the septohippocampal cholinergic system fail to produce reliable spatial learning deficits (Baxter et al 1995a, 1996; Berger-Sweeney et al 1994, Torres et al 1994). Young rats with over 90% depletion of the cholinergic-specific enzyme choline acetyltransferase (ChAT) in hippocampus perform normally on a spatial learning protocol that is highly sensitive to deficits in aged rats (Baxter et al 1995a), and no impairment is even detected after removal of the entire basal forebrain cholinergic system, including the input to the hippocampal formation and the widespread innervation of the cerebral cortex (Baxter et al 1996). Moreover, comparable cholinergic lesions in aged rats do not appear to exacerbate or induce impairment in spatial tasks (Baxter & Gallagher 1996). Thus it is unlikely that deterioration in the septohippocampal cholinergic system by itself provides a sufficient basis for age-related deficits that are commonly observed in spatial tasks. We return in a later section of this review to the function of the cholinergic innervation of the hippocampus and its possible contribution to behavioral deficits in aging.

A current theme in research on normal aging is that a reduction in the number of synaptic connections, rather than frank neurodegeneration, provides a basis for age-related alterations in cognition. For example, atrophy and degeneration in the basal forebrain cholinergic system is likely to result in some loss of hippocampal innervation by these neurons. In agreement with this expectation, the cholinergic response mediated by stimulation of the septohippocampal input is reduced in all areas of the aged rat hippocampal formation (Shen & Barnes 1996). However, the failure of specific cholinergic lesions to reproduce memory deficits that have been well documented in aged rodents makes it unlikely that this alteration, by itself, serves a broad basis for impairments in aged rats.

Apart from the subcortical input to the hippocampus that originates in the septal region, an additional loss of synaptic input from another source is well documented to occur in aging. That input, which provides the primary route for transfer of highly processed cortical information to the hippocampus, derives from neurons in the entorhinal cortex (refer to Figure 1). Ultrastructural studies of rat brain have demonstrated a significant loss of synaptic connections in the hippocampal formation that are formed by entorhinal cortex input (Geinisman et al 1992). In addition, individual differences in cognitive decline among aged rats are reported to coincide with differences in the loss of this

innervation (Geinisman et al 1986). Reduced numbers of synaptic connections may also occur in other areas of the hippocampal formation (Barnes et al 1994).

It might be reasonable to expect that reduced numbers of synaptic connections in the hippocampal formation could provide a basis for behavioral deficits that depend on the integrity of this system. However, it should be recognized that a number of factors might argue against that outcome. Neurobiological systems possess a number of mechanisms that are geared to maintain function. Considerable evidence indicates that such mechanisms are recruited in the aged brain. For example, although fewer synaptic connections are made in the dentate gyrus of the hippocampal formation in aged rats, the response to input at the remaining synapses is greatly increased (Foster et al 1991). In addition, a loss of synapses from cortical input induces a sprouting response in which new connections are formed by inputs from other sources. Evidence for such sprouting in the hippocampal dentate gyrus has come from studies of aged brains and is also observed in Alzheimer's disease (Geddes et al 1992, Nicolle et al 1996). This type of sprouting may be compensatory in nature, as new connections are made to replace those that are lost. However, such reactive growth may not always be beneficial. New connections might add to the adverse effects of aging because they come from a different source than the original input. Studies of aging often lack the functional analysis necessary to distinguish between these possibilities. Recent studies using behavioral assessment along with neurobiological analysis are being conducted to evaluate whether such alterations in the brain provide protection or impose further adverse effects on outcome (Nicolle et al 1996, Stack et al 1995, Stenvers et al 1996). If a neurobiological response in the aged brain is compensatory, then the degree to which this response occurs should predict a better outcome, i.e. less behavioral impairment. However, if a reactive process only adds to dysfunction then the presence of such a change in the brain might be associated with greater impairment. Research of this type should lead to a better understanding of the consequences of reactive and reorganizational processes that occur in the aged brain.

Studies of neurodegeneration and synaptic connectivity provide important information about structural features of the brain during aging. Apart from such structural features, effects of aging are evident in the functional integrity of existing neurons and connections. Such changes may be important factors in diminishing the overall performance of the medial temporal lobe system during aging.

Neurons in the hippocampal system possess a complex array of biological mechanisms for information processing. In addition to specialized receptors for specific inputs, receptors are coupled to a variety of transduction systems

that are necessary to produce physiological responses to those inputs (refer to Figure 2). Furthermore, transduction mechanisms are not only used for the processing of information transmitted between neurons but also play a role in altering the functional properties of synaptic connections. Long-term potentiation (LTP), referring to the long-lasting increase in the effectiveness of synaptic connections that can be readily induced in the hippocampal system, has attracted widespread interest as a possible physiological mechanism for the storage of information in the mammalian brain.

Studies on transduction mechanisms may provide insight into the basis for changes in information processing and information storage during aging. The findings from such research are especially informative in a system where neurodegeneration is not a prominent feature of aging. In such a setting, measurable decreases in components of transduction systems, including receptors, coupling mechanisms, and second and third messengers, do not merely reflect a loss of neurons but indicate a change in the functional integrity of existing neurons. For this reason, recent evidence for preserved numbers of

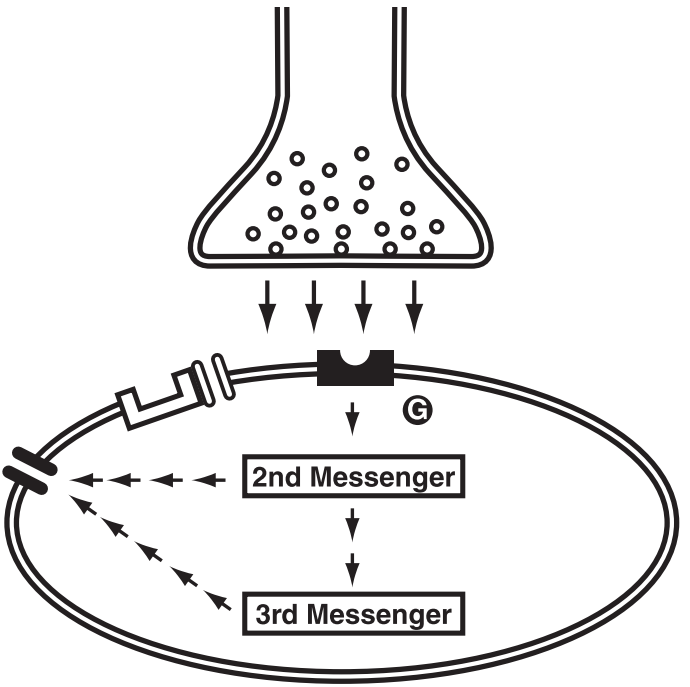

Figure 2 Schematic illustrates interneuron communication. Transmission from an input produces a postsynaptic response through a variety of transduction mechanisms. The components of this communication system include receptors that either directly regulate a neuron's excitability or work through biochemical cascades (2nd and 3rd messenger systems).

neurons in the hippocampus is important for interpreting the effects of aging on other neurobiological measures.

In addition to an absence of frank neurodegeneration within the hippocampus during aging, at least some types of receptors that serve as targets for neurotransmitters are also relatively unaffected by aging in this structure. For example, substantial preservation of postsynaptic receptors for acetylcholine is reported in a number of studies (Chouinard et al 1995, Quirion et al 1995, Smith et al 1995). To the extent that postsynaptic targets are preserved, then strategies to address the effects of aging might be developed to increase function at these sites. Such a rationale has served as a basis for developing drugs to compensate for age-related deterioration of the basal forebrain cholinergic neurons. Acetylcholinesterase inhibitors (e.g. Tacrine) are intended to augment the action of acetylcholine at its receptors in the forebrain by preventing the degradation of this transmitter (Davis et al 1992, Thal et al 1989). Because such drug treatments can improve cognitive function in young rats, some benefit might be achieved in aged animals even if the basis for impairment is not solely due to a cholinergic defect (Gallagher & Colombo 1995). The effectiveness of augmenting cholinergic function would depend, however, on an intact physiological response at cholinergic receptors. In the case of those receptors, however, a blunted response to cholinergic stimulation has recently been documented in the aged rodent hippocampus (Chouinard et al 1995, Undie et al 1995). In one of these studies, a greater reduction in the postsynaptic response to cholinergic stimulation was seen in aged rats that were found to have more pronounced cognitive impairment (Chouinard et al 1995). Moreover, the neurobiological defect in this case appeared to reside at a point in the biochemical machinery that would potentially affect the physiological response to other transmitter/receptor inputs that use the same transduction pathway.

In addition to the role that transduction mechanisms serve in information processing, long-lasting changes in the properties of synapses depend on the functional integrity of neurons. It has long been recognized that alterations in the mechanisms required for neural plasticity could provide a basis for cognitive decline during aging. One of the earliest studies of individual differences in spatial learning in aged rats showed that this impairment correlated with a deficiency in neural plasticity in hippocampus (Barnes 1979). In those experiments an in vivo study of LTP at perforant/dentate synapses was conducted in the same rats that were behaviorally tested in a spatial learning task. Although asymptotic (saturated) LTP did not differ between the age groups, this LTP was achieved less readily and decayed more rapidly in the aged rats than in young rats. Furthermore, the impairment in behavioral learning was significantly correlated with the effect of aging on LTP. Additional studies continue to document that LTP is adversely affected during the aging process (Barnes &

McNaughton 1985, Moore et al 1993). A modest loss of the receptors required for induction of LTP may occur in the aged hippocampus in both primates and rodents (Clark et al 1992, Gazzaley et al 1996, Nicolle et al 1996, Wang et al 1996). A highly active area of research aimed at defining the mechanisms underlying LTP in adult animals will provide a route for better understanding the basis of the deterioration seen in aging.

Consistent with a variety of evidence for functional alterations in the aged hippocampal formation, recording the activity of hippocampal neurons while animals perform certain tasks has provided evidence that the representation of information in this system is altered in older animals. Such studies have shown less reliability and specificity of the information encoded by hippocampal neurons (Barnes et al 1983, Mizumori et al 1996; but see Markus et al 1994). In a recent study of aged rats, individual differences were also evident. In aged rats that were impaired in a cognitive assessment of spatial learning, representations of relationships among stimuli in a spatial environment were relatively impoverished and inflexible compared with either young rats or aged cohorts with preserved behavioral functions (Tanila et al 1996). Further research of this type will help to elucidate the computational cost of the neurobiological effects of aging within this brain system. Identification of mechanisms underlying diminished function within that circuitry will undoubtedly provide an impetus to the development of new therapeutic strategies to treat age-related impairment.

In conclusion, cognitive impairments that resemble those seen in elderly human beings can be observed in the study of aged laboratory animals. Individual differences in the effects of aging on tasks sensitive to the integrity of the medial temporal lobe are also mirrored in the presence and severity of some neurobiological changes found in this system. Beyond the effort to construct a description of normal aging, research using animal models promises to provide a setting for productive research on mechanisms of brain aging. This may include a better understanding of how the rate or severity of aging provides a basis for individual differences in cognitive abilities late in life.

FRONTAL LOBE SYSTEMS

Psychological Functions of Frontal Lobe Systems

In contrast with amnesia resulting from medial temporal lobe damage, human beings with frontal lobe lesions perform accurately on many standard tests of declarative memory (reviewed in Moscovitch & Ulmita 1991). Current perspectives instead emphasize that the prefrontal cortex supports a variety of organizational processes that importantly influence the strategic use of memory. In addition, compelling evidence has revealed functional heterogeneity

across the regions comprising the prefrontal cortex. A popular view is that these areas function in a "central executive" capacity, mediating the on-line manipulation of memory, particularly under circumstances emphasizing the spatial, temporal, or other contextual attributes of acquired information (reviewed in Moscovitch & Ulmita 1991). Recent evidence consistent with this view comes from neuroimaging studies in normal human subjects. Cerebral blood flow is selectively increased in a region of the dorsolateral prefrontal cortex when memory for temporal order is necessary for successful performance relative to conditions involving the same sensory and motor demands but lacking a temporal order component (Petrides et al 1993a,b). A slightly more posterior prefrontal region (area 8), by comparison, is activated during a conditional discrimination procedure placing relatively greater emphasis on the environmental contingencies governing ongoing behavior (Petrides et al 1993a). Such data support the concept that the prefrontal cortex comprises a variety of functionally distinct subsystems. In addition, this background of information helps to account for the pattern of impairments observed following frontal lobe damage, which includes prominent deficits in memory for temporal order, impaired recall for the source of acquired information (i.e. source amnesia), and difficulties modifying behavior appropriately in response to changing environmental contingencies (i.e. perseveration) (Janowsky et al 1989a,b; Shimamura et al 1990).

Another feature of specialization within the prefrontal cortex is suggested by studies focusing on the component processes of declarative memory, e.g. encoding, retrieval, and so forth. As noted previously, encoding processes and the successful conscious recollection of events are associated with hippocampal activation (Grady et al 1995, Schacter et al 1996). Lateralized prefrontal cortical activation is particularly associated with effortful retrieval of information from memory (Schacter et al 1996). This observation supports the concept that the activity of prefrontal cortex is engaged by specific retrieval strategies in support of declarative memory (Buckner & Petersen 1996). By this account, successful performance on tests of declarative memory in patients with frontal damage presumably reflects the utilization of alternate retrieval mechanisms mediated by intact structures. Findings from studies of normal human aging, reviewed in the next section, are consistent with this proposal.

Psychological Functions of Frontal Lobe Systems in Normal Aging: Human Beings

Although deficits in declarative memory are frequently observed in the elderly, older subjects exhibit a variety of impairments that would not be anticipated as a consequence of dysfunction restricted to the medial temporal lobe. Many of the most prominent and consistent signs of age-related cognitive decline in-

stead occur in the information-processing capacities traditionally associated with the prefrontal cortex (for recent reviews, see Rapp & Heindel 1994, Shimamura 1994). For example, normal elderly individuals have difficulty remembering the source of acquired information (Janowsky et al 1989b, McIntyre & Craik 1987, Naveh-Benjamin & Craik 1995), even under circumstances where explicit recollection of target items is relatively intact (Dywan et al 1994, Glisky et al 1995). Source memory deficits can also predict performance on other tests of frontal lobe function, which suggests that a common neurobiological basis may underlie these impairments (Craik et al 1990, Glisky et al 1995; but see Spencer & Raz 1994). A further parallel with the effects of frank frontal lobe damage is that memory for temporal order appears particularly susceptible to decline as human beings age (Daigneault & Braun 1993, Parkin et al 1995).

It is noteworthy that certain impairments associated with the function of prefrontal cortex emerge relatively early in the life span, during middle-age, and are unrelated to the status of encoding and retrieval processes that support normal declarative memory. Moreover, when age-related impairments that resemble both medial temporal and prefrontal dysfunction coexist in the same persons, these cognitive deficits may be somewhat dissociable. A particularly interesting report relevant to this point studied healthy aged individuals between the ages of 65 and 87 years (Glisky et al 1995). Two factors were obtained in a factor analysis of the neuropsychological test data. Tests traditionally viewed as assessing the status of prefrontal cortex (e.g. Wisconsin Card Sorting) loaded onto one factor, whereas assessments of declarative memory sensitive to medial temporal lobe status (e.g. paired associates, delayed cued recall) loaded strongly onto a second factor. A subsequent study of item and source memory showed a double dissociation among these elderly individuals that corresponded with their relative functioning on medial temporal lobe and prefrontal assessments, respectively. In addition to suggesting that there is not necessarily an obligatory relationship in the effects of aging across different information processing domains, these data suggest that the underlying biological alterations that cause decline in medial temporal lobe- and prefrontal cortex–dependent functions may occur somewhat independently.

In agreement with the neuropsychological assessments of aged human beings noted above, assessment of the neurobiological status of the prefrontal cortex indicates its susceptibility to age-related decline. Cortical atrophy during normal human aging is especially pronounced in the frontal lobe, progressing at a rate greatly exceeding atrophy observed in the cerebral hemispheres as a whole (Coffey et al 1992). Measurements of regional cerebral blood flow under a variety of testing conditions also provide an indication of diminished function. One of the principal findings to emerge from this approach is that

task demands sufficient to produce prefrontal cortical activation in young subjects fail to increase activity in this same region in older adults (Grady et al 1995). Neuroimaging has also localized different patterns of activation coincident with efforts to retrieve information, relative to activity induced by the conscious recollection of target items (Schacter et al 1996). In young subjects, retrieval efforts are accompanied by significant activation in anterior aspects of the frontal lobe, but a more posterior frontal region is activated in aged subjects under the same testing conditions. No age difference, in contrast, was observed during the successful recollection of target information, which predominantly engages medial temporal lobe structures. The interesting implication of these results is that when recollection is not readily achieved, young and aged subjects may use different retrieval strategies, mediated by distinct prefrontal processing systems. Independent of the validity of this particular hypothesis, it is evident that abnormalities in the activation of prefrontal cortex occur in relation to cognitive aging.

Psychological Functions of Frontal Lobe Systems in Normal Aging: Animal Models

The development of a nonhuman primate model of normal cognitive aging has revealed a number of interesting parallels with findings in human beings. Deficits on delayed response tests of short-term memory are among the most conspicuous and well characterized signs of behavioral decline in the aged monkey (Bartus et al 1978, Dean & Bartus 1988). In the standard delayed response task, a reward, placed in one of two locations, is retrieved by the monkey after a varying delay. There is compelling evidence, however, that the delayed response deficit is not necessarily symptomatic of a general memory impairment of the type that results from damage to the medial temporal lobe. For example, aged monkeys with pronounced delayed response deficits often perform normally on standard tests of recognition memory (i.e. delayed nonmatch-to-sample) and on a variety of other procedures that are sensitive to medial temporal lobe lesions (Bachevalier et al 1991, Rapp & Amaral 1989). In addition, delayed response impairments emerge relatively early in the life span, preceding the decline in memory abilities that require the functional integrity of the medial temporal lobe (Bachevalier et al 1991). Consistent with conclusions from human research discussed in the prior section (Glisky et al 1995), these findings emphasize that age effects are not uniform across different information-processing domains, and that medial temporal lobe dysfunction alone may fail to account for certain key features of cognitive aging in nonhuman primates (for recent reviews, see Dean & Bartus 1988, Rapp 1995).

A number of the behavioral impairments observed in aged monkeys appear to reflect a decline in memory-related processes mediated by the prefrontal

cortex (Dean & Bartus 1988, Rapp 1995). In this context, a noteworthy aspect of standard delayed response testing is that it makes substantial demands on memory for temporal order. This is a consequence of the procedural arrangement in which a reward is hidden randomly, across trials, among a relatively small number of possible locations. Accurate performance therefore requires memory for the location baited most recently, and the ability to discriminate the current trial from information presented earlier in testing. Standard delayed response testing also incorporates an explicit spatial component that is thought to specifically engage processing functions of the dorsolateral prefrontal cortex (Wilson et al 1993). Consistent with the view that delayed response deficits reflect prefrontal cortical decline, aged monkeys exhibit deficits on other tasks as a function of demands on temporal ordering (Rapp & Amaral 1989). Increased perseveration is also observed in aged nonhuman primates (Anderson et al 1993, Bartus et al 1979), similar to effects seen in aged human beings (Janowsky et al 1989b), and qualitatively resembling the difficulties young subjects with frontal lobe damage display in modifying behavior under conditions of shifting task contingencies (Janowsky et al 1989a).

A unified perspective on the functional organization of the prefrontal cortex that accommodates results from both rats and primates has yet to be achieved. Nonetheless, studies of aged rats have noted a number of qualitative similarities with the behavioral effects of frontal lobe damage in young adult rats. In a direct comparison of this type, Winocur (1992) evaluated delayed nonmatch-to-sample performance in young and aged groups, and in young rats with lesions of either the prefrontal cortex or dorsal hippocampus. The sample stimulus in this operant procedure consisted of a panel light that was illuminated at one of two intensities. During the recognition phase of each trial, reward was contingent on the rat's committing or withholding a lever response (i.e. "go," "no-go") depending on whether a matching or nonmatching light intensity was presented. Similar to delayed response testing in monkeys, the opportunity for intertrial interference is substantial in this procedure, and successful performance requires animals to distinguish between the current sample and the same items presented in earlier trials. Aged rats, and young rats with prefrontal cortical lesions, displayed substantial acquisition deficits under conditions where no delay was imposed between the sample presentation and recognition test. In contrast, young rats with hippocampal lesions acquired the task at a normal rate. These findings broadly parallel results in monkeys and human beings, consistent with the view that the temporal organization of memory is significantly disrupted in the aged rat. Qualitative similarities in the effects of aging and direct prefrontal cortical damage have also been noted in studies using other behavioral testing procedures (Winocur 1991, Zyzak et al 1995).

Neurobiology of Aging in Frontal Lobe Systems

Compared with the research on the medial temporal lobe system reviewed above, only limited experimental attention has focused on defining the neurobiological consequences of prefrontal cortical aging. Recent neuroimaging, however, has revealed that metabolic activity in the monkey prefrontal cortex declines with age, and interestingly, that variability among aged subjects is substantially greater than among young animals (Eberling et al 1995). On this basis, it is tempting to speculate that individual differences in metabolic activity might predict the status of cognitive processes mediated by the prefrontal cortex. Preliminary findings from a study combining functional neuroimaging and delayed response assessment in the same subjects suggest that this may be the case (Roberts et al 1996).

Changes in the structural integrity of the prefrontal cortex are currently under examination as a possible basis for age-related cognitive decline. Consistent with a growing body of evidence indicating that neuron number is generally preserved during normal aging in the medial temporal lobe cortical structures (Rapp & Gallagher 1996, Rasmussen et al 1996, West 1993, West et al 1993; and see section on "Neurobiology of Aging in the Medial-Temporal Lobe"), Peters et al (1994) failed to observe any age-related decline in neuron density in the dorsolateral prefrontal cortex. A subjective scoring of white matter pathology in the same subjects, however, revealed prominent age effects, with the greatest degree of change apparently observed among aged monkeys that were most impaired on standard tests of learning and memory. Subtle age-related alterations in other morphological parameters have also been noted, including a decline in the dendritic arborization of prefrontal cortical neurons (Cupp & Uemura 1980). Providing an additional parallel with studies of the medial temporal lobe, structural features in the prefrontal cortex are relatively intact, with possibly greater alterations in neuropil and connectivity as opposed to frank neurodegeneration of cortical neurons.

Compared with the relatively preserved structural features of prefrontal cortex, considerable evidence points to a substantial impact of age on subcortical systems that project to cortex. In addition to the cholinergic neurons in the basal forebrain system, several collections of monoamine neurons in the brainstem appear to undergo significant degeneration and/or atrophy during aging (DeKeyser et al 1990, Irwin et al 1994). In young subjects, systemic pharmacological manipulations of noradrenergic and dopaminergic function significantly influence spatial and temporal aspects of memory, and at least some of these effects appear to be mediated at the level of cortical projection targets in the frontal lobe (Murphy et al 1996). These normative findings, then, lead to the expectation that age-related alterations in neurochemically defined subcor-

tical projection systems might significantly disrupt information processing functions dependent on the prefrontal cortex.

Concerning the function of prefrontal cortex, considerable evidence indicates that age-related alterations in its dopaminergic innervation may be particularly important. This interpretation is consistent with electrophysiological results demonstrating that application of dopamine receptor antagonists can modulate the memory-related firing properties of single prefrontal cortical neurons (Williams & Goldman-Rakic 1995). Research addressing the neurochemistry of aging in the monkey indicates that endogenous dopamine concentrations are markedly reduced in the prefrontal cortex and that this decline is substantially greater than that observed in other cortical regions (Goldman-Rakic & Brown 1981, Wenk et al 1989). In addition, Luine et al (1990) observed that during aging in the rat, a dopamine deficiency in the frontal cortex was significantly correlated with impaired working memory performance on a radial maze. Although dopamine agonist administration in young subjects can affect a variety of behavioral domains including motor function, effects of dopaminergic agents in aged monkeys are selectively attenuated on tasks that require the functional integrity of the prefrontal cortex, such as the standard delayed response task (Arnsten et al 1995). Combined with a substantial body of earlier research (reviewed in Arnsten 1993), these findings raise the possibility that alterations in subcortical systems, such as the mesocortical dopaminergic neurons, might contribute to certain aspects of cognitive aging by disrupting the information processing functions of cortical target regions in the frontal lobe. This area of research also supports the broader theme, developed throughout this review, that cortical and subcortical brain systems are differentially sensitive to the neurobiological consequences of normal aging. The neurodegeneration often associated with brain aging appears to be more characteristic of certain subcortical systems that innervate forebrain structures than of cortical neurons themselves.

AGING AND ATTENTION IN HUMAN BEINGS AND ANIMAL MODELS

As noted in the preceding sections, certain effects of aging on cognition resemble, in mild form, damage to systems in the forebrain, including the medial temporal lobe and prefrontal cortex, for which a substantial background of neuropsychological research exists. Furthermore, neurobiological studies are beginning to provide an understanding of alterations in the brain that are most likely to serve as a basis for cognitive decline in functions associated with those systems. Alongside these areas of research, interest in the study of attention in aging has grown in recent years.

Attention refers to multiple component functions that are important in the selection and processing of information. The study of attention in aging is currently benefiting from advances in cognitive neuroscience that are providing a better definition of the neural systems that are critical for the normal regulation of attention. For example, these include systems that regulate overall levels of sustained attention (arousal or vigilance) and systems that are important for the selective processing of information among competing inputs. Sustained attention can be assessed in settings that require performance of a simple task without the subject losing track of the task objective, a function that appears to be little affected by aging (Albert & Moss 1996). In contrast, other evidence points to an effect of aging on the selective processing of information, particularly under conditions of competition among many items for processing resources (Greenwood et al 1993, Mouloua & Parasuraman 1995).

As recounted in the chapter in this volume on "Central Cholinergic Systems and Cognition" (Everitt & Robbins 1997), a role in the regulation of attention may represent the primary function of the basal forebrain cholinergic neurons that innervate cortex. Furthermore, a growing consensus now views the neurodegeneration within this system that occurs in aging, and to a more severe degree in Alzheimer's disease, as providing a basis for deficits in attention rather than underlying a decline in memory processes (Parasuraman & Haxby 1993).

The cholinergic neurons in the basal forebrain that provide widespread innervation of the cortex in rats, monkeys, and human beings are located posterior to the cholinergic neurons in the basal forebrain that target the hippocampal formation (Koliatsos et al 1990). Previous studies have revealed deficits in attention as a consequence of lesioning the area of the basal forebrain that supplies cortical cholinergic innervation. In one well-studied paradigm, such lesions interfere with the ability of rats to detect and respond to a briefly presented target stimulus that can appear in any of several locations (five-choice reaction time task) (Muir et al 1994, Robbins et al 1989). Those lesions decrease the accuracy of performance, an effect that can be overcome by increasing the target duration, which suggests that the impairment is attentional in nature. Impairments in the ability of aged rats to detect targets in the five-choice reaction time task that resemble the effects of basal forebrain lesions in young rats have recently been reported (Jones et al 1995). Another paradigm, a spatial cueing task originally designed for studies of attention in human beings, has also shown sensitivity to lesions of the basal forebrain in monkeys (Voytko et al 1994). Although the lesion methods used in this line of research with laboratory animals, until recently, have been relatively nonselective, removing both cholinergic and noncholinergic neurons in the basal fore-

brain, studies using a selective immunotoxin for cholinergic neurons have successfully produced deficits in attention when the cortical cholinergic projections are removed (Chiba et al 1995a,b).

The role of the basal forebrain cholinergic system in attention may extend to the component of this system that provides innervation of the hippocampal formation. As noted in an earlier section of this review, removal of those neurons with the selective immunotoxin fails to reproduce deficits in spatial tasks that are readily observed in aged rats (Baxter et al 1995a). In the chapter by Everitt & Robbins, the effects of less selective lesions are cited as evidence that the septohippocampal cholinergic system plays a role in memory. However, whether any substantial deficit in memory is observed with selective removal of these cholinergic neurons has yet to be demonstrated. In contrast, young rats with selective immunotoxic lesions of the cholinergic neurons that project to the hippocampal formation do have a marked impairment in a task in which attentional processing is modified in intact young rats (Baxter et al 1995b). The task involves repeated exposure to a cue that is subsequently used as a conditioned stimulus in associative learning. Preexposure to the cue usually retards subsequent learning, a phenomenon referred to as latent inhibition. Although more than one psychological explanation of latent inhibition has been offered, a number of explanations converge on the concept that decrements in attention to, or processing of, the preexposed cue serve as a basis for latent inhibition. In this context it is notable that either selective damage to the hippocampus (Han et al 1995) or selective removal of the cholinergic projection to the hippocampus impairs latent inhibition in rats (Baxter et al 1995b). The concept that a latent inhibition deficit might exist in aged rats because of diminished function of the cholinergic projection to the hippocampus has not yet been tested directly. It is interesting to note, however, that a recent study showed that information encoding of neurons in hippocampus in young rats will become unresponsive to cues that are not reliable features of a spatial environment, an effect not seen to the same extent in aged rats (Tanila et al 1996). Thus, apparently the selection of information that is subject to processing and encoding by hippocampal neurons is altered during aging in a manner that might be predicted from the effects of removing cholinergic neurons in young rats.

CONCLUSION

As information accumulates about the alterations that occur during aging in the brain, it becomes increasingly clear that a number of different types of changes can be identified in different neural systems. Moreover, the severity of age-related changes in particular brain systems often coincides with the extent of decline in cognitive functions associated with those systems. Certain evidence

has also indicated that heterogeneity in the effects of aging may exist in different cognitive domains and neurobiological systems. All these lines of evidence suggest that aging is not a global process, a conclusion that can be applied to the information derived from animal models as well as human studies.

In those cases where comparisons can be made across studies of human beings and laboratory animals, an important insight into the neurobiology of aging is emerging. Research using advanced stereological methods indicates that neuron loss is not characteristic of cortical systems, including the hippocampus, but that neurodegeneration does affect distinct populations of subcortical neurons that provide cortical innervation. Apart from such structural features of the brain, other aspects of functional integrity are also affected during aging. Although many of the detailed analyses available from studies of animal models have yet to be extended to studies of human brains, neuroimaging research provides support for the concept that processing within the existing circuits of the brain can be compromised during aging.

The comparison of functional analyses across species, including neuroimaging research with human beings, highlights the need to advance new models for understanding the neurobiological basis of cognitive alterations that occur late in life. Aging differs from many conditions involving brain damage, which neuropsychological studies were originally intended to address. Animal models for those conditions frequently entail the virtual destruction of a brain system to test hypotheses about the underlying substrate for cognitive functions of interest, e.g. the medial temporal lobe and declarative memory. During normal aging, in contrast, substantial structural integrity is preserved over the entire life span, and neurons that do exhibit appreciable neurodegeneration, such as those in the basal forebrain cholinergic system, are by no means eliminated. For this reason, lesion models may have limited utility for capturing the performance of neural systems in the aged brain, in which considerable remodeling occurs and a variety of functional alterations within the existing systems can be detected (Gallagher et al 1994).

Finally, the theme of individual differences in aging is well supported by studies of laboratory animals, including behavioral models developed for their sensitivity to memory functions subserved by the medial temporal lobe. Moreover, individual differences in behavioral capacities within these models often correlate with the severity of neurobiological alterations in the relevant brain systems. These lines of research give credence to the concept that age-associated memory decline in human beings can reflect a normal aging process, as distinct from a preclinical condition that heralds dementia. An understanding of the basis for individual differences in the effects of aging is likely to be advanced by further studies on the neurobiology of aging using animal models

as an important adjunct to the study of human beings. In this endeavor, it will be particularly important to determine the factors that distinguish those aged individuals that maintain preserved function from those that experience decline, an undertaking that will benefit from the bridges that can be formed between human beings and the study of aging in well-developed animal models.

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