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FUNCTIONAL AND NEUROBIOLOGICAL SIMILARITIES OF AGING IN MONKEYS AND HUMANS

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ABSTRACT

Aging in humans may be accompanied by alterations in several functional abilities. However, there is a great deal of individual variability in the functions that may be altered with age within and across aged people. One potential source of age-related behavioral variation may lie in a differential vulnerability of neurobiological systems to the aging process in particular individuals. Aged monkeys demonstrate behavioral and brain alterations that have many parallels with those observed in aged humans and are valuable animal models in which to investigate the interrelationships between age, behavior and neurobiological measures. This review outlines the similarities of functional and neurobiological aging in monkeys and humans, notes the variability that exists in both behavioral and neural systems in aging, and identifies some of the areas of aging that are in need of further investigation.

KEY WORDS: monkeys, aging, learning, memory, attention, motor skills, neurotransmitters, morphology, pharmacology

INTRODUCTION

There is considerable evidence that several functional abilities may be altered with normal aging of humans, including aspects of learning, memory, attention and motor skills (Welford, 1982; Plude & Hoyer, 1985; Poon, 1985; Albert, 1988; Craik & Jennings, 1992; Hartley, 1992). However, not all aged individuals necessarily will demonstrate alterations in functional abilities. Moreover, within a given aged individual, not all functional abilities may be equally compromised. The reasons for this heterogeneity with age are unclear. One potential source of age-related behavioral variation may lie in a differential vulnerability of neurobiological systems to the aging process. However, the regional distribution of neural changes in normal aging or the relationship of these neural changes to behavioral impairments have not been well analyzed and can be problematic to investigate in humans.

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In view of the limitations of determining the neural basis of age-associated functional impairments in humans, numerous animal models have been employed to pursue these analyses. Aged rhesus monkeys have proven to be a very valuable animal model in which to study the functional and neurobiological effects of the aging process as they demonstrate behavioral and brain alterations that have many parallels with those observed in aged humans. This review outlines the similarities between functional and neurobiological aging in monkeys and humans, notes the variability that exists in both behavioral and neural systems in aging, and identifies some of the areas of aging that are in critical need of further investigation.

Functional Aging

One of the first reports of the effects of normal aging on learning in monkeys appeared in 1962 (Fletcher & Mowbray, 1962). Since that time, numerous behavioral studies of aged monkeys have identified several functional domains that are compromised by age. Not surprisingly, there are some functions that appear to remain intact in aged monkeys. Moreover, recent studies note that individual variation in functional abilities also can be found in aged monkey populations as has been reported in aged humans. The following sections discuss the alterations in learning, flexibility, memory, attention and motor skills that have been discovered in aged monkeys and the parallels that they have with observations made in aged humans.

Learning. There are numerous studies that have demonstrated impairments in learning new information in aged humans (Poon, 1985; Shimamura, 1990; Craik & Jennings, 1992). Acquisition of new information has been examined in the majority of studies of elderly humans by presenting the individual with some information to learn and then measuring the recall or recognition of this information after some delay. Aged monkeys demonstrate difficulties in initially acquiring the strategies required to perform similar complex memory tasks (e.g., delayed response and delayed nonmatch-to-sample, see below) (Presty et al., 1987; Moss et al., 1988; Rapp and Amaral, 1989; Voytko, unpublished observations). However, in general, acquisition of new information has been assessed in aged monkeys primarily with the use of discrimination tasks. In one version of this task, a pair of stimuli (objects, patterns, colors or spatial location) is simultaneously presented to the subject until the subject is consistently responding to

the stimulus that is associated with delivery of a reward. In a majority of studies, groups of aged monkeys did not take longer to learn this type of information than young monkeys regardless of the stimulus classification (Bartus et al., 1979; Arnsten & Goldman-Rakic, 1985a; Moss et al., 1988; Rapp, 1990; Bachevalier et al., 1991; Lai et al., 1995). Although group means were not significant in these studies, within several of the groups of aged monkeys there were some monkeys that were demonstrating greater difficulty in the learning of visual discriminations than the other aged monkeys. In contrast to these studies, a group of aged monkeys in my laboratory have demonstrated significant impairments in learning object discriminations compared to young monkeys (Voytko, 1993). Interestingly, on a subsequent pattern discrimination, and with additional numbers of aged subjects, only a subset of the group of aged monkeys demonstrated significant learning deficits compared to the young monkeys (Voytko, unpublished observations). The remaining subset of aged monkeys were not significantly different in learning the pattern discrimination from the young monkeys, but were significantly better than the impaired group of aged monkeys.

There are several reasons to explain why impairments in learning visual discriminations were observed in my colony of aged monkeys and not in previously reported aged monkey populations. For example, aged monkeys in all but one (Moss et al., 1988) previous study of learning had been exposed to more demanding memory tasks such as delayed nonmatching-to-sample or delayed response prior to assessment of visual discrimination learning. The prior training and testing on these memory tasks may have influenced subsequent learning of visual discriminations. In contrast, the monkeys in my study were behaviorally naive at the start of visual discrimination assessments. Additionally, the larger number of aged subjects (n=12 vs n=5-6 in other studies) and the greater age of the monkeys involved in my study (28-34 years old vs 18-28 years old in other studies) also may have been factors contributing to the observation of impairments and the ability to detect significant individual differences in learning.

The effects of interference on learning ability have been assessed in aged monkeys with the use of a concurrent visual discrimination task in which several visual discriminations are learned more or less simultaneously. Learning under these conditions was disrupted in aged monkeys (Bachevalier et al., 1991; Bakner & Treichler, 1993). Although data from an additional study of this issue were interpreted to suggest no impairment of acquisition of concurrent discrimination problems by aged monkeys (Medin et al., 1973), the discrepancy between studies may be explained by the procedural properties that were used to define acquisition and retention measures (Bakner & Treichler, 1993). In particular, Medin et al. (1979) interpreted an impairment following a 24 hour delay as a retention deficit, whereas Bakner and Treichler (1993) interpreted a similar impairment as an acquisition deficit.

Flexibility. Reductions in cognitive flexibility, i.e. the ability to shift from one strategy of problem solving to another, occur with advanced age in humans (Botwinick, 1978). Reductions in flexibility also have been observed in some aged monkey populations. The reversal learning problem has been used to assess this functional construct in monkeys. In this task, the subject first learns a visual discrimination. Following this original learning, the reward contingencies of the stimuli are reversed so that now the previously unrewarded stimulus becomes the rewarded stimulus and vice versa. Thus, the subject must unlearn the original stimulus-reward association and learn a new one.

Although the findings from studies of reversal learning in aged monkeys may seem contradictory at first, in general the results do support the notion that reductions in flexibility exist in aged monkey populations. For example, impairments in performing reversals of pattern discriminations have been reported in some studies of aged monkeys (Bartus et al., 1979; Voytko, 1993) but not others (Rapp, 1990). Similar conflicting reports have been made regarding object reversals (Davis, 1978; Rapp, 1990; Voytko, 1993; Lai et al., 1995) and spatial reversals (Voytko, 1993; Lai et al., 1995). Again, prior behavioral testing experience may have influenced the outcomes in several of these investigations. Specifically, prior experience in performing a delayed response task in which reward is provided for returning to a previous location may have established a particular response strategy that may have been difficult to overcome in performance of reversals in which reward is provided for switching to a different stimulus (Bartus et al., 1979). Conversely, most recent experience in performing a delayed nonmatching-to-sample task in which reward is provided for approaching a new stimulus may have favored reversal learning performance in aged monkeys (Rapp, 1990; Lai et al., 1995). Regardless of the specific conflicting findings, overall these studies still emphasize the fact that aged monkeys may not be as flexible in shifting their strategies as younger monkeys. Thus, prior behavioral exposure to a particular task by aged monkeys may encourage development of certain strategies to solving problems that may either enhance or diminish performance on subsequent behavioral tasks that may depend upon either similar or novel strategies for success.

Although prior behavioral experience was not a confoundment in my reversal study (Voytko, 1993), there is a possibility that an order effect amongst reversal problems was present as deficits were observed in object and pattern reversals but not subsequent spatial reversals. These results were initially interpreted as potentially indicating that the type of information being processed may be of importance in reversal learning. However, a recent study found that spatial reversal learning was impaired in a group of aged monkeys (Lai et al., 1995); although a subset of aged monkeys performed within the range of young monkeys by the second spatial reversal in that study. Additional studies

will be needed to clarify the issue of modality specificity and prior behavioral experience on reversal learning in aged monkeys.

Memory. A great deal of research has focused on age-associated impairments in memory as alterations in memory are clearly the most significant symptom of cognitive decline noted by aged humans. Many types of memory can decline with age including memory for verbal and nonverbal items, recall and recognition (see reviews in Poon, 1985; Craik & Jennings, 1992; Kausler, 1994). Despite the evidence of memory failure with age, there are marked individual differences in memory performance among aged people (Craik et al., 1987; West et al., 1992; Morse, 1993; Zelinski et al., 1993). Moreover, there is evidence that memory can be improved in aged people with practice and training (Ciocon & Potter, 1988; La Rue, 1992). As is discussed below, aged monkeys share many of these phemonena with aged people.

Spatial memory was one of the first types of memory to be examined in aged monkeys with the delayed response task (DR). In this task, recent memory for spatial information is assessed by cueing the animal to observe a spatial location during a cue phase of a trial. After some delay, two or more spatial locations may be shown to the animal and the correct strategy is to respond to the same location that was presented in the cue phase. Numerous studies have demonstrated that older monkeys have significantly greater difficulty remembering spatial information as delays are increased in the DR task (Medin, 1969; Bartus et al., 1978; Marriott & Abelson, 1980; Rapp & Amaral, 1989; Bachevalier et al., 1991; Voytko, 1993). Parallel impairments in delayed memory for spatial location have been reported in aged humans on a similar delayed spatial recognition task in which the subjects must remember which room of a house had been illuminated (Flicker et al., 1984). There is potential for considerable proactive interference in the DR task and an increased sensitivity to interference found in aged monkeys is thought to contribute to their impairments in DR (Bartus & Dean, 1979).

Despite the overwhelming data that support the notion that spatial recent memory is impaired with age in monkeys, there is evidence to suggest that spatial memory can improve with practice in aged monkeys and that not all aged monkeys have deficits of spatial memory. For example, aged monkeys showed considerable improvements in correct responding at long delays with repeated exposure to DR (Marriott & Abelson, 1980; Davis et al., 1982). Similar observations have been made in my own laboratory. In a study in which I was determining the appropriate delays to use in a DR task to obtain an accuracy function that ranged from 100% - 65% correct, I found that aged monkeys continued to improve in their accuracy with repeated practice over 5 months so that the delays continually had to be lengthened to maintain a 65% accuracy level at the longest delay (Voytko, unpublished observations). Furthermore, some aged monkeys may learn and perform DR at levels that are comparable to young monkeys. For example, Rapp & Amaral (1989) reported that 2 aged monkeys outperformed all of the young monkeys in learning DR, 2 aged monkeys took longer to learn than any of the young monkeys, and 1 aged monkey achieved learning criterion within the range of scores for the young group of monkeys. In a study by Bachevalier et al. (1991), some aged monkeys failed to learn DR while others did achieve learning criterion. Moreover, some aged monkeys are capable of performing as accurately as young monkeys across a series of delays ranging from 0-30 sec (Bachevalier et al., 1991; Voytko, unpublished observations).

Visual recognition memory has been examined in aged monkeys with the delayed nonmatching-to-sample task (DNMS) that uses a similar procedure to DR except that the correct strategy is to respond to the novel stimulus rather than the familiar stimulus. In contrast to the delay-dependent impairments in DR accuracy of aged monkeys, the majority of studies examining DNMS performance of aged monkeys have reported only general impairments that were related to age or delay alone (Presty et al., 1987; Moss et al., 1988; Rapp & Amaral, 1989). Interestingly, the interaction between age and delay was not significant in these studies indicating that the aged monkeys were not disproportionately affected by the increased demands on memory. These findings in aged monkeys are in agreement with delayed matching-to-sample performance by aged humans (Oscar-Berman & Bonner, 1985; Albert & Moss, 1992). Moreover, studies of aged people suggest that the rate of forgetting may not be impaired if older subjects initially learn the material to the same level of proficiency as younger subjects (Petersen et al., 1992). Although rate of forgetting over a 24 hour interval during four days of acquisition of concurrent visual discriminations was found to be impaired in aged monkeys (Medin et al., 1973), if aged monkeys are initially trained to criterion on a task, retention may not be impaired (Davis, 1974, pp. 170-173; Bakner & Treichler, 1993). Thus, some aged people and aged monkeys may require more time to learn certain types of information but their rate of forgetting this information may be comparable to that of young subjects.

It seemed curious that the type of memory assessed by DNMS should be spared by the aging process in monkeys when spatial memory was so sensitive to increased age. Closer examination of visual recognition memory of aged monkeys revealed two important points. Firstly, although memory of aged monkeys was not impaired when the standard version of DNMS was used in which a different pair of objects appeared as stimuli on each trial (trial-unique version), significantly greater difficulty with increasing delays was observed when the same pair of objects appeared as stimuli on each trial (repeated-object version of DNMS) (Rapp & Amaral, 1989). It was reasoned that memory of aged monkeys

was impaired on the repeated-object DNMS because this version of the task involved temporal memory requirements related to performing a recency discrimination; subjects must remember which of two objects was most recently presented in order to respond correctly (Rapp & Amaral, 1989). Alternatively, it was proposed that an increased sensitivity to interference associated with using the same pair of objects on every trial could explain the greater memory impairment of aged monkeys in repeated-object DNMS, as aged monkeys demonstrated a hypersensitivity to interference in DR studies (Bartus & Dean, 1979). Secondly, in each of these DNMS studies of aged monkeys, performance was not homogeneous but the small sample sizes precluded closer examination of the greater variability of performance among aged monkeys. This individual variation of DNMS performance of aged monkeys was investigated further in a separate study of nine aged monkeys (Rapp & Amaral, 1991). As a group, the aged monkeys were not disproportionately affected by increasing memory demands. However, six of the aged monkeys demonstrated significantly greater difficulty with increasing delays than the young monkeys or the remaining three aged monkeys. This study was the first to specifically examine the issue of behavioral variation of aging in monkeys and served to highlight the fact that greater individual variability occurs in aged monkey populations as had been noted in aged human populations.

Recognition memory of aged monkeys also has been assessed using a delayed recognition span task (DRST). In this task, the subject must respond to the novel stimulus (location, color, object) in an increasing array of familiar stimuli. Aged monkeys are impaired relative to young monkeys on both spatial and color conditions of this task (Moss, 1993). Similar results were obtained in assessing young and aged people on spatial and color versions of DRST (Moss, 1993). Moreover, longitudinal assessments of the aged monkeys revealed marked individual differences where some aged monkeys continued to decline in recognition span, others remained stable, and others improved in their ability (Moss, 1993).

Attention. Several attentional processes decline with age in humans (Schneider et al., 1977; Plude & Hoyer, 1985; Ponds et al., 1988; McDowd & Birren, 1990) and others appear to be relatively unaltered (Hartley et al., 1990; Greenwood et al., 1993). Although several cognitive domains have been examined in aged monkeys, interestingly, attentional processes have not been well investigated. Other than a study by Davis (1974, pp. 164-169), which demonstrated that aged monkeys are more distracted during initial registration of information, the extent to which aging alters attention in monkeys is unknown. Because attentional processing of information controls allocation of information processing resources to incoming stimuli, the integrity of attention processes is an important issue in aged monkeys as deficits in attention could produce behavioral impairments that are unrelated to the specific cognitive demands of the tasks.

We have begun to investigate aspects of attention in aged monkeys in my laboratory. Our initial investigations have focused on visuospatial attention using a peripherally-cued task that was adapted from one developed by Posner (Posner, 1980; Posner & Cohen, 1984). In this task, a peripheral cue identifies the probable location of a target appearing in one of two spatial locations. The cue can be "valid", appearing in the same location as the target, "invalid", appearing in the opposite location as the target, or "neutral", providing no information about the spatial location of the target. Facilitation of processing was determined by having the target appear at different times following the cue (stimulus onset asynchrony). Usually, response times to the target are faster when the target is preceded by a valid cue than when it is preceded by an invalid cue, especially when the target appears shortly after the cue. This increased efficiency in responding to a target following a valid cue (benefits) and decreased efficiency in responding following an invalid cue (costs) is an index of shifting or orienting of attention (Posner, 1980).

This task was chosen for our initial assessments of attention in aged monkeys for two major reasons. Firstly, the aged monkeys in our colony had significant difficulty on DR (Voytko, 1993). In this task, a peripheral cue identifies the spatial location that is to be remembered. An impairment in shifting or orienting attention to a spatial location could impair performance in DR even if mnemonic ability were intact. Thus, it was important to determine if shifting of attention to a peripherally-cued location was impaired in these aged monkeys. Secondly, the efficiency with which attention is shifted to a peripherally-cued spatial location appears to be relatively unaltered with normal aging in humans (Hartley et al., 1990; Robinson & Kertzman, 1990; Folk & Hoyer, 1992; Greenwood et al., 1993; Madden et al., 1994). Because one of our aims in studying aged monkeys is to identify the extent to which functional aging is similar in monkeys and humans, we were interested in determining if shifting of attention to a peripherally-cued location was unaltered with normal aging in monkeys.

In our investigation, aged monkeys demonstrated equivalent proficiency as young monkeys at shifting attention to a peripherally-cued spatial location (Baxter & Voytko, 1996). Both young and aged monkeys had faster reaction times following valid cues and slower reaction times following invalid cues. In general, the costs or benefits associated with attention to the cues were equivalent in young and aged monkeys in three separate experiments. Furthermore, facilitation of processing at the cued location was not affected differentially by age, was most apparent at a stimulus onset asynchrony of 200 msec, and was eliminated at longer asynchrony durations. Our findings in aged monkeys are in direct correspondence with reports of intact orienting of attention in aged humans when examined

with similar peripherally-cued tasks (Hartley et al., 1990; Folk & Hoyer, 1992; Greenwood et al., 1993). In those studies, young and aged subjects were faster in responding to targets following valid cues than following invalid cues and age did not alter the combined costs plus benefits associated with attention to a peripheral cue. Moreover, the time course of facilitation of processing the peripheral cues in young and aged humans were analogous to that of our study of young and aged monkeys (Baxter & Voytko, 1996). Thus, orienting of attention to peripheral cues is preserved with age in humans and monkeys. The extent to which this correspondence is generalizable to other aspects of attention remains to be determined.

Motor Skills. Another function for which little information exists in aged monkeys is that of the integrity of motor skills. Slowed motor responses are commonly observed in older people (Welford, 1982; Spirduso & MacRae, 1990). However, motor performance variability increases in aged human populations (Light & Spirduso, 1990; Spirduso & MacRae, 1990). Complexity of stimulus display and required movements to the stimulus can influence the degree of age-related motor slowing. For example, simple reaction time in which a single movement is made at the appearance of a target can be maintained into old age (Gottsdanker, 1982; Welford, 1982; Stuss et al., 1989; Spirduso & MacRae, 1990). However, age-related differences in reaction time increase as stimulus discriminations and choices increase (Welford, 1982; Light & Spirduso, 1990). Nevertheless, individuals of all ages will improve reaction time with practice (Jordan & Rabbitt, 1977; Light, 1990; Spirduso & MacRae, 1990).

Measures of reaction time or response speed have been assessed directly in only a handful of studies of aged monkeys. The first reports of measures of response time of aged monkeys were from Davis and colleagues (Davis & Ruggiero, 1973; Davis, 1978) who recorded response speeds in a version of a DR task. In this study, the monkeys observed the illumination of 1-4 cells of a 4 x 4 matrix of translucent panels. After a delay, responses were to be made to the previously illuminated cells. Thus, response speeds were recorded as a measure of remembering 1-4 light displays in the matrix. Old monkeys were considerably slower than young monkeys in their response speeds, even when only one cell had been illuminated. Response speed decreased as a function of delay particularly in the old monkeys but was not influenced by pattern complexity. Similar age-related impairments in reaction time of monkeys have been reported recently by Bachevalier et al. (1991). In this study, an illuminated bar was displayed in the center of a touch screen. Following a response to this bar, it disappeared and an identical bar appeared on either the right or left side of the screen. The position of the bar and duration of its appearance was varied from trial to trial. Response latencies, but not number of trials to criterion, were greater in older than young monkeys on this test of reaction time.

In contrast to these studies, we did not find that reaction time was increased with age in monkeys. We recently assessed simple reaction time of aged monkeys using a fairly straightforward task (Baxter & Voytko, 1996). In this task, the monkeys had to release hold of a centrally illuminated screen and respond to a peripherally illuminated side screen ("target"). The target always appeared in the same spatial location and the duration of target appearance was decreased incrementally until the time at which the monkey could no longer make a response while the target was available. Fastest reaction time was defined as the shortest time in which the target could appear and a response made to it. Using this task, we found that the fastest reaction time achieved by aged monkeys was comparable to that achieved by young monkeys. Moreover, the number of trials to achieve the fastest reaction time was equivalent in young and aged monkeys.

The differences between these studies of reaction time in aged monkeys may be explained on the same basis as differences noted in the human literature, i.e., by the complexity of the tasks used to measure reaction time. For example, the DR task used by Davis (Davis & Ruggiero, 1973; Davis, 1978) to assess response speeds (calculated from response latencies) contained mnemonic elements that may have slowed response speeds in the aged monkeys. The task used by Bachevalier et al. (1991) contained an element of uncertainty in terms of where and when the target would appear. There were no mnemonic or unpredictable elements in the simple reaction time task used in our experiment (Baxter & Voytko, 1996). For example, the target appeared in the same location on each trial, the target was present for a stable period of time within a block of trials, and as many trials as was necessary to achieve the individual fastest reaction time possible was provided. Our findings parallel reports that simple reaction time is not increased with age in people when task parameters are kept stable (Gottsdanker, 1982; Stuss et al., 1989; Light, 1990). Additional evidence that impairments in reaction time may not be observed under all testing conditions in aged monkeys comes from a recent investigation in which response latencies were not slower in aged monkeys compared to young monkeys in learning hierarchial relationships (Rapp et al., in press). However, it is clear from studies of aged humans that age effects on reaction time are more striking as task complexity increases. The studies of Davis and Bachevalier suggest that this phenomenon also may occur in aged monkey populations, but further investigations specifically addressing this issue are necessary.

Brain Aging

Neurobiological studies of the changes that occur in the brain with normal advanced age have not kept pace with the concentrated efforts to identify the neurobiological alterations associated with Alzheimer's disease. Moreover, the findings between studies of aging have not been consistent. Nevertheless, the available informa-

tion indicates that the aging primate brain undergoes structural and chemical changes that may underlie the functional alterations noted in aging populations. Many of the age-related brain changes that occur in humans also occur in monkeys. In both instances, these brain changes are not global but tend to be region-specific and sometimes variable. It is this regional specificity and variability that may play an important role in the individual variations in behavior that have been noted with aging in people and monkeys.

Morphology. Early investigations of the brains of aged monkeys reported neuronal loss in the CA1 region of the hippocampus, the principal gyrus and cortical regions 1, 3, and 4 (Ordy, 1975; Brizzee et al., 1980). Subsequent investigations have found that the neuronal loss in hippocampus or neocortical regions may be regionally specific as several hippocampal and neocortical regions do not show a loss of neurons in aged monkeys (Vincent et al., 1989; Tigges et al., 1990; Peters & Sethares, 1993; Peters, 1993; Rosene, 1993; West et al., 1993; Peters et al., 1994). Similar observations have been made in studies of the aged human brain; numerous studies have reported loss of neurons in hippocampus and cerebral cortex (see reviews in Coleman & Flood, 1987 and Kemper, 1994; West, 1993) but several suggest that there is no change in numbers of neurons (Haug, 1984; Terry et al., 1987).

Neuronal loss has been reported in some subcortical structures in aged human brains (e.g. locus coeruleus and substantia nigra) but not in others (e.g. mammillary bodies, dorsal tegmental nucleus) (see review in Coleman & Flood, 1987). The extent of subcortical neuronal loss has not been well investigated in aged monkey brains. Age-related loss of neurons was found in the brainstem nucleus raphe dorsalis and nucleus centralis superior of aged monkeys (Kemper, 1993) and preliminary studies indicate a loss of neurons with age in the substantia nigra and ventral tegmental area of monkeys (Siddiqi et al., 1994; Siddiqi et al., 1995).

Recently, three studies have examined the integrity of the nuclei in the cholinergic basal forebrain complex of aged monkeys. In the medial septal nucleus (Stroessner-Johnson et al., 1992), loss of choline acetyltransferase-positive neurons was observed only at caudal levels but not at rostral levels, while neuronal hypertrophy was marked in rostral levels. This neuronal hypertrophy was present in two aged monkeys that previously had demonstrated impairments on a DNMS task, but was not present in two other aged monkeys that were unimpaired on this task. In the nucleus basalis of Meynert (Voytko et al., 1995), numbers of cholinergic neurons (nerve growth factor receptor p75-positive neurons) were preserved with age across the subdivisions of the nucleus, but the size of basal forebrain neurons was larger overall in the aged monkeys than young monkeys, particularly in the posterior aspects of the nucleus basalis. Partial correlation analyses revealed that increased age was associated with declines in performance on several behavioral tasks independent of cholinergic cell number. However, decreased numbers of cholinergic neurons in the intermediate regions of the nucleus basalis were associated with poorer spatial recent memory on a DR task and difficulty learning concurrent object discriminations independent of age (Voytko et al., 1995). These relationships are consistent with the innervation of lateral prefrontal and lateral temporal cortices by the intermediate regions of the nucleus basalis and the involvement of these brain regions in these behaviors.

In contrast to these basal forebrain studies, a progressive loss of cholinergic (acetylcholinesterase-positive) neurons was observed in the medial septal nucleus, nuclei of the diagonal band of Broca, and the nucleus basalis of Meynert in aged monkeys (Rosene, 1993). The reasons for the discrepancy between this study and the others are not clear as each study used cholinergic markers to identify neurons in the basal forebrain. Similar conflicting reports regarding the integrity of the basal forebrain cholinergic system exist in aged human brains, especially for the nucleus basalis which has been the most well studied. For example, reduced numbers of nucleus basalis neurons were reported in some studies of aged humans (Mann et al., 1984ab; McGeer et al., 1984; Lowes-Hummel et al., 1989; De Lacalle et al., 1991), but not others (Whitehouse et al., 1983; Chui et al., 1984; Bigl et al., 1987). Moreover, age-related increases (De Lacalle et al., 1991) and decreases (Mann et al., 1984ab) in the size of nucleus basalis neurons also have been reported in aged humans. Explanations for the discrepancies between human studies of the nucleus basalis are not evident but do not seem to be related to the ages of the subject or the regions of the nucleus sampled. For example, cell loss was not reported in the anterior or intermediate nucleus basalis in subjects 25-90 years of age in three separate studies (Whitehouse et al., 1983; Chui et al., 1984; Bigl et al., 1987) whereas cell loss was reported in the anterior nucleus basalis in similarly aged subjects of another study (Mann et al., 1984a). One possibility may be related to the fact that all these studies in humans were performed on Nissl-stained preparations. Thus, the inconsistency between these studies may be because neurochemical-specific methods were not employed to identify the cholinergic neurons in the basal forebrain and therefore, the neuronal counts included both cholinergic and noncholinergic neurons in this region.

Dendritic extent appears to be variable and region-specific in people and monkeys. Reports of dendritic growth (Buell & Coleman, 1979, 1981; Flood et al., 1985; Flood et al., 1987), stability (Flood, 1991; Hanks & Flood, 1991) and regression (Scheibel et al., 1975, 1976; Flood et al., 1985; Nakamura et al., 1985; Flood et al., 1987) have been made for aged humans. While dendritic growth in the frontal lobe and subiculum has been observed in middle-aged monkey brains, dendritic regression was observed in older monkeys (Cupp &

Uemura, 1980; Uemura, 1985). Moreover, synaptic density is reduced by almost 20% in the prefrontal cortex of aged monkeys (Uemura, 1980), but only 3% in the dentate gyrus (Tigges et al., 1995).

Biochemistry. Markers of a variety of neurotransmitter systems are reduced with age in humans but these reductions may be neurotransmitter- and region-specific. For example, dopamine concentrations are reduced significantly in the striatum but not in the cerebral cortex or hippocampus (DeKosky & Palmer, 1994). Levels of choline acetyltransferase (ChAT) are decreased in the cortex and striatum but not necessarily in the hippocampus (DeKosky & Palmer, 1994). For the most part, concentrations of norepinephrine or its major metabolite and markers of serotonin are not reduced with age (DeKosky & Palmer, 1994).

Relatively few studies specifically have investigated the integrity of neurotransmitter systems in aged monkey populations. As in aged humans, the changes that have been noted are regional and sometimes variable. For example, while reductions in endogenous levels of dopamine and serotonin were reported in the frontal pole of aged monkeys, they were not found in other prefrontal cortical regions (Wenk et al., 1989). In contrast, another study reported significant drops in levels of dopamine but not serotonin in prefrontal cortex of aged monkeys (Goldman-Rakic & Brown, 1981). Norepinephrine and serotonin levels are reduced in the postcentral gyrus of aged monkeys, while dopamine and norepinephrine levels are reduced in the temporal cortex (Goldman-Rakic & Brown, 1981). However, these neurochemical alterations were not noted in a subsequent study of aged monkeys (Wenk et al., 1989). Similar variability has been reported for monoaminergic levels in striatum (Goldman-Rakic & Brown, 1981; Wenk et al., 1989; Irwin et al., 1994; Gerhardt et al., 1995). Levels of norepinephrine, several markers of serotonergic activity, and neuropeptides were significantly reduced in the occipital lobe but not the posterior cingulate cortex of aged monkeys (Beal et al., 1991). In aged human brains, there is considerable evidence that levels of dopamine decline with age especially in the striatum, however there is little indication of age-related changes in the concentrations of serotonin or norepinephrine (Morgan et al., 1987; McEntee & Crook, 1991; DeKosky & Palmer, 1994).

Measures of cholinergic activity have also been variable across and within studies of aged monkeys and aged humans. Levels of ChAT activity were reduced in the frontal pole and motor cortex, but not in other cortical regions of aged monkeys (Wenk et al., 1989). However, a later study from the same laboratory reported that ChAT activity was not reduced in any cortical region examined (Wenk et al., 1991). Still others report significant declines in ChAT activity as a function of age in several cortical regions (Gorman, 1993). The appreciable degree of variability in levels of ChAT activity that exists between individual monkeys of various ages (Wenk et al., 1989) may account for the discrepancies between studies (Wenk, 1993). In aged humans, reduced levels of ChAT have been reported in frontal, temporal or parietal cortex (Davies, 1978, 1979; McGeer et al., 1984; DeKosky et al., 1985) hippocampus and entorhinal cortex (Davies, 1978, 1979; Perry et al., 1992) and nucleus basalis (Sparks et al., 1992). However, others have found relatively small or no age-related changes in ChAT activity in cortex or hippocampus of people (reviewed in Decker, 1987 and DeKosky and Palmer, 1994).

Neurotransmitter receptors are reduced in aged monkey and human brains, but these alterations may be variable. Age-related decreases in D2 dopamine receptors were found in the caudate and putamen of monkeys, however there was some variability within the aged monkeys (Lai et al., 1987). There is some discrepancy between studies of aged human brains regarding the status of dopamine receptors. For example, declines in D2 receptors have been noted in the basal ganglia of some studies (Severson et al., 1982; Rinne, 1987; Rinne et al., 1990), but not others (De Keyser et al., 1991). Similar inconsistencies have been found with D1 receptors (Morgan et al., 1987; De Keyser et al., 1990ab; Rinne et al., 1990).

There is regional and laminar specificity in the age-related reductions in adrenergic and serotonergic receptors noted in monkeys (Bigham & Lidow, 1995). For example, densities of a1 receptors were decreased in somatosensory cortex, densities of a2 receptors were decreased in prefrontal, motor and somatosensory cortex, 5-HT1 receptors were decreased in somatosensory cortex and 5-HT2 receptors decline in visual and motor cortex of aged monkeys (Bigham & Lidow, 1995). In contrast, no age-related declines were found for adrenergic beta receptors in any brain region of aged monkeys. Reductions in the density of serotonin 5-HT2 also have been described in the frontal pole of aged monkeys (Wenk et al., 1989). These findings in aged monkeys parallel to some extent the observations of adrenergic and serotonergic receptors in aged human brain. For example, decreases in a2 receptors were found in the prefrontal cortex of aged humans (Kalaria & Andorn, 1991) and reductions in binding of several subtypes of serotonergic receptors have been found in a number of cortical and hippocampal regions and in the raphe nuclei with advanced age in humans (Morgan et al., 1987; Dillon et al., 1991; McEntee & Crook, 1991; DeKosky & Palmer, 1994). In contrast to aged monkeys, numbers of beta-1 adrenergic receptors in prefrontal cortex showed a weak negative correlation with age in people (Kalaria et al., 1989).

Muscarinic receptor binding (M1 or M2) is reduced in prefrontal, motor, somatosensory, temporal and parahippocampal cortices of aged monkeys (Wenk et al., 1989; Wagster et al., 1990; Vannucchi & Goldman-Rakic, 1991). Moreover, significant correlations have been noted between individual differences in task performance and muscarinic receptor binding in aged

monkeys. Specifically, M1 binding in the inferior parietal lobe was related to visuospatial abilities and M1 binding in motor cortex was related to reaction time in aged monkeys (Wagster, 1993). Nicotinic binding also is reduced in temporal cortex of aged monkeys (Wenk et al., 1989; Wagster et al., 1990). The data from studies of aged human brains are inconsistent regarding cholinergic receptors. For example, there are some reports of reduced M1 and M2 muscarinic receptors in aged human brains (Nordberg & Winblad, 1986; Decker, 1987; Rinne, 1987; Nordberg et al., 1992), but not in others (Whitehouse & Au 1986; Decker, 1987). Reductions in nicotinic receptors also have been reported in frontal cortex and hippocampus of aged humans (Nordberg & Winblad, 1986; Nordberg et al., 1992).

In concert with studies of aged humans, there are two reports of reduced N-methyl-D-aspartate (NMDA) receptors in aged monkey brain. In particular, NMDA-displaceable l-[^{3}H]glutamate binding sites were significantly reduced in many regions of the frontal and temporal lobes of aged monkeys (Wenk et al., 1991). More recently, a 30% decrease in the dendritic intensity of NMDA, but not non-NMDA, receptor immunofluorescence was noted in the outer molecular layer relative to the inner molecular layer of the hippocampus of aged monkeys but not young monkeys (Gazzaley et al., 1996). These reductions were observed in the presence of intact dendritic area and synaptic density in these hippocampal regions. In agreement with these monkey studies, age-related declines in NMDA receptors have been reported in frontal cortex (Brodmann area 8 or 9) and hippocampus of humans (Kornhuber et al., 1988; Mouradian et al., 1988; Kornhuber et al., 1989; Piggott et al., 1992).

Another means by which the integrity of neurotransmitter systems in aged individuals has been determined, without the need for autopsy material, is through in vivo functional imaging studies using Positron Emission Tomography (PET). Using this technology, several studies have observed significant age-related reductions in human brain in D2 receptors in the striatum (Wong et al., 1984; Antonini et al., 1993; Antonini & Leenders, 1993; Rinne et al., 1993), in D1 receptors in striatum and frontal cortex (Suhara et al., 1991), in serotonin 5-HT2 receptors in frontal cortex (Wong et al., 1984), and in muscarinic receptors in several cortical regions, the striatum, and the hippocampus (Dewey et al., 1990; Lee et al., 1991; Suhara et al., 1993). Until recently, PET methodology has not been used to assess the effects of age on the integrity of neurotransmitter systems in aged monkeys. Currently, my laboratory is in the process of addressing this issue by conducting a series of PET studies to determine the functional activity of the cholinergic system in aged monkeys. For these studies, we are using [^{18}F]fluorobenzyltrozamicol ([^{18}F]FBT) as the cholinergic radiotracer. [^{18}F]FBT has a high affinity and selectivity for the vesicular acetylcholine transporter (Parsons & Rogers, 1993; Parsons et al., 1993; Efange et al., 1994; Efange et al., 1995a). Moreover, binding of this radiotracer is correlated with ChAT activity (Enfange et al., 1995b). Thus, this ligand provides information about the presynaptic functional activity of the cholinergic system. In preliminary PET studies of young and aged rhesus monkeys using [^{18}F]FBT, we have found that the highest uptake of this radiotracer is in the basal ganglia and that the binding of [^{18}F]FBT is significantly reduced in aged monkeys compared to young monkeys. However, we also have found individual differences in the binding of [^{18}F]FBT in aged monkeys, so that binding in some aged monkeys was comparable to that observed in young monkeys.

Regional cerebral metabolic rates for glucose (rCMRglc) also have been investigated recently with PET in aged rhesus monkeys. As a group, aged monkeys demonstrated lowered rCMRglc in the left temporal cortex compared to adult monkeys (Eberling et al., 1995). However, there was a great amount of variability amongst the aged animals so that some individual animals also showed lowered rCMRglc in the other brain regions studied (parahippocampal gyrus, hippocampus, frontal cortex). Declines in rCMRglc with aging of humans have been reported in some studies (Kuhl et al., 1982; Moeller et al., 1996) but not others (DeLeon et al., 1983; Duara et al., 1983; Duara et al., 1984; Yoshii et al., 1988). Several reasons have been postulated to explain the discrepancies between clinical studies of rCMRglc with age including differences in the health of the patients studied, in the resting state of the patients, and in the methods of scan analysis. An alternative possibility is that changes in rCMRglc may be variable enough across aged individuals to diminish the ability to detect specific age-related topographic group differences in rCMRglc in aged human populations, as suggested by the study conducted in aged monkeys (Eberling et al., 1995). Moreover, heterogeneity in level of cognitive functioning within the aged subject population also may contribute to the variability across and within metabolic studies of aged humans and may explain some of the inconsistencies between clinical studies of rCMRglc.

Although PET measures of cerebral glucose metabolism provide information about generalized physiological changes in the brain, the underlying specific neuroanatomical or neurochemical alterations responsible for these physiological changes cannot be determined by this methodology. Nevertheless, measures of cerebral metabolic rates for glucose (or cerebral blood flow or oxygen) can be used as a screening device to guide subsequent PET investigations employing receptor-specific ligands.

The individual differences in cholinergic activity and cerebral glucose metabolic rate of aged rhesus monkeys that are beginning to be revealed by PET serve to emphasize the individual variation that occurs in the neurobiology of the brain of aged monkeys. This neurobiological variability may underlie some of the variations in cognition that we and others have noted in aged rhesus monkey populations. Thus, the variability within and between biochemical studies of aged monkeys may

be due in part to inclusion of mixed populations of monkeys that may be cognitively-impaired and cognitively-intact. Indeed, significant biochemical changes may occur selectively among aged monkeys with cognitive impairments but not in aged monkeys that are cognitively intact, as has been demonstrated recently for morphological measures of neurons in the septal nuclei of aged rhesus monkeys (Stroessner-Johnson et al., 1992). These points highlight the importance of performing behavioral and neurobiological evaluations in the same subjects to clarify the relationship between these measures and their contribution to the variability observed within aged populations.

Pharmacology. Pharmacological approaches have been another fruitful means of determining the neural substrates of cognitive impairments that occur with advanced age and for determining potential therapeutic treatments of memory impairments associated with normal and pathological aging. Aged monkeys have proven to be particularly valuable resources in this research endeavor. Pharmacological enhancement of the cholinergic and catecholaminergic systems can improve some aspects of cognitive function in aged monkeys. For example, Arnsten and colleagues have repeatedly demonstrated that augmentation of the dopaminergic and adrenergic systems will improve spatial recent memory of aged monkeys (Arnsten & Goldman-Rakic, 1985b, 1990; Arnsten et al., 1988; Arnsten & Contant, 1992; Arnsten et al., 1994; Arnsten et al., 1995); although there has been some controversy regarding the enhanced effects produced by the a2 adrenergic receptor agonist clonidine (Bartus & Dean, 1988). Numerous studies have demonstrated that memory or attention can be impaired in young monkeys with the anticholinergic agent scopolamine (e.g., Bartus & Johnson, 1976; Aigner & Mishkin, 1986; Rupniak et al., 1989; Aigner et al., 1991; Callahan et al., 1993) and improved in aged monkeys following treatment with a variety of cholinomimetic drugs, including acetylcholinesterase inhibitors and muscarinic and nicotinic receptor agonists (Bartus, 1979; Bartus et al., 1980; Bartus et al., 1983; Fitten et al., 1988; Buccafusco & Jackson, 1991; Jackson et al., 1995). Several other pharmacological approaches also improve cognitive function of aged monkeys, including the calcium channel blocker, nimodipine (Sandin et al., 1990; LeVere and Levere, 1994) several neuropeptides (Bartus et al., 1982), and combined treatment strategies (Terry et al., 1993). An important caveat to the majority of these studies is that the cognitive improvements have been quite variable and sometimes dependent upon determining the "best dose" of each pharmacological agent for each individual monkey. Similar caveats apply to the improvements in cognitive functioning observed in patients with Alzheimer's disease who have been treated with some of these same pharmacological agents (Christie et al., 1981; Davidson & Stern, 1991; Eagger et al., 1991; Ebmeier et al., 1992; Growdon, 1992). Thus, individual differences in response to these treatments by both aged monkeys and aged humans may diminish the potential for generalized use of these agents to enhance cognitive function in aged or demented human populations. Nevertheless, a great deal of information about the neurobiological substrates of age-related cognitive impairments has been gained from pharmacological studies of aged monkeys.

CONCLUSIONS

Although the intense effort to determine the neural basis of cognitive impairments in Alzheimer's disease has overshadowed to a large part the continuing efforts to understand the development, extent, and neural basis of functional impairments associated with normal aging, there is a considerable base of knowledge about many of the functional changes that may accompany the normal process of senescence in people. In addition, we are cognizant of the variation in behavior that can be present within and across elderly individuals. As this review has identified, there are several parallels between functional aging in humans and functional aging in monkeys. In particular, more recent studies of aged monkeys have noted unique parallels in aspects of learning, memory, attention and motor skills with those of aged humans and have identified variations in behavior in aged monkey populations. However, several other aspects of cognition (e.g., divided attention, choice reaction times) remain to be investigated in aged monkeys to fully realize the correspondence between psychological aging of humans and monkeys.

It is evident that the quantity and depth of neurobiological information that is available about the integrity of brain systems in normal aged humans and monkeys is minimal compared to our knowledge about the psychology of aging. To remedy this situation, a great deal of further investigation is required at all levels of neural circuitry and with a variety of neurobiological approaches, including molecular and functional imaging, to unveil the full complement of structural and neurochemical changes that occur with advanced age in particular individuals. Most importantly, as new neurobiological information becomes available, we need to continue to take advantage of the opportunities to determine the neural substrates of age-related cognitive impairments. Such endeavors require behavioral and neurobiological evaluations to be conducted in the same subject populations. Although difficult to pursue in humans (as few aged people are behaviorally well characterized just prior to death), these studies can be performed in monkeys. Because aged monkeys demonstrate impairments in cognition and exhibit some of the brain changes observed in aged people, these animals will continue to be an extremely valuable resource in which to conduct brain/behavior studies to determine these relationships. Furthermore, the existence of individual differences in the behavior of aged monkeys provides the unique opportunity to continue to explore the interrelationships

between age, cognition and neurobiological measures. Although to date rarely performed in either humans or monkeys, continued efforts along these lines clearly are important as recent studies in monkeys suggest that age alone cannot account for certain impairments in cognition (Voytko et al., 1995). Thus, the continued study of aged monkeys not only will provide information about the neurobiological basis of age-related cognitive impairments, but also will identify unique relationships between neural and behavioral changes that are independent of age and that may underlie the behavioral variation that occurs in aged monkeys and aged humans.

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ABBREVIATIONS

DR	Delayed Response Task
DNMS	Delayed Nonmatching-To-Sample Task
DRST	Delayed Recognition Span Task
ChAT	choline acetyltransferase
PET	Positron Emission Tomography
[^{18}F]FBT	[^{18}F]fluorobenzyltrozamicol

REFERENCES

Aigner, TG, and Mishkin, M: The effects of physostigmine and scopolamine on recognition memory in monkeys. Behav. Neural. Biol., 45:81-87, 1986.

Aigner, TG, Walker, DL, and Mishkin, M: Comparison of the effects of scopolamine administered before and after acquisition in a test of visual recognition memory in monkeys. Behav. Neural. Biol., 55:61-67, 1991.

Albert, MS: Cognitive Function, in Geriatric Neuropsychology, edited by Albert, MS, and Moss, MB, New York, Guilford Press, 1988, pp. 33-53.

Albert, M, and Moss, M: The assessment of memory disorders in patients with Alzheimer disease, in Neuropsychology of Memory, edited by Squire, LR, and Butters, NE, New York, Guilford Press, 1992, pp. 236-246.

Antonini, A, and Leenders, KL: Dopamine D2 receptors in normal human brain: effect of age measured by positron emission tomography (PET) and [^{11}]C-raclopride. Ann. N.Y. Acad. Sci., 695:81-85, 1993.

Antonini, A, Leenders, KL, Reist, H, Thomann, R, Beer, H-F, and Locher, J: Effect of age on D_2 dopamine receptors in normal human brain measured by positron emission tomography and ^{11}C-raclopride. Arch. Neurol., 50:474-480, 1993.

Arnsten, AFT, and Contant, TA: Alpha-2 adrenergic agonists decrease distractibility in aged monkeys performing the delayed response task. Psychopharmacology, 108:159-169, 1992.

Arnsten, AF, and Goldman-Rakic, PS: Catecholamines and cognitive decline in aged nonhuman primates. Ann. N.Y. Acad. Sci., 444:218-234, 1985a.

Arnsten, AFT, and Goldman-Rakic, PS: a_2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science, 230:1273-1276, 1985b.

Arnsten, AFT, and Goldman-Rakic, PS: Analysis of alpha-2 adrenergic agonist effects on the delayed nonmatch-to-sample performance of aged rhesus monkeys. Neurobiol. Aging, 11:583-590, 1990.

Arnsten, AFT, Cai, JX, and Goldman-Rakic, PS: The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes. J. Neurosci., 8:4287-4298, 1988.

Arnsten, AFT, Cai, JX, Murphy, BL, and Goldman-Rakic, PS: Dopamine D_1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology, 116:143-151, 1994.

Arnsten, AFT, Cai, JX, Steere, JC, and Goldman-Rakic, PS:Dopamine D2 receptor mechanisms contribute to age-related cognitive decline: the effects of quinpirole on memory and motor performance in monkeys. J. Neurosci., 15:3429-3439, 1995.

Bachevalier, J, Landis, LS, Walker, LC, Brickson, M, Mishkin, M, Price, DL, and Cork, LC: Aged monkeys exhibit behavioral deficits indicative of widespread cerebral dysfunction. Neurobiol. Aging, 12:99-111, 1991.

Bakner, L, and Treichler, FR: Age differences in the acquisition and retention of concurrent discriminations by monkeys. Anim. Learn. Behav., 21:51-58, 1993.

Bartus, RT: Physostigmine and recent memory: effects in young and aged nonhuman primates. Science, 206:1087-1089, 1979.

Bartus, RT, and Dean, RL: Recent memory in aged nonhuman primates: hypersensitivity to visual interference during retention. Exp. Aging Res., 5:385-400, 1979.

Bartus, RT, and Dean, RL: Lack of efficacy of clonidine on memory in aged cebus monkeys. Neurobiol. Aging, 9:409-411, 1988.

Bartus, RT, and Johnson, HR: Short-term memory in the rhesus monkey: disruption from the anti-cholinergic scopolamine. Pharmacol. Biochem. Behav., 5:39-46, 1976.

Bartus, RT, Dean, RL, and Beer, B: Memory deficits in aged cebus monkeys and facilitation with central cholinomimetics. Neurobiol. Aging, 1:145-152, 1980.

Bartus, RT, Dean, RL, and Beer, B: Neuropeptide effects on memory in aged monkeys. Neurobiol. Aging, 3:61-68, 1982.

Bartus, RT, Dean, RL, and Beer, B: An evaluation of drugs for improving memory in aged monkeys: implications for clinical trials in humans. Psychopharmacology Bull., 19:168-184, 1983.

Bartus, RT, Dean, RL, and Fleming, DL: Aging in the rhesus monkey: effects on visual discrimination learning and reversal learning. J. Gerontol., 34:209-219, 1979.

Bartus, RT, Fleming, D, and Johnson, HR: Aging in the rhesus monkey: debilitating effects on short-term memory. J. Gerontol., 33:858-871, 1978.

Baxter, MG, and Voytko, ML: Spatial orienting of attention in adult and aged rhesus monkeys. Behav. Neurosci., 110:898-904, 1996.

Beal, MF, Walker, LC, Storey, E, Segar, L, Price, DL, and Cork LC: Neurotransmitters in neocortex of aged rhesus monkeys. Neurobiol. Aging, 12:407-412, 1991.

Bigham, MH, and Lidow, MS: Adrenergic and serotonergic receptors in aged monkey neocortex. Neurobiol. Aging, 16:91-104, 1995.

Bigl, V, Arendt, T, Fischer, S, Fischer, S, Werner, M, and Arendt, A: The cholinergic system in aging. Gerontology, 33:172-180, 1987.

Botwinick, J: Aging and Behavior, New York, Springer Publishing Co., 1978, pp. 87-112.

Buccafusco, JJ, and Jackson, WJ: Beneficial effects of nicotine administered prior to a delayed matching-to-sample task in young and aged monkeys. Neurobiol. Aging, 12:233-238, 1991.

Buell, SJ, and Coleman, PD: Dendritic growth in the aged human brain and failure of growth in senile dementia. Science, 206:854-856, 1979.

Buell, SJ, and Coleman, PD: Quantitative evidence for selective dendritic growth in normal human aging but not in senile dementia. Brain, 214:23-41, 1981.

Brizzee, KR, Ordy, JM, and Bartus, RT. Localization of cellular changes within multimodal sensory regions in aged monkey brain: possible implications for age-related cognitive loss. Neurobiol. Aging, 1:45-52, 1980.

Callahan, MJ, Kinsora, JJ, Harbaugh, RE, Reeder, TM, and Davis, RE: Continuous ICV infusion of scopolamine impairs sustained attention of rhesus monkeys. Neurobiol. Aging, 14:147-151, 1993.

Christie, JE, Shering, A, Ferguson, J, and Glen, AIM: Phsyostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. Br. J. Psychiatry, 138:46-50, 1981.

Chui, HC, Bondareff, W, Zarow, C, and Slager, U: Stability of neuronal number in the human nucleus basalis of Meynert with age. Neurobiol. Aging, 5:83-88, 1984.

Ciocon, JO, and Potter, JF: Age-related changes in human memory: normal and abnormal. Geriatrics, 43:43-48, 1988.

Coleman, PD, and Flood, DG: Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. Neurobiol. Aging, 8:521-545, 1987.

Craik, FIM, and Jennings, JM: Human memory, in Handbook of Aging and Cognition, edited by Craik, FIM, and Salthouse, TA, New Jersey, Lawrence Erlbaum Assoc., 1992, pp. 51-110.

Craik, FIM, Byrd, M, and Swanson, JM: Patterns of memory loss in three elderly samples. Psychol. Aging, 2:79-86, 1987.

Cupp, CJ, and Uemura, E: Age-related changes in prefrontal cortex of Macaca mulatta: quantitative analysis of dendritic branching patterns. Exp. Neurol., 69:143-163, 1980.

Davidson, M, and Stern, RG: The treatment of cognitive impairment in Alzheimer's disease: beyond the cholinergic approach. Psychiatr. Clin. North Am., 14:461-482, 1991.

Davies, P: Loss of choline acetyltransferase activity in normal aging and in senile dementia. Adv. Exp. Med. Biol., 113:251-256, 1978.

Davies, P: Neurotransmitter-related enzymes in senile dementia of the Alzheimer's type. Brain Res., 171:319-327, 1979.

Davis, RT: Monkeys as perceivers, in Primate Behavior: Developments in the Field and Laboratory Research, edited by Rosenblum, LA, vol. 3 (whole volume), New York, Academic Press, 1974.

Davis, RT: Old monkey behavior. Exp. Gerontol., 13:237-250, 1978.

Davis, RT, Bennett, CA, and Weisenburger, WP. Repeated measurements of forgetting by rhesus monkeys (*Macaca mulatta*). Percept. Mot. Skills, 55:703-709, 1982.

Davis, RT, and Ruggiero, FT: Memory in monkeys as a function of preparatory interval and pattern complexity of matrix displays. Amer. J. Phys. Anthropol., 38:573-577, 1973.

Decker, MW: The effects of aging on hippocampal and cortical projections of the forebrain cholinergic system. Brain Res. Rev., 12:423-438, 1987.

De Keyser, J, De Backer, J-P, Vauquelin, G, and Ebinger, G: D_1 and D_2 dopamine receptors in human substantia nigra: localization and the effect of aging. J. Neurochem., 56:1130-1133, 1991.

De Keyser, J, De Backer, JP, Vauquelin, G, and Ebinger, G: The effect of aging on the D1 dopamine receptors in human frontal cortex. Brain Res., 528:308-310, 1990a.

De Keyser, J, Ebinger, G, and Vauquelin, G: Age-related changes in the human nigrostriatal dopaminergic system. Ann. Neurol., 27:157-161, 1990b.

DeKosky, ST, and Palmer, AM: Neurochemistry of aging, in Clinical Neurology of Aging, edited by Albert, ML, and Knoefel, JE, New York, Oxford University Press, 1994, pp. 79-101.

DeKosky, ST, Scheff, SW, and Markesbery, WR: Laminar organization of cholinergic circuits in human frontal cortex in Alzheimer's disease and aging. Neurology, 35:1425-1431, 1985.

De Lacalle, S, Iraizoz, I, and Ma Gonzalo, L: Differential changes in cell size and number in topographic subdivisions of human basal nucleus in normal aging. Neuroscience, 43:445-456, 1991.

De Leon, MJ, Ferris, SH, George, AE, Reisberg, B, Christman, DR, Kricheff, II, and Wolf, AP: Computed tomography and positron emission transaxial tomography evaluations of normal aging and Alzheimer's disease. J. Cereb. Blood Flow Metab., 3:391-394, 1983.

Dewey, SL, Volkow, ND, Logan, J, MacGregor, RR, Folwer, JS, Schlyer, DJ, and Bendriem, B: Age-related decreases in muscarinic cholinergic receptor binding in the human brain measured with positron emission tomography (PET). J. Neurosci. Res., 27:569-575, 1990.

Dillon, KA, Gross-Isseroff, R, Israeli, M, and Biegon, A: Autoradiographic analysis of serotonin 5-HT_{1A} receptor binding in the human brain postmortem: effects of age and alcohol. Brain Res., 554:56-64, 1991.

Duara, R, Grady, C, Haxby, J, Ingvar, D, Sokoloff, L, Margolin, RA, Manning, RG, Cutler, NR and Rapoport, SI: Human brain glucose utilization and cognitive function in relation to age. Ann. Neurol., 16:702-713, 1984.

Duara, R, Margolin, RA, Robertson-Tchabo, EA, London, ED, Schwartz, M, Renfrew, JW, Koziarz, BJ, Sundaram, M, Grady, C, Moore, AM, Ingvar, DH, Sokoloff, L, Weingartner, H, Kessler, RM, Manning RG, Channing MA, Cutler, NR, and Rapoport, SI: Cerebral glucose utilization as measured with positron emission tomography in 21 resting healthy men between the ages of 21 and 83 years. Brain, 106:761-775, 1983.

Eagger, SA, Levy, R, and Sahakian, BJ: Tacrine in Alzheimer's disease. Lancet, 337:989-992, 1991.

Eberling, JL, Roberts, JA, De Manincor, D, Brennan, KM, Hanrahan, SM, Vanbrocklin, HF, Roos, MS, and Jagust, WJ: PET studies of cerebral glucose metabolism in conscious rhesus macaques. Neurobiol. Aging, 16:825-832, 1995.

Ebmeier, KP, Hunter, R, Curran, SM, Dougal, NJ, Murray, CL, Wyper, DJ, Patterson, J, Hanson, MT, Siegfried, K, and Goodwin, GM: Effects of a single dose of acetylcholinesterase inhibitor velnacrine on recognition memory and regional cerebral blood flow in Alzheimer's disease. Psychopharmacology, 108:103-109, 1992.

Efange, SMN, Garland, EM, Staley, JK, and Mash, DC: (+)-[^{125}I]MIBT binding in human temporal cortex reveals cholinergic hypofunction in Alzheimer's disease. Eleventh International Symposium on Radiopharmaceutical Chemistry Abstracts, 1995b, 376-377.

Efange, SMN, Mach, RH, Khare, A, Michelson, RH, Nowak, PA, and Evora, PH: p-[^{18}F]Fluorobenzyltrozamicol ([^{18}F]FBT): molecular decomposition-reconstitution approach to vesamicol receptor radioligands for positron emission tomography. Appl. Radiat. Isot., 45:465-472, 1994.

Efange, SMN, Mach, RH, Smith, CR, Khare, AB, Foulon, C, Akella, SK, Childers, SR, and Parsons, SM: Vesamicol analogues as sigma ligands. Molecular determinants of selectivity at the vesamicol receptor. Biochem. Pharmacol., 49:791-797, 1995a.

Fitten, LJ, Perryman, K, Tachiki, K, and Kling, A: Oral tacrine administration in middle-aged monkeys: effects on discrimination learning. Neurobiol. Aging, 9:221-224, 1988.

Fletcher, HJ, and Mowbray, JB: Note on learning in an aged monkey. Psychol. Rep., 10:11-13, 1962.

Flicker, C, Bartus, RT, Crook, TH, and Ferris, SH: Effects of aging and dementia upon recent visuospatial memory. Neurobiol. Aging, 5, 275-283, 1984.

Flood, DG: Region-specific stability of dendritic extent in normal aging and regression in Alzheimer's disease. II. Subiculum. Brain Res., 540:83-95, 1991.

Flood, DG, Buell, SJ, De Fiore, CH, Horwitz, GJ, and Coleman, PD: Age-related dendritic growth in dentate gyrus of human brain is followed by regression in the "oldest old". Brain Res., 345:366-368, 1985.

Flood, DG, Buell, SJ, Horwitz, GJ, and Coleman, PD: Dendritic extent in human dentate gyrus granule cells in normal aging and senile dementia. Brain Res., 402:205-216, 1987.

Folk, CL, and Hoyer, WJ: Aging and shifts of visual spatial attention. Psychol. Aging, 7:453-463, 1992.

Gazzaley, AH, Siegel, SJ, Kordower, JH, Mufson, EJ, and Morrison, JH: Circuit-specific alterations of N-methyl-D-aspartate receptor subunit 1 in the dentate gyrus of aged monkeys. Proc. Natl. Acad. Sci. U.S.A., 93:3121-3125, 1996.

Gerhardt, GA, Cass, WA, Henson, M, Zhang, Z, Ovadia, A, Hoffer, BJ, and Gash, DM: Age-related changes in potassium-evoked overflow of dopamine in the striatum of the rhesus monkey. Neurobiol. Aging, 16:939-946, 1995.

Goldman-Rakic, PS, and Brown, RM: Regional changes of monoamines in cerebral cortex and subcortical structures of aging rhesus monkeys. Neuroscience, 6:177-187, 1981.

Gorman, LK: Age-related behavioral and neurochemical deficits: the cholinergic system revisited. Neurobiol. Aging, 14:699-702, 1993.

Gottsdanker, R: Age and simple reaction time. J. Gerontol., 37:342-348, 1982.

Greenwood, PM, Parasuraman, R, and Haxby, JV: Changes in visuospatial attention over the adult lifespan. Neuropsychologia 31:471-485, 1993.

Growdon, JH: Biologic therapies for Alzheimer's disease, in Dementia, edited by Whitehouse, PJ, Philadelphia, F.A. Davis, 1993, pp. 375-399.

Hanks, SD, and Flood, DG: Region-specific stability of dendritic extent in normal aging and regression in Alzheimer's disease. I. CA1 of hippocampus. Brain Res., 540:63-82, 1991.

Hartley, AA: Attention, in Handbook of Aging and Cognition, edited by Craik, FIM, and Salthouse, TA, New Jersey, Erlbaum Assoc., 1992, pp. 3-49.

Hartley, AA, Kieley, JM, and Slabach, EH: Age differences and similarities in the effects of cues and prompts. J. Exper. Psychol. Human Perception Performance, 16:523-537, 1990.

Haug, H: Macroscopic and microscopic morphometry of the human brain and cortex. A survey in the light of new results. Brain Pathol., 1:123-149, 1984.

Irwin, I, DeLanney, LE, McNeill, T, Chan, P, Forno, L, Murphy, MM, DiMonte, DA, Sandy, MS, and Langston, JW: Aging and the nigrostriatal dopamine system: a nonhuman primate study. Neurodegeneration, 3:251-265, 1994.

Jackson, WJ, Buccafusco, JJ, Terry, AV, Turk, DJ, and Rush, DK: Velnacrine maleate improves delayed matching performance by aged monkeys. Psychopharmacology, 119:391-398, 1995.

Jordan, TC, and Rabbitt, PMA: Response times to stimuli of increasing complexity as a function of ageing. Br. J. Psychol., 68:189-201, 1977.

Kalaria, RN, Andorn, AC, Tabaton, M, Whitehouse, PJ, Harik, SI, and Unnerstall, JR: Adrenergic receptors in aging and Alzheimer's disease: increased beta-2-receptors in prefrontal cortex and hippocampus. J. Neurochem., 53:1772-1781, 1989.

Kalaria, RN, and Andorn, AC: Adrenergic receptors in aging and Alzheimer's disease: decreased alpha-2 receptors demonstrated by [^{3}H]*p*-aminoclonidine binding in prefrontal cortex. Neurobiol. Aging, 12, 131-136, 1991.

Kausler, DH: Learning and Memory in Normal Aging. New York, Academic Press, 1994.

Kemper, TL: Relationship of cerebral cortical changes to nuclei in the brainstem. Neurobiol. Aging, 14:659-660, 1993.

Kemper, TL: Neuroanatomical and neuropathological changes during aging and dementia, in Clinical Neurology of Aging, Albert, ML, and Knoefel, JE, New York, Oxford University Press, 1994, pp. 3-67.

Kornhuber, J, Retz, W, Riederer, P, Heinsen, H, and Fritze, J: Effect of antemortem and postmortem factors on [^{3}H]glutamate binding in the human brain. Neurosci. Lett., 93:312-317, 1988.

Kornhuber, J, Mack-Burkhardt, F, Konradi, C, Fritze, J, and Riederer, P: Effect of antemortem and postmortem factors on [^{3}H]MK-801 binding in the human brain: transient elevation during early childhood. Life Sci., 45:745-749, 1989.

Kuhl, DE, Metter, EJ, Riege, WH, and Phelps, ME: Effects of human aging on patterns of local cerebral glucose utilization determined by the [^{18}F]fluorodeoxyglucose method. Ann. Neurol., 15:419-424, 1982.

Lai, J, Bowden, DM, and Horita, A: Age-related decreases in dopamine receptors in the caudate nucleus and putamen of the rhesus monkey (*Macaca mulatta*). Neurobiol. Aging, 8:45-49, 1987.

Lai, ZC, Moss, MB, Killiany, RJ, Rosene, DL, and Herndon, JG: Executive system dysfunction in the aged monkey: spatial and object reversal learning. Neurobiol. Aging, 16:947-954, 1995.

La Rue, A: Aging and Neuropsychological Assessment, New York, Plenum Press, 1992, pp. 47-44.

Lee, KS, Frey, KA, Koeppe, RA, Buck, A, Mulholland, GK, Foster, NL and Kuhl, DE: Quantification of muscarinic cholinergic receptors in aging and Alzheimer's disease. J. Nucl. Med., 32: 942-943, 1991.

LeVere, SD, and Levere, TE: Old age and cognition: evaluation of a human short-term memory test with nonhuman primates and the memory-enhancing effects of nimodipine. Psychobiology, 22:106-111, 1994.

Light, KE: Information processing for motor performance in aging adults. Phys. Ther., 70:820-826, 1990.

Light, KE, and Spirduso, WW: Effects of adult aging on the movement complexity factor of response programming. J. Gerontol.: Psychol. Sci., 45:P107-109, 1990.

Lowes-Hummel, P, Gertz, H-J, Ferszt, R, and Cervos-Navarro, J: The basal nucleus of Meynert revised: the nerve cell number decreases with age. Arch. Gerontol. Geriatr., 8:21-27, 1989.

Madden, DJ: Adult age differences in the time course of visual attention. J. Gerontol.: Psychol. Sci., 45:9-16, 1994.

Mann, DMA, Yates, PO, and Marcyniuk, B: Changes in nerve cells of the nucleus basalis of Meynert in Alzheimer's disease and their relationship to ageing and to the accumulation of lipofuscin pigment. Mech. Ageing Dev., 25:189-204, 1984a.

Mann, DMA, Yates, PO, and Marcyniuk, B: Alzheimer's presenile dementia, senile dementia of Alzheimer type and Down's syndrome in middle age form an age-related continuum of pathological changes. Neuropathol. Appl. Neurobiol., 10:185-207, 1984b.

Marriott, JG, and Abelson, JS: Age differences in short-term memory of test-sophisticated rhesus monkeys. Age, 3:7-9, 1980.

McDowd, JM, and Birren, JE: Aging and attentional processes, in Handbook of the Psychology of Aging, third edition, edited by Birren, JE, and Schaie, KW, New York, Academic Press, 1990, pp. 222-233.

McEntee, WJ, and Crook, TH: Serotonin, memory, and the aging brain. Psychopharmacology, 103:143-149, 1991.

McGeer, PL, McGeer, EG, Suzuki, J, Dolman, CE, and Nagai T: Aging, Alzheimer's disease, and the cholinergic system of the basal forebrain. Neurology, 34:741-745, 1984.

Medin, DL: Form perception and pattern reproduction in monkeys. J. Comp. Physiol. Psychol., 68:412-419, 1969.

Medin, DL, O'Neil, P, Smeltz, E, and Davis, RT: Age differences in retention of concurrent discrimination problems in monkeys. J. Gerontol., 28:63-67, 1973.

Moeller, JR, Ishikawa, T, Dhawan, V, Spetsieris, P, Mandel, F, Alexander, GE, Grady, C, Pietrini, P, and Eidelberg, D: The metabolic topography of normal aging. J. Cereb. Blood Flow Metab., 16:385-398, 1996.

Morgan, DG, May, PC, and Finch, CE: Dopamine and serotonin systems in human and rodent brain: effects of age and neurodegenerative disease. J. Amer. Gerontol. Soc., 35:334-345, 1987.

Morse, CK: Does variability increase with age? An archival study of cognitive measures. Psychol. Aging, 8:156-164, 1993.

Mouradian, MM, Contreras, PC, Monahan, JB, and Chase, TN: [^{3}H]MK-801 binding in Alzheimer's disease. Neurosci. Lett., 93:225-230, 1988.

Moss, MB: The longitudinal assessment of recognition memory in aged rhesus monkeys. Neurobiol. Aging, 14:635-636, 1993.

Moss, MB, Rosene, DL, Peters, A: Effects of aging on visual recognition memory in the rhesus monkey. Neurobiol. Aging, 9:495-502, 1988.

Nakamura, S, Akiguchi, I, Kameyama, M, and Mizuno, N: Age-related changes of pyramidal cell basal dendrites in layers III and V of human motor cortex: a quantitative Golgi study. Acta. Neuropathol. (Berl.), 65:281-284, 1985.

Norberg, A, and Winblad, B: Brain nicotinic and muscarinic receptors in normal aging and dementia, in Alzheimer's and Parkinson's Disease, Advances in Behavioral Biology, Vol. 29, edited by Fischer, A, Hanin, I, and Lachman, C, New York, Plenum Press, 1986, pp. 95-108.

Nordberg, A, Alafuzoff, I, and Winblad, B: Nicotinic and muscarinic subtypes in the human brain: changes with aging and dementia. J. Neurosci. Res., 31:103-111, 1992.

Ordy, JM: Neurobiology and aging in nonhuman primates, in Neurobiology of Aging, Advances in Behavioral Biology, Vol. 16, edited by Ordy, JM, and Brizzee, KR, New York, Plenum Press, 1975, pp. 575-594.

Oscar-Berman, M, and Bonner, RT: Matching- and delayed matching-to-sample performance as measures of visual processing, selective attention, and memory in aging and alcoholic individuals. Neuropsychologia, 23:639-651, 1985.

Parsons, SM, Prior, C, and Marshall, IG: Acetylcholine transport, storage and release. Int. Rev. Neurobiol., 35:279-390, 1993.

Parsons, SM, and Rogers, G: In vivo diagnostics for Alzheimer's disease based on the acetylcholine transporter. Ann. Reports Med. Chem., 28:247-255, 1993.

Perry, EK, Johnson, M, Kerwin, JM, Piggott, MA, Court, JA, Shaw, PJ, Ince, PG, Brown, A, and Perry, RH: Convergent cholinergic activities in aging and Alzheimer's disease. Neurobiol. Aging, 13:393-400, 1992.

Peters, A: The absence of significant neuronal loss from cerebral cortex with age. Neurobiol. Aging, 14:657-658, 1993.

Peters, A, Leahu, D, Moss, MB, and McNally, KJ: The effects of aging on area 46 of the frontal cortex of the rhesus monkey. Cerebr. Cortex, 6:621-635, 1994.

Peters, A, and Sethares, C: Aging and the Meynert cells in rhesus monkey primary visual cortex. Anat. Rec., 236:721-729, 1993.

Petersen, RC, Smith, G, Kokmen, E, Ivnik, RJ, and Tangalos, EG: Memory function in normal aging. Neurology, 42:396-401, 1992.

Piggott, MA, Perry EK, Perry, RH, and Court, JA: [^{3}H]MK-801 binding to the NMDA receptor complex, and its modulation in human frontal cortex during development and aging. Brain Res., 588:277-286, 1992.

Plude, DJ, and Hoyer, WJ: Attention and performance: identifying and localizing age deficits, in Aging and Human Performance, edited by Charness, N, New York, Wiley & Sons, 1985, pp. 47-99.

Ponds, RWHM, Vrouwer, WH, and van Wolffelaar, PC: Age differences in divided attention in a simulated driving task. J. Gerontol.: Psychol. Sci., 43:151-156, 1988.

Poon, LW: Differences in human memory with aging: nature, causes, and clinical implications, in Handbook of the Psychology of Aging, edited by Birren, JE and Schaie, KW, New York, Van Nostrand Reinhold Co., 1985, pp. 427-462.

Posner, MI: Orienting of attention. Quart. J. Exp. Psychol., 32:3-25, 1980..

Posner, MI, and Cohen Y: Components of visual orienting, in Attention and Performance X: Control of Language Processes, edited by Bouma, H, and Bowhuis, DG, New Jersey, Lawrence Erlbaum Assoc., 1984, pp. 531-556.

Presty, SK, Bachevalier, J, Walker, LC, Struble, RG, Price, DL, Mishkin, M, and Cork, LC: Age differences in recognition memory of the rhesus monkeys (*Macaca mulatta*). Neurobiol. Aging, 8:435-440, 1987.

Rapp, PR: Visual discrimination and reversal learning in the aged monkey (*Macaca mulatta*). Behav. Neurosci., 104:876-884, 1990.

Rapp, PR, and Amaral, DG: Evidence for task-dependent memory dysfunction in the aged monkey. J. Neurosci., 9:3568-3576, 1989.

Rapp, PR, and Amaral, DG: Recognition memory deficits in a subpopulation of aged monkeys resemble the effects of medial temporal lobe damage. Neurobiol. Aging, 12:481-486, 1991.

Rapp, PR, Kansky, MT and Eichenbaum, H: Learning and memory for hierarchical relationships in the monkey: effects of aging. Behav. Neurosci., in press.

Rinne, JO: Muscarinic and dopaminergic receptors in the aging human brain. Brain Res., 404:162-168, 1987.

Rinne, JO, Hietala, J, Ruotsalainen, U, Säkö, E, Laihinen, A, Någren, K, Lehikoinen, P, Oikonen, V, and Syvälahti, E: Decrease in human striatal dopamine D_2 receptor density with age: a PET study with [^{11}]C-raclopride. J. Cereb. Blood Flow Metab., 13:310-314, 1993.

Rinne, JO, Lönnberg, P, and Marjamäki, P: Age-dependent decline in human brain dopamine D_1 and D_2 receptors. Brain Res., 508:349-352, 1990.

Robinson, DL, and Kertzman, C: Visuospatial attention: effects of age, gender, and spatial reference. Neuropsychologia, 28:291-301, 1990.

Rosene, DL: Comparing age-related changes in the basal forebrain and hippocampus of the rhesus monkey. Neurobiol. Aging, 14:669-670, 1993.

Rupniak, NMJ, Steventon, MJ, Field, MJ, Jennings, CA, and Iversen, SD: Comparison of the effects of four cholinomimetic agents on cognition in primates following disruption by scopolamine or by lists of objects. Psychopharmacology, 99:189-195, 1989.

Sandin, M, Jasmin, S, and Levere, TE: Aging and cognition: facilitation of recent memory in aged nonhuman primates by nimodipine. Neurobiol. Aging, 11:573-575, 1990.

Scheibel, ME, Lindsay, RD, Tomiyasu, U, and Scheibel, AB: Progressive dendritic changes in aging human cortex. Exp. Neurol., 47:392-403, 1975.

Scheibel, ME, Lindsay, RD, Tomiyasu, U, and Scheibel, AB: Progressive dendritic changes in aging human limbic system. Exp. Neurol., 53:420-430, 1976.

Schneider, NG, Gritz, ER, and Jarvik ME: Age differences in simple paced tasks of attention and perception. Gerontology, 23:142-147, 1977.

Severson, JA, Marcusson, J, Winblad, B, and Finch, CE: Age-correlated loss of dopaminergic binding sites in human basal ganglia. J. Neurochem., 39:1623-1631, 1982.

Shimamura, AP: Aging and memory disorders: a neuropsychological analysis, in Cognitive and Behavioral Performance Factors in Atypical Aging, edited by Howe, ML, Stones, MJ, and Brainerd, CJ, New York, Springer Verglag, 1990, pp. 37-65.

Siddiqi, ZA, Kemper, TL, and Blatt GJ: Age-related neuronal loss in the substantia nigra of rhesus monkey. Soc. Neurosci. Abstr., 20:49, 1994.

Siddiqi, ZA, Kemper, TL, Rosene, DL, Feldman, ML: Age-related changes in the rhesus monkey: neuronal loss in substantia nigra, pars compacta and ventral tegmental area. Soc. Neurosci. Abstr., 21:1565, 1995.

Sparks, DL, Hunsaker, JC, Slevin, JT, DeKosky, ST, Kryscio, RJ, and Markesbery, WR: Monoaminergic and cholinergic synaptic markers in the nucleus basalis of Meynert (nbM): normal age-related changes and the effect of heart disease and Alzheimer's disease. Ann. Neurol., 31:611-620, 1992.

Spirduso, WW, and MacRae, PG: Motor performance and aging, in Handbook of Psychology of Aging, edited by Birren, JE, and Schaie, KW, second edition, New York, Academic Press, 1990, pp. 184-200.

Stroessner-Johnson, HM, Rapp, PR, and Amaral, DG: Cholinergic cell loss and hypertrophy in the medial septal nucleus of the behaviorally characterized aged rhesus monkey. J. Neurosci., 12:1936-1944, 1992.

Suhara, T, Inoue, O, Kobayashi, K, Suzuki, K, and Tateno, Y: Age-related changes in human muscarinic acetylcholine receptors measured by positron emission tomography. Neurosci. Lett., 149: 225-228, 1993.

Suhara, T, Fukuda, H, Inoue, O, Itoh, T, Suzuki, K, Yamasaki, T, and Tateno, Y: Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology, 103:41-45, 1991.

Stuss, DT, Stethem, LL, Picton, TW, Leech, EE, and Pelchat, G: Traumatic brain injury, aging and reaction time. Can. J. Neurol. Sci., 16:161-167, 1989.

Terry, RD, De Teresa, R, and Hansen, LA: Neocortical cell counts in normal human adult aging. Ann. Neurol., 21:530-539, 1987.

Terry, AV, Jackson, WJ, and Buccafusco, JJ: Effects of concomitant cholinergic and adrenergic stimulation on learning and memory performance by young and aged monkeys. Cereb. Cortex, 3:304-312, 1993.

Tigges, J, Herndon, JA, and Peters, A: Neuronal population of area 4 during the life span of the rhesus monkeys. Neurobiol. Aging, 11:201-208, 1990.

Tigges, J, Herndon, JG, and Rosene, DL: Mild age-related changes in the dentate gyrus of adult rhesus monkeys. Acta Anat., 153:39-48, 1995.

Uemura, E: Age-related changes in prefrontal cortex of Macaca mulatta: synaptic density. Exp. Neurol., 69:164-172, 1980.

Uemura, E: Age-related changes in the subiculum of Macaca mulatta: dendritic branching pattern. Exp. Neurol., 87:412-427, 1985.

Vannucchi, MG, and Goldman-Rakic, PS: Age-dependent decrease in the affinity of muscarinic M1 receptors in neocortex of rhesus monkeys. Proc. Natl. Acad. Sci. U.S.A., 88:11475-11479, 1991.

Vincent, SL, Peters, A, and Tigges, J: Effects of aging on the neurons within area 17 of rhesus monkey cerebral cortex. Anat. Rec., 223:329-341, 1989.

Voytko, ML: Cognitive changes during normal aging in monkeys assessed with an automated test apparatus. Neurobiol. Aging, 14:634-644, 1993.

Voytko, ML, Sukhov, RR, Walker, LC, Breckler, SJ, Price, DL, and Koliatsos, VE: Neuronal number and size are preserved in the nucleus basalis of aged rhesus monkeys. Dementia, 6:131-141, 1995.

Wagster, MV: Changes in cholinergic receptor subtypes in behaviorally-tested, aged monkeys. Neurobiol. Aging, 14:693-694, 1993.

Wagster, MV, Whitehouse, PJ, Walker, LC, Kellar, KJ, and Price, DL: Laminar organization and age-related loss of cholinergic receptors in temporal neocortex of rhesus monkey. J. Neurosci., 10:2879-2885, 1990.

Welford, AT: Motor skills and aging, in The Aging Motor System, Advances in Neurogerontology, Vol. 3, edited by Mortimer, JA, Pirozzolo, FJ, and Maletta, GJ, New York, Praeger Publishers, 1982, pp. 152-187.

Wenk, GL: Age-related changes in monkey and rodent neurochemistry. Neurobiol. Aging, 14:689-690, 1993.

Wenk, GL, Pierce, DJ, Struble, RG, Price, DL, and Cork, LC: Age-related changes in multiple neurotransmitter systems in the monkey brain, Neurobiol. Aging, 10:11-19, 1989.

Wenk, GL, Walker, LC, Price, DL, and Cork, LC: Loss of NMDA, but not GABA-A, binding in the brains of aged rats and monkeys. Neurobiol. Aging, 12:93-98, 1991.

West, MJ: Regionally specific loss of neurons in the aging human hippocampus. Neurobiol. Aging, 14:287-293, 1993.

West, MJ, Amaral, DG, and Rapp, PR: Preserved hippocampal cell number in aged rhesus monkeys with recognition memory deficits. Soc. Neurosci. Abstr., 19:599, 1993.

West, RL, Crook, TH, and Barron KL: Everyday memory performance across the life span: effects of age and noncognitive individual differences. Psychol. Aging, 7:72-82, 1992.

Whitehouse, PJ, Parhad, IM, Hedreen, JC, Clark, AW, White, CL, Struble, RG, and Price, DL: Integrity of the nucleus basalis of Meynert in normal aging. Neurology, 33 (Suppl 2):159, 1983.

Whitehouse, PJ, and Au, KS: Cholinergic receptors in aging and Alzheimer's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry, 10:665-676, 1986.

Wong, DF, Wagner, HN, Dannals, RF, Links, JM, Frost, JJ, Ravert, HT, Wilson, AA, Rosenbaum, AE, Gjedde, A, Douglass, KH, Petronis, JD, Folstein, MF, Toung, JKT, Burns, HD, and Kuhar, MJ: Effects of age on dopamine and serotonin receptors measured by positron emission tomography in the living human brain. Science, 226:1393-1396, 1984.

Yoshii, F, Barker, WW, Chang, JY, Loewenstein, D, Apicella, A, Smith, D, Boothe, T, Ginsberg, MD, Pascal, S, and Duara, R: Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. J. Cereb. Blood Flow Metab., 8:654-661, 1988.

Zelinski, EM, Gilewski, MJ, and Schaie, KW: Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. Psychol. Aging, 8: 176-186, 1993.