The ageing brain: normal and abnormal memory

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SUMMARY

With advancing age, the majority of individuals experience declines in their ability to learn and remember. An examination of brain structure and function in healthy older persons across the age range indicates that there are substantial changes in the brain that appear to be related to alterations in memory. The nature of the cognitive and neurobiological alterations associated with age-related change is substantially different from that seen in the early stages of a dementing illness, such as Alzheimer's disease. These differences have implications for potential intervention strategies.

1. INTRODUCTION

Changes in memory occur with age, but memory changes are also the earliest cognitive change seen in Alzheimer's disease (AD). Recent studies indicate that there is a considerable difference between the nature of the memory changes in ageing and in AD and the underlying neurobiology responsible for those changes. The present paper will review the changes in memory seen in healthy individuals across the age range and those that appear to characterize the early stages of AD, along with their neurobiologic correlates.

2. AGE-RELATED CHANGES IN MEMORY

There are substantial changes with age in explicit secondary memory, in contrast to the minimal age changes in sensory and primary memory (for reviews, see Craik 1977; Poon 1985). The age at which changes in secondary memory occur depends on the methods that are used to test the memory store. Difficult explicit memory tasks (e.g. delayed recall) demonstrate statistically significant differences by subjects in their 50s, in comparison to younger individuals (Albert *et al.* 1987). Age decrements are greater on recall than recognition tasks. This is true whether words or pictures are used. Cueing during encoding or retrieval also alters the appearance of an age decline. Cueing at both encoding and retrieval produces the smallest age differences, whereas no cueing at either stage of the task maximizes age differences (Craik *et al.* 1987). However, even with cued recall and recognition, there are often declines. Rabinowitz (1986) reported a 33% age-related decrement in cued recall, and an 11% age-related decrement in recognition, when comparing young and old subjects (mean age 19 vs 68).

Figure 1 shows the performance of subjects across the age range on delayed recall of two lengthy paragraphs. That is, each subject is read two lengthy paragraphs

and, immediately after hearing each one, and then again after 20 minutes, the subject is asked to state what he or she can recall of the paragraphs.

A close examination of these data indicates that the older individuals are not more rapidly forgetting what they learned, but rather they are taking longer to learn the new information. For example, if one compares the difference between immediate and delayed recall over the lifespan, there are no statistically significant age differences (Petersen *et al.* 1992). Thus, if one allows older subjects to learn material well (i.e. to the point where few errors are made), they do not forget what they have learned more rapidly than the young (see figure 2). However, if older subjects are not given the ability to learn material to the same level of proficiency as younger individuals, after a delay, less information will be retained by the average older person.

However, there is considerable variability among older subjects on tasks of this sort. There are many healthy older subjects who have test scores that overlap those of subjects many years younger than themselves (e.g. about one-third of healthy 70-year-old humans have delayed recall scores that overlap those of 30-year-olds, equated for education).

Similar findings have emerged from studies in monkeys. As free recall cannot be easily tested in monkeys, considerable effort has gone into developing a memory task that uses recognition, but determines the quantity of information ageing monkeys can retain across varying delay intervals. The delayed non-matching to sample task (DNMS) is the most widely used method for assessing recognition memory in the non-human primate (Bachevalier & Mishkin 1989; Murray & Mishkin 1984, 1986; Mishkin 1978; Mahut *et al.* 1982; Zola-Morgan & Squire 1984). This task relies on a two-alternative forced choice paradigm in which the monkey is required to discriminate which of two objects was recently presented. By using the delayed non-matching to sample task, many studies have shown that aged monkeys are impaired at

Figure 1. Delayed recall performance of subjects 30 to 80 years old. The subjects are asked to report what they remember of two lengthy paragraphs after a 15 min delay.

Figure 2. Difference between immediate and delayed recall performance in subjects aged 30–80. The task is the same as that shown in figure 1.

learning the non-matching principle but are, at best, only mildly impaired across the delay conditions of the test (Moss *et al.* 1988; Arnsten & Goldman-Rakic 1990; Bachevalier *et al.* 1991; Presty *et al.* 1987; Rapp & Amaral 1989). Thus, like humans, the old monkeys take longer to learn something new, but do not appear to forget this information more rapidly over lengthening delays than younger monkeys.

Another task, the delayed recognition span test (DRST) (Rehbein 1983; Moss 1983), has demonstrated similar findings. This test requires a monkey to identify a novel stimulus from an increasing array of previously presented stimuli. The task has been administered to monkeys with two types of conditions: a spatial version and an object version. In both conditions the monkey first sees a board with 18 positions (food wells) and a stimulus object on one position. A second stimulus is added, while the board is obscured from view, and the animal is required to point to the new stimulus. On the first trial of the spatial version, the animal's task is to indicate which of two disks is occupying the new position on the board (i.e. a non-matching to position task). On the first trial of the object version, the animal's task is to indicate which of two objects on the board is the new one (i.e. in essence, a non-matching to sample task). However, as new disks/objects are then added in series to the previous ones on the board, the task becomes increasingly difficult. For example, young adult monkeys often achieve a span of five or greater before committing an error.

Middle-aged monkeys (16–23 years) are impaired on the spatial version of the DRST but not on the colour version (figure 3) (Moss *et al.* 1997). This finding is similar to the declines in performance on delayed recall seen in middle-aged humans. Aged monkeys (25–27 years) are impaired relative to young adults (5–7 years) under both conditions of the task. This suggests that the performance of monkeys on the spatial version of the DRST may be functionally equivalent to the performance of humans on difficult delayed recall tasks. In addition, the difference between performance on the DNMS and the spatial condition of the DRST appears to be similar to what one sees between recall and recognition paradigms in ageing humans.

Like ageing humans, there is also considerable variability in the performance of ageing monkeys. Among the oldest animals there are subjects who perform within the range of younger animals, even though the mean performance of the group declines significantly. For example, on DNMS, the number of trials to criterion ranges from 50 to 220 and the number of errors range from 29 to 60. Among the older monkeys, the trials to criterion range from 200 to 516 and the number of errors range from 50 to 115.

3. AGE-RELATED CHANGES IN BRAIN STRUCTURE AND FUNCTION

There is substantial evidence that, as people age, they show significant increases in cerebrospinal fluid (CSF) and decreases in brain tissue (Stafford *et al.* 1988; Zatz *et al.* 1982). That is, there is increasing atrophy with age. This alteration becomes statistically significant when subjects are in their 70s (Stafford *et al.* 1988).

However, recent studies in humans suggest that the decrease in brain tissue observed is primarily the result of decreases in white matter with age ($p < 0.001$). Decreases in grey matter are only marginally statistically significant; approximately 48% of brain tissue consists of grey matter among both 30-year-olds and 70-year-olds (Guttmann *et al.* 1997). These findings are consistent with recent data in humans (Haug 1984; Terry *et al.* 1987; Leuba & Garey 1989), indicating that, with advancing age, neuronal loss in the cortex is either not significant or not as extensive as earlier reports (i.e. reports prior to 1984) had suggested (Brody 1955, 1970; Colon 1972; Shefer 1973; Henderson *et al.* 1980; Anderson *et al.* 1983).

There are comparable data in monkeys. A recent study of magnetic resonance images (MRIs) in young and old monkeys demonstrates significant decreases in white matter volume with age, but minimal decreases in grey matter volume (Rosene *et al.* 1998). Neuronal counts of numerous brain regions in young and old monkeys also demonstrate minimal neuronal cortical loss with age, including the striate cortex (Vincent *et al.* 1989), motor cortex (Tigges *et al.* 1992), frontal cortex (Peters *et al.* 1994), and the entorhinal cortex

Figure 3. Spatial delayed recognition span scores by young adult monkeys (aged 5–7), middle-aged monkeys (aged 16–23 years) and elderly monkeys (aged 25–27 years).

(Amaral 1993). (It should be noted that these findings do not exclude focal changes with age in small areas of grey matter, such as selected areas of cortex or small subcortical nuclei, as discussed further below.)

Data in monkeys and humans also indicate that neuronal loss is highly selective within the hippocampal formation. For example, the subiculum shows a significant age-related loss in humans and a similar trend in monkeys, but the CA1, CA2 and CA3 fields show no evidence of an age-related neuronal loss (Amaral 1993; Rosene 1993; West *et al.* 1994).

A recent positron emission tomography (PET) study also suggests that the hippocampal formation is more highly functional with age than previously thought (Schacter *et al.* 1996). In this investigation, young and elderly subjects attempted to learn two types of word lists. The testing conditions were such that high levels of recall were achieved with one set of word lists, while low levels of recall were achieved with the other. Analyses of the PET data from both the young and older adults revealed blood flow increases in the hippocampal formation in comparisons in which the high recall condition was emphasized; bilateral blood flow increases were seen in the high recall minus baseline comparison, and right unilateral increases were seen in the high recall minus low recall comparison (see figure 4). The pattern of blood flow increases were similar in both the young and older subjects, in both *z*-score units and location of change. This suggests that the features of recollection indexed by hippocampal activity operates in a similar manner in old and young.

These PET studies, however, also demonstrate differences in brain activation between young and older subjects. These were evident in comparisons emphasizing the low recall condition. Most striking was the difference between the groups in the low recall minus baseline comparison, which produced blood flow increases bilaterally in the anterior frontal lobe (centring on Area 10), for the young subjects but not the older ones. By contrast, the older subjects demonstrated unilateral blood flow increases in the right posterior frontal lobe (centring on Area 46) and the right motor area (centring on Area 4/6). These differences in frontal activation between the young and

older adults may reflect differences in retrieval strategies when subjects are attempting to recall information that is not well learned. It seems unlikely, based on the reports of preserved neuronal populations in the cortex cited above, that these frontal activation differences between young and old are the result of substantial cortical neuronal loss. Age-related alterations in subcortical nuclei that project to the cortex seem to be the more likely explanation for these findings, as there is substantial neuronal loss in selected subcortical regions involved in neurotransmitter systems important for memory function, such as the basal forebrain and the locus coeruleus (e.g. Chan-Palay & Asan 1989; Rosene 1993). For example, in humans and monkeys there is approximately a 50% neuronal loss with age in the basal forebrain and 35–40% loss in the locus coeruleus and dorsal raphe (Kemper 1993). This compares with an approximate loss of 5% in CA1 of the hippocampus. Although neuronal loss appears to be minimal in the hippocampus with age, recent reports suggest alterations in specific receptor types (e.g. NMDA receptors) that may play a role in memory function (Gazzaley *et al.* 1996).

In addition, there is an age-related decrease in dopaminergic binding sites in the caudate nucleus (Severson *et al.* 1982) and the substantia nigra and a loss of neurons in the substantia nigra of about 6% per year (McGeer *et al.* 1977). This loss of dopamine is thought to be responsible for many neurological symptoms that increase in frequency with age, such as decreased armswing and increased rigidity (Odenheimer *et al.* 1994). Changes in dopamine levels may also cause age-related changes in cognitive flexibility. This is suggested by the fact that patients with Parkinson's disease (a disorder associated with a loss of cells in the substantia nigra and a severe decline in dopamine levels) have cognitive deficits that have variably been described as 'mental inflexibility' (Lees & Smith 1983), a disorder of the 'shifting attitude' (Cools *et al.* 1984), an 'instability of cognitive set' (Flowers & Robertson 1985) and difficulty with 'set formation, maintenance and shifting' (Taylor *et al.* 1987). An age-related functional loss of dopamine has been demonstrated in monkeys (Arnsten *et al.* 1994), making it possible to study this hypothesis in non-human primates.

4. MEMORY CHANGES IN EARLY ALZHEIMER'S DISEASE

The alterations in memory associated with early Alzheimer's disease differ in important ways from those associated with age-related changes in memory. Difficulty with the acquisition of new information is generally the first and most salient symptom to emerge in patients with AD. When clinical neuropsychological tests are used to evaluate memory in AD patients, it is clear that recall and recognition performance are impaired in both the verbal and non-verbal domain (Wilson *et al.* 1983; Storandt & Hill 1989).

Experimental studies have examined AD patients to determine whether the manner in which information is lost over brief delays is unique in any way to this patient group. The results of these studies suggest that a

Figure 4. PET statistical maps showing regions of activation transformed to Talairach space, coregistered with an average MRI scan. (a) Low recall minus baseline, (b) High recall minus low recall.

comparison of immediate and delayed recall performance may be a useful diagnostic measure for identifying patients with AD.

The first such study was conducted by Moss *et al.* (1986). They compared patients with AD to a group of amnesic patients who had alcoholic Korsakoff's syndrome (KS), a group of dementing patients with Huntington's disease (HD), and a group of normal controls (NC). All of the subjects were administered the delayed recognition span test (DRST), the task mentioned above with respect to studies of memory in monkeys. The recognition portion of the task is entirely comparable to that used in monkeys. Disks are employed on which are placed a variety of stimuli (words, colours, faces, patterns, etc.). During the recognition portion of the task, the disks are placed on a board one at a time (there are 16 disks in all). As each disk is added, the board is hidden from view. The subject is then asked to point to the disk that was added during the delay interval. In order to do this, the subject must keep track of an increasingly long series of disks. The disks are then added one at a time, until the subject makes an error. This yields a delayed recognition span for each of the stimuli sets. All of the patient groups were impaired in their recognition performance with respect to controls, but there is overlap among the patient groups. There was no significant difference among the three patient groups in their ability to recognize new spatial, colour, pattern or facial stimuli; patients with HD performed significantly better than the other two groups when verbal stimuli were used.

However, when the DRST was given to humans, a recall portion was added to the verbal recognition span paradigm that is unique. Fifteen seconds and 2 min after completion of the last verbal recognition trial, the subject was asked to recall the words that had been on the disks. In this condition, the AD patients differ considerably from the other patients. They recall significantly fewer words over this brief delay interval (2 min) than either HD or KS patients.

Although all three patient groups were equally impaired relative to normal controls at the 15 s interval, patients with AD recalled significantly fewer words than either the HD or KS groups at the 2 min interval; in fact, only the AD group performed significantly worse at the longer, as compared with the shorter interval (figure 5). It is notable that by the end of the 2 min interval, 11 of the 12 patients in the AD group could recall fewer than three of the 16 words presented repeatedly during recognition testing. Of these 11 patients, seven were unable to recall any of the 16 words at the longer interval. Whereas the KS, HD and normal control subjects lost an average of 10–15% of the verbal information between the 15 s and 2 min delay intervals, patients with AD lost an average of 75% of the material. This pattern of recall performance demonstrated for the first time that patients with AD lose more information over a brief delay than other patients with amnesic or dementing disorders.

A similar pattern of results has been since reported by numerous other investigators (e.g. Butters *et al.* 1988; Hart *et al.* 1988; Welsh *et al.* 1991; Tierney *et al.* 1994). The findings of Hart *et al.* (1988) are particularly notable. They administered a continuous recognition task to AD patients and controls, and equated both groups of subjects for retention 90 s after the task was completed. They then retested the subjects 10 min, 2 h and 48 h after completion of the task. The AD patients showed a greater loss of information than the controls between the 90 s interval and the 10 min interval, but not between the 10 min and 2 h or 48 h intervals, suggesting that intervals of 10 min or less may be optimal for differentiating AD patients from other patient groups and from controls.

Since these findings were first reported, additional patient groups have been compared to AD patients on tasks of this nature. They, likewise, appear to recall more information after a delay than patients with AD. Milberg & Albert (1989) compared the performance of AD patients with that of progressive supranuclear palsy (PSP) patients. The two groups were equated for

Figure 5. The difference between immediate and delayed recall on the verbal recall portion of the delayed recognition span test. The groups compared are normal controls (N), patients with Alzheimer's disease (AD), patients with Huntington's disease (HD) and patients with alcoholic Korsakoff's syndrome (KS).

overall level of impairment on the basis of the Mattis Dementia Rating Scale (Mattis 1976) and were equivalent in years of education. There was no difference between the patient groups on most of the tasks administered (e.g. vocabulary, digit span forward, similarities, block design). There was, however, a striking difference between the groups on both of the memory tasks. The AD patients were significantly impaired in comparison to the PSP patients on tests of both verbal and non-verbal memory.

A comparison of patients with AD and patients with frontotemporal dementia (FTD) (Moss & Albert 1988) also demonstrates the severe recall deficits of the AD patients. Here again, patients with AD and patients with FTD, equated for overall level of cognitive impairment, were administered the DRST, described earlier. As in the earlier study, the difference in total recall between the 15 s and the 2 min delay interval (i.e. the savings score) differentiated the groups (figure 6). The retention of the FTD patients over this delay interval approaches normality, whereas the AD patients lose a substantial amount of information.

In general, these findings suggest that the nature and severity of the AD patients memory disturbance, in relation to delays spanning the first 10 min after encoding is likely to be the result of a unique pattern of neuropathological and/or neurochemical dysfunction.

Figure 6. The difference between immediate and delayed recall on the verbal recall portion of the delayed recognition span test. The groups compared are patients with Alzheimer's disease (AD), patients with frontotemporal dementia (FTD).

5. CHANGES IN BRAIN STRUCTURE IN EARLY ALZHEIMER'S DISEASE

The most likely explanation for the abnormalities in memory that characterize the early stage of AD pertains to the damage to the hippocampal formation seen in these patients (Ball 1977; Hyman *et al.* 1985). In the hippocampal formation, neuronal loss and abnormal formations with the cells (e.g. neurofibrillary tangles and neuritic plaques) are seen primarily in the entorhinal cortex and subiculum, the primary pathways that convey information into and out of the hippocampus. It has been suggested that abnormalities in these regions produce a functional isolation of the hippocampus (Hyman *et al.* 1985, 1986). These findings suggest that neuropathological damage to these medial temporal lobe structures may be responsible for the marked short-term memory impairment evident in the early stages of AD.

These results were first observed in patients with end stage disease. However, they have recently been extended to patients with very mild disease (Gomez-Isla *et al.* 1996). Most striking is the fact that the entorhinal cortex has neuronal loss of approximately 60% and 40% in layers 2 and 4 of the entorhinal cortex, respectively. The normal controls examined in this investigation spanned the ages of 60–90. They were carefully screened to exclude individuals with AD and demonstrated no significant neuronal loss in layers 2 and 4 of the entorhinal cortex. As this region is known to be critically important for the acquisition and retention of new information (Zola-Morgan *et al.* 1994), abnormalities in these regions are likely to be responsible for the severe anterograde memory loss evident early in the course of AD. Taken together with the findings described above, that there is significant age-related neuronal loss in the subiculum of the hippocampal formation, but no significant age-related change in the CA1, CA2 and CA3 regions of the hippocampus, these data suggest that a comparison of activation patterns in the subfields of the hippocampal formation (e.g. with newer functional MR techniques) may differentiate patients in the very earliest stages of Alzheimer's disease from those with age-related changes in memory.

6. CONCLUSION

These findings indicate that the memory changes that occur with age differ in important and significant ways from those seen in the early stages of AD and that selected, and differing, alterations in the brain are responsible for them. Understanding the nature of these cognitive changes and the brain alterations associated with them, is the first step in developing methods of changing them.

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