Cognitive problems in the elderly

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We have summarized the literature on cognitive changes in normal aging. The concepts of normal aging, age-associated memory impairment, and their possible continuum with dementia are discussed. Epidemiologic, genetic, radiological, as well as neuropsychological and endocrine contributions to the understanding of cognition in the elderly, are reviewed.

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Introduction

The rapid growth of the number of older people in the population has led to increased awareness and interest in diseases that affect cognitive function in the elderly. Although the amount of information on Alzheimer's disease, as well as on vascular and other types of dementing illnesses, has increased greatly in recent years, research on cognitive problems in 'normal aging' has been relatively sparse. Many cultures accept some intellectual decline as an accompaniment of aging, but its scientific characterization has proved difficult. A major obstacle has been lack of agreement on what 'normality' is. On one hand, one might consider normal only the performance of optimally aged individuals with virtually no cognitive decline. However, another approach is to define normal cognitive aging as the most representative performance of a sample population with a 'normal distribution'. Both concepts have limitations. The first approach might select an unusual subset of individuals gifted from the beginning that might not be sufficiently representative of the general population. Choosing the most typical performance as the standard reference instead means equating what is 'normative' to what is 'normal', that is, nonpathologic. Although probably true in most situations, this assumption becomes less clear in elderly populations. In fact, given the increasing prevalence of dementias with age and the slow onset and progression of most dementias, normative values are likely to derive from samples that include individuals affected by early and preclinical dementia, that is, pathologic aging. Exclusion of these individuals from normative samples is difficult. Current criteria to define dementia probably detect only relatively well established cases. Broadening criteria for dementia, however, is likely to exclude many normal 'nonpathologic' elderly individuals who are presumably demonstrating age-related changes in cognition.

Age-associated cognitive changes

Cognitive changes that are generally accepted as normal in the elderly include decreases in fluency and naming, sustained concentration, problem-solving abilities, analysis of complex perception, constructional abilities, and general loss of processing resources [1]. For memory, changes occur in the realm of explicit memory. Petersen *et al.* [2] have shown that the acquisition of new information declines, that is, the transferral of newly learned material from a primary to a secondary, more long-term memory store. When controlled for acquisition of information, however, the ability to retain and retrieve information is preserved. Acquisition or learning most likely requires information processing, a task that is probably subserved by the frontal lobes. In contrast, subsequent encoding and retrieval primarily depend on mesial temporal lobe and hippocampal systems. An anatomical correlation of these functions has been reviewed by Rapp and Heindel [3]. Whether mild memory abnormalities can be included in the spectrum of normal aging, though, is still debatable. In a different study, Petersen *et al.* [4] published data on the longitudinal outcome of mildly impaired patients [CDR (Clinical Dementia Rating)=0.5 and poor memory performance], and demonstrated that almost 25% of memory-impaired patients became demented in 18 months and 50% progressed within 36 months. At baseline, the psychometric characteristics that predicted future dementia were poor utilization of semantic cueing and acquisition of information [4,5]. This finding would indicate that poor acquisition, rather than a normal correlate of aging as previously suggested, identifies preclinical dementia in many individuals. Despite this observation, both objective and self-reported memory difficulties are so prevalent that numerous attempts to define them in a diagnostic category have been only marginally successful. A work group from the National Institute of Mental Health [6] has defined

Abbreviations

AAMI—age-associated memory impairment; **apoE**—apolipoprotein E; **ERT**—estrogen replacement therapy; **MRI**—magnetic resonance imaging.

an entity called age-associated memory impairment (AAMI) that identifies individuals with self-reported difficulties, performance on memory tests one standard deviation below the mean of young individuals, adequate intellectual function (assessed by the Wechsler Adult Intelligence Scale–Revised), and absence of dementia defined by a score of 24 or more on the Mini-Mental State Examination. Several exclusion criteria eliminate medical, neurologic, and psychiatric conditions that potentially impair memory. The Diagnostic and Statistical Manual of the American Psychiatric Association has retained, in its fourth edition (DSM-IV), a similar concept under the rubric 'age-related cognitive decline' [7]. Much controversy exists on the reliability of the diagnostic criteria proposed. Self-report of memory difficulty as an inclusion criterion has been criticized, based on studies [8,9] that showed how the perception of forgetfulness related more to mood than actual performance; unawareness of deficits is one of the characteristics of many dementias with severe memory loss. In AAMI, objective memory decline, as defined by performance one or more standard deviations below the mean, could also be already detecting early dementia. The broad exclusion criteria for AAMI have been criticized as well because they might exclude too many legitimate cases of normal elderly people with chronic medical conditions. Most importantly, these definitions give no information regarding prognosis and include individuals who will go on to develop dementia, as well as clinically stable individuals. In this paper, we will review some of the recent investigations of cognitive changes in nondemented elderly people.

The prevalence of AAMI has not been clearly defined. Depending on methodology and ages of the samples studied, the reported prevalence ranges from 4.6–34.9% [10,11]. Recently, Koivisto *et al.* [12•] reported AAMI prevalence in a randomly selected population from Finland by applying the National Institute of Mental Health work group criteria. If only inclusion criteria were used, up to 53.8% of the population reported memory impairment; however, when all the exclusion criteria were applied, the prevalence decreased to 38.4%. Interestingly, prevalence rates of AAMI differed in different age groups, and instead of increasing with age, as would be expected, the prevalence rate declined in the oldest age groups, whereas objective memory decline increased. AAMI was also noted to be more prevalent in men than women. The authors concluded from these epidemiologic differences of Alzheimer's disease and AAMI that the two entities did not form a continuum as believed by many. In an excellent review by Larrabee and McEntee [13•], it is suggested that this finding might be an artifact of psychometric testing and the definition of dementia. One additional explanation might be that the prevalence of AAMI declines because a significant proportion of AAMI individuals develop dementia.

To support the hypothesis that mild memory impairment could represent an early phase of dementia, Small *et al.* [14•] have analyzed the cerebral glucose metabolism, as measured by positron emission tomography, in a sample of individuals considered at risk for Alzheimer's disease. The participants had a family history of Alzheimer's disease, mild memory complaint, but normal cognitive performance for their age. They were genotyped for the presence or absence of the apolipoprotein E (apoE) allele ε4, the gene described to be strongly associated with sporadic and late-onset familial Alzheimer's disease. The individuals who were found to have the ε4 allele differed from those without it, with respect to glucose utilization, showing significantly lower parietal metabolism and left/right asymmetry, which suggests already impaired cerebral function in the ε4 positive group before clinical manifestations. Indeed, the role of demographic and genetic characteristics in the pathogenesis and etiology of cognitive loss as well as Alzheimer's disease is becoming more evident, particularly in the case of apoE ε4. Petersen *et al.* [15•] have shown that the presence of the ε4 allele is the strongest predictor of future dementia in a group of elderly people with mild cognitive impairment.

Neuropsychological studies and prediction of future decline

Neuropsychological measures of performance are often examined as possible predictors of future decline. Masur *et al.* [16•] have demonstrated, with the use of an actuarial model, that several measures of cognitive function, in this case a measure of delayed recall, verbal fluency, visual memory, and the Wechsler Adult Intelligence Scale digit symbol subtest, could be used to calculate the probability of developing or not developing dementia in a cohort of healthy elderly people. Although the overall positive predictive value was only 68%, more importantly the negative predictive value for absence of future dementia (4 years of follow-up) was reasonably high at 88%. Using a similar statistical model but with a slightly different neuropsychological battery, we [17] also attempted to demonstrate whether the probability of future dementia could be determined in a longitudinal cohort of healthy elderly individuals. Although the measures in our study that best predicted the outcome of dementia were slightly different, the positive and negative predictive values were very similar. A measure of visual memory in the same longitudinal cohort (the Benton Visual Retention Test) indicated that a poorer performance as early as 10 years before the development of clinical signs identified those individuals who would decline cognitively in the future [18].

Similarly, Linn *et al.* [19] reported that most neuropsychological measures given to participants of the Framingham cohort, appeared to identify, 7 years or more in advance, those individuals who would subsequently develop Alzheimer's disease. All of these studies, together with previous investigations that demonstrate with univariate analysis that single psychological measures are predictive of future dementia, seem to indicate that at least for Alzheimer's disease, but probably for other types of dementia as well, the preclinical phase may start many years before the onset of symptoms, and that the

ability to detect dementia in advance depends essentially on the sensitivity of the instruments used. Far from being purely of academic interest, the demonstration of very early changes years before what is considered to be the usual clinical disease seems to indicate that for most dementias, the pathogenetic mechanisms operate earlier than previously suspected. These findings would seem to confirm the view of those who believe that mild cognitive impairment is on this continuum with future development of dementia. Along the same lines of a continuum, Corder *et al.* [20] have demonstrated a gene dose effect on the age of onset of Alzheimer's disease according to the apoE genotype. In this view, the presence of apoE$_4$ and the lack of a possible protective role of E$_3$ or E$_2$ apoE, determine accelerated pathological aging, a process that would occur anyway but more slowly. This opinion is similar to that of those individuals who think that we will all inevitably develop dementia should we live long enough. How the apoE genotype affects brain aging is still unclear. Many studies have shown that E$_4$ is associated with Alzheimer's disease but not with other types of dementia. If it is true that E$_4$ affects the rate of neuronal degeneration in the human brain from birth, it is conceivable that differences in cognitive performance could be identified in normal, elderly and even in younger individuals. Reed *et al.* [21•] studied a cohort of normal adult fraternal twin men (average age, 63 years), who were discordant for apoE genotype, and found that the men with at least one ε4 allele performed more poorly on several tests of cognitive function, compared with men without an ε4 allele.

Neuroimaging studies

Traditional anatomical as well as functional neuroimaging studies have also been employed in the investigation of cognitive function in normal elderly people. A magnetic resonance imaging (MRI) study by Soininen *et al.* [22] in patients with AAMI demonstrated volumetric asymmetry between the hippocampi, with more atrophy in the right hippocampus. The magnitude of this asymmetry correlated with scores on the Benton Visual Retention Test. A subset of these individuals also had smaller right amygdala compared with nonimpaired individuals. Breteler *et al.* [23] conducted a population-based study of the prevalence of white matter lesions in elderly individuals using MRI. They found that white matter lesions were associated with a poorer test performance, as well as subjective cognitive decline. These authors [24] also reported that the ventricular enlargement was associated with poorer scores on tests of global cognitive function, whereas white matter lesions were associated with poor performance on tests of executive function, suggesting impairment of the fronto–striatal systems. Rapp and Heindel [3] have previously reviewed the evidence of fronto–striatal dysfunction in normal aging. Given the great prevalence of white matter lesions in normal elderly people, it is possible that impairment of executive function in aging is related to these lesions. DeCarli *et al.* [25] have shown that temporal lobe volume does not decline in normal aging, whereas the posterior frontal lobe volume declines approximately 1% per decade. An interesting approach with neuroimaging was used by Stern *et al.* [26•] to analyze the effect of occupation before the development of Alzheimer's disease. This study demonstrated that individuals with occupations requiring higher interpersonal and cognitive skills, independent of previous education, had less perfusion in the parietal regions compared with individuals with less demanding jobs. This finding is similar to that demonstrating poorer parietal perfusion in Alzheimer's disease patients with higher educational levels when matched for severity of disease [27]. Although these studies were performed on demented individuals, it appears that individuals with higher levels of social and educational functioning tolerate a more significant decline in cerebral metabolism before demonstrating the same degree of dementia. Whether functional neuroimaging will become a tool to detect early changes in otherwise normal individuals is difficult to predict. Functional MRI may provide, in the future, higher sensitivity and better anatomical resolution than positron emission tomography. Grady *et al.* [28] analyzed the regional cerebral blood flow while individuals performed a face and a location matching task. Young participants had greater activation of the prestriate cortex, whereas older individuals demonstrated greater increases in cerebral blood flow in the occipital–temporal cortex. These findings suggest a more efficient utilization of visual cortical areas in young people compared with the old. Whether this finding can be generalized to other aspects of cortical and cognitive function remains to be demonstrated.

Endocrine function and cognition

The determinants of normal cognitive function in aging are being investigated in many aspects. A body of evidence is developing that describes a role for estrogens in female cognitive function. Henderson *et al.* [29•] found, in a sample of volunteers from the community recruited for a study of Alzheimer's disease and nondemented control individuals, that the latter were more likely to have used estrogen replacement therapy (ERT). In addition, demented patients who were using estrogens performed significantly better on the Mini-Mental State Examination compared with Alzheimer's disease patients not using ERT, and no differences in age, education or duration of symptoms were noted. Robinson *et al.* [30] reported that estrogen use in normal elderly women was associated with enhanced recall of proper names, but not of common words. The effect appears mild, but could be due to the difficulty of measuring cognitive changes in otherwise normal individuals with tests currently available, rather than to the little importance of estrogens in brain function.

Abnormalities in cortisol metabolism have been described in Alzheimer's disease [31,32]. In addition, several authors have described impaired cognitive per-

formance in depressed patients with hypocortisolism [33]. The role of cortisol in normal human cognition has not been fully explained, but increased cortisol levels also have been associated with poor cognitive performance. Lupien *et al.* [34] found that impaired cognitive performance was associated with evidence of hypothalamic–pituitary–adrenal dysfunction, and in particular with elevation of basal cortisol levels. Glucocorticoid-induced cognitive changes have been demonstrated in other studies. O'Brien *et al.* [35] showed, in a small number of patients from his sample, that lack of suppression of cortisol release, indicative of impaired glucocorticoid feedback, correlated with poor performance on a measure of cognitive function. Newcomer *et al.* [36] demonstrated impairment of verbal memory in normal adults after relatively low doses of dexamethasone; the effects were maximal at study day 4. The authors hypothesized that this was due to maximal binding of dexamethasone to hippocampal glucocorticoid receptors, indicating a specific effect of this steroid hormone on the anatomical structures essential in memory systems.

These studies, together with previous ones [37–40] showing an effect of glucose on memory performance in both normal elderly individuals and Alzheimer's disease patients, as well as abnormalities in glucose metabolism in Alzheimer's disease, suggest that hormones and alterations of endocrine function play a significant role in cognition in pathologic and nonpathologic aging.

Anti-inflammatories and prevention

Bruce-Jones *et al.* [41] studied cognitive function in healthy elderly persons during the administration of indomethacin and a placebo. Improved performance was demonstrated with paired-word associations after 8 days of treatment with indomethacin compared with the placebo. Similarly, a beneficial role of anti-inflammatories in cognition was suggested by Rogers *et al.* [42]. Supporting these observations, Breitner *et al.* [43•] studied 50 elderly Alzheimer's disease twin pairs with different ages of onset, and noted that the onset of Alzheimer's disease was inversely associated with prior use of nonsteroidals, corticosteroids, or adrenocorticotropic hormone. Rich *et al.* [44] found that Alzheimer's disease patients who used daily aspirin or nonsteroidal anti-inflammatory drugs performed better on several measures of cognitive function and declined less over 1 year on verbal fluency, spatial recognition, and orientation than nonusers. These findings support of a potential role for anti-inflammatory drugs in protection against Alzheimer's disease, and, less directly, suggest a possible role for these agents in mild cognitive abnormalities of the elderly.

Conclusion

Mild cognitive changes in the elderly, felt by many to be a normal correlate of aging, may in fact represent harbingers of future decline on a continuum with dementia. Answering this question depends partly on the methodological problems associated with longitudinal studies of aging populations and partly on the complexity of cognitive function in humans when anatomical, hormonal, environmental, and cultural factors interplay to produce the final result. The instruments used to study cognition may also contribute to the improvement of our understanding. Neuropsychological measures and functional neuroimaging appear at this point to be the most promising tools in this regard. A better understanding of mechanisms of cognitive impairment, together with early detection, will be helpful to devise possible future interventions.

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