Cerebral aging: neuropsychological, neuroradiological, and neurometabolic correlates

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The aging process is associated with a progressive cognitive decline, but both the extent of this decline and the profile of age-related cognitive changes remain to be clearly established. Currently, cognitive deficits associated with aging may be diagnosed under the categories of age-associated memory impairment, age-associated cognitive impairment, or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) category of age-related cognitive decline. Age-related decline has been reported for several cognitive domains, such as language (eg, verb naming, verbal fluency), visuospatial abilities (eg, facial discrimination), executive functions (eg, set shifting, problem solving), and memory functions (eg, declarative learning, source memory). There is an age-related decline in brain cortical volume, which primarily involves association cortices and limbic regions. Studies of brain metabolic activity demonstrate an age-related decline in neocortical areas. Activation studies using cognitive tasks demonstrate that older healthy individuals have a different pattern of activation from younger subjects, suggesting that older subjects may recruit additional brain areas in order to maintain performance.

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One of the most critical issues in geriatric medicine is how to separate the cognitive and radiological changes associated with the aging process from changes that pertain to highly prevalent diseases of the aged, such as dementia. To answer this important question, this review will focus on age-related changes in cognitive functions, brain structure, and brain metabolism, and will discuss methodological aspects relevant to the study of the aging process.

Phenomenological aspects of aging

Kral[1] proposed the term *benign senile forgetfulness* to describe the condition of aged individuals with nonprogressing memory problems, and considered dementia as a malignant type of senile forgetfulness. However, he later suggested that both types of senile forgetfulness could represent the extremes of a single underlying pathological process.[2] The benign character of this condition was further questioned by O'Brien et al,[3] who found that individuals with this diagnosis progressed to dementia at a rate of 9% per year.

An ad hoc National Institutes of Mental Health (NIMH) work group[4] proposed the term *age-associated memory impairment* (AAMI) to refer to the memory decline in otherwise healthy aged individuals and listed specific criteria for this condition *(Table I)*. These criteria define impairment respective to the healthy young, and allow all aged individuals to be diagnosed with AAMI provided they meet the criteria in *Table I*. Larrabee and Crook[5] reported that the frequency of

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- Age 50 years or over
- Complaint of memory loss affecting everyday functioning with gradual onset
- Memory test performance at least 1 SD below the mean established for young adults on a standardized test of secondary memory with adequate normative data
- Adequate intellectual function as determined by a scaled score of at least 9 on the vocabulary subtest of the WAIS
- Absence of dementia as determined by a score of 24 or higher on the MMSE
- Exclusion criteria, such as absence of specific medical conditions, depression, risk factors for stroke, history of repeated minor or single major head injury, drug or alcohol abuse, or recent use of psychotropic medications that might affect cognitive function

Table I. Diagnostic criteria for age-associated memory impairment. WAIS, Wechsler Adult Intelligence Scale; MMSE, Mini-Mental State Examination.

Adapted from reference 4 with permission: Crook T, Bartus RT, Ferris SH, Whitehouse P, Cohen GD, Gershon S. Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change: report of a National Institute of Mental Health Work Group. *Dev Neuropsychol.* 1986;2:261-276. Copyright © 1986, Lawrence Erlbaum Associates, Inc.

AAMI ranged from 26% for individuals aged between 30 and 39 years to 85% for individuals aged 80 years or older. Ratcliff and Saxton[6] pointed out that a diagnosis of AAMI does not imply a nonprogressive disorder, but could be an early stage of dementia for a subset of individuals with this diagnosis. Recent evidence suggests that cognitive deficits in AAMI may be not restricted to memory functions: Hänninen et al[7] found that a group of AAMI individ-uals were impaired in three out of four tasks assessing frontal lobe functions, and suggested that the label of AAMI may include a heterogeneous group of individuals.

Levy[8] proposed the term *age-associated cognitive decline* for those elderly individuals with deficits in memory and other cognitive domains, who do not meet criteria for dementia. The diagnosis of age-associated cognitive decline requires a report by an individual or reliable documentation of cognitive decline, an insidious onset or decline for at least 6 months, and impairment in two or more cognitive domains, such as memory, language, attention, concentration, thought, or visual functioning. The cognitive impairment needs to be documented by abnormal performance on cognitive testing, and performance may be at least one standard deviation below the mean value for the appropriate population, in the context of minimal impairment in activities of daily living. Exclusion criteria are psychiatric disorders, such as depression, organic amnestic syndrome, delirium, postencephalitic syndrome, postconcussion syndrome, or cognitive impairment related to drug effects. Koivisto et al[9] examined the prevalence of age-related cognitive decline in a randomly selected population from eastern Finland and found that 29% met criteria for this diagnosis.

Mild cognitive impairment (MCI) is the term proposed for those individuals with a memory impairment beyond that expected for age and education, who are otherwise not demented.[10] The diagnostic criteria for MCI are the following: (i) presence of memory complaint; (ii) normal activities of daily living; (iii) normal general cognitive function; (iv) abnormal memory for age; and (v) absence of clinical dementia.[11]

Petersen et al[11] demonstrated that about 12% of individuals with MCI may progress to Alzheimer's disease (AD), but a large proportion of MCI individuals will never convert to dementia. Quantitative measurements of brain atrophy and activation studies with functional magnetic resonance imaging (MRI) have separated MCI decliners from nondecliners (see reference 12 for a comprehensive review). Other authors[13] suggested that most individuals with MCI may eventually develop the neuropathology of AD, and question the usefulness of the definition MCI.

The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*[14] includes the category of *age-related cognitive decline,* which may be used whenever a decline in cognitive functions, as identified with specific neuropsychological instruments, lies "within normal limits given the person's age," with the provision that the cognitive impairment should not be caused by a psychiatric disorder (eg, depression) or a neurological condition (eg, AD). The *DSM-IV* also includes criteria for mild neurocognitive disorder with the provision that these criteria are subject to further study. The main feature of this syndrome is that the cognitive deficit should be the result of a medical condition *(Table II)*. The cognitive disorder is characterized by deficits in at least two cognitive domains, which may be confirmed through neuropsychological testing. The severity of the disorder is mild by definition, but should be severe enough to interfere with the patient's social and/or workplace functioning. The main differential diagnoses of mild neurocognitive disorder are dementia (with relatively more severe cogni-

A.	**The presence of two (or more) of the following impairments in cognitive functioning, lasting most of the time for a period of at least 2 weeks (as reported by the individual or reliable informant):** **(1) memory impairment as identified by a reduced ability to learn or recall information** **(2) disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)** **(3) disturbance in attention or speed of information processing** **(4) impairment in perceptual-motor abilities** **(5) impairment in language (eg, comprehension, word finding)**
B.	**There is objective evidence of a neurological or general medical condition that is judged to be etiologically related to the cognitive disturbance**
C.	**There is evidence from neuropsychological testing of an abnormality or decline in performance**
D.	**The cognitive deficits cause marked distress or impai ment in social, occupational, or other important areas of functioning and represent a decline from a previous level of functioning**
E.	**The cognitive disturbance does not meet criteria for a delirium, a dementia, or an amnestic disorder and is not better accounted for by another mental disorder**

Table II. Research criteria for mild neurocognitive disorder.
Adapted from reference 14 with permission: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV).* Washington, DC: American Psychiatric Press; 1994. Copyright © 1994, American Psychiatric Association.

tive deficits and more severe impairments in activities of daily living), a slowly evolving delirium, a postconcussion disorder, and cognitive deficits due to substance abuse or medications. The *International Classification of Diseases–10th revision (ICD-10) Classification of Mental and Behavioral Disorders*[15] includes the category of mild cognitive disorder with the cautionary note that this construct is still under consideration *(Table III)*.

In conclusion, a wide variety of terms and diagnostic criteria have been proposed for the process of age-related cognitive decline, from benign senile forgetfulness (whenever cognitive deficits are restricted to memory functions) to age-related cognitive decline (with more widespread cognitive deficits in the absence of dementia). One limitation of these criteria is that they fail to separate with adequate sensitivity and specificity those individuals with true benign cognitive decline from those that will progress to full-blown dementia.

Methodological issues

Most studies addressing age-related cognitive and neuroradiological changes have a cross-sectional design, ie, they examine differences between cohorts of young and elderly healthy individuals at a single point in time. One limitation of this strategy is the risk of a cohort effect (a cohort is defined as those people within a specific population who experienced the same significant life events within a given period of time). Thus, clinical differences between young and old groups of individuals may be more strongly related to different life experiences at certain ages, rather than to a true age effect. For instance, later-born subjects were reported to perform better on cognitive testing than earlier-born subjects tested at the same age.[16]

Longitudinal studies, in which the same group of subjects are examined over time, have a lower risk of cohort effects, but may suffer from important attrition, producing skewed samples at the end of the study. This may result in a "survivor effect," ie, a relative overrepresentation of healthier subjects at the end of a longitudinal study.[17] Medical conditions with a relatively higher prevalence in the elderly, such as chronic respiratory disorders, cardiovascular disease, and diabetes, may themselves produce cognitive deficits and also influence the results of longitudinal studies.

A.	The general criteria for F06 must be met (ie, evidence of systemic physical dysfunction)
B.	There is a disorder in cognitive function for most of the time over a period of at least 2 weeks, as reported by the individual or a reliable informant. The disorder is exemplified by difficulties in any of the following areas: (1) memory (particularly recall) or new learning (2) attention or concentration (3) thinking (eg, slowing in problem solving or abstraction) (4) language (eg, comprehension, word finding) (5) visuospatial functioning
C.	There is an abnormality or decline in performance in quantified cognitive assessments
D.	No *ICD-10*-based diagnosis of dementia, organic amnestic syndrome, delirium, postencephalitic syndrome, postconcussional syndrome, or other persisting cognitive impairment due to psychoactive substance use

Table III. Mild cognitive disorder.
Adapted from reference 15 with permission: World Health Association. *International Statistical Classification of Disease, and Related Health Problems–10th revision. The ICD-10 Classification of Mental and Behavioral Disorders. Clinical Description and Diagnostic Guidelines.* Geneva: World Health Organization; 1992. Copyright © 1992, World Health Organization.

In summary, cross-sectional studies comparing groups of young versus elderly individuals may suffer from a cohort effect, ie, differences may result not from a true age effect, but from the effects of membership in different birth cohorts. On the other hand, longitudinal studies may suffer from both significant attrition effects and a greater influence of medical problems on cognition among the elderly.

Age-related neuropsychological changes

The aging process is characterized by a progressive decline in cognitive function, which is illustrated by the fact that norms on the Wechsler Memory Scale for individuals over 70 years are about 54% lower than those for young adults.[6] Salthouse[18] found that age explained 17% to 31% of the variance in measures of reasoning in healthy individuals from 20 to 84 years of age. Most of these age-related effects were found on tasks of simple perceptual comparison speed and working memory. Age-related cognitive decline has been related to a variety of mechanisms, such as slowing of cognitive functions,[19] decline in attentional resources,[20] reduction in the efficiency of inhibitory processes,[21] deficits in associating aspects of an event into a coherent representation,[22] deficits in active and internally organized routines,[23] and a higher sensitivity to the information-processing requirements of cognitive tasks.[6] Schretlen et al[24] reported that age-related cognitive deficits are more pronounced on tasks that involve on-line problem solving and visuospatial information processing (also known as "fluid" spatial abilities) compared with tasks that involve overlearned knowledge and skills (also known as "crystallized" verbal abilities).

There are several longitudinal studies of cognitive decline in cohorts of young and old adults. Mortensen and Kleven[25] used the Wechsler Adult Intelligence Scale (WAIS) to examine a random sample of healthy individuals 50 years of age at the time of the initial evaluation, who had repeated evaluations 10 and 20 years later. They found a slight (3-point) decline on verbal IQ and a 7-point decline on performance IQ. The Seattle Longitudinal Study[26] examined a series of 500 healthy individuals between 21 to 70 years of age every 7 years, and found an earlier decline in fluid than in crystallized cognitive abilities. The Baltimore Longitudinal Study of Aging[27] assessed a series of healthy individuals between 30 and 80 years of age every 6 years. They found age-related declines in memory tasks, but minimal changes on tests of crystallized intelligence. The Duke Longitudinal Study of Normal Aging[28] assessed 267 healthy community-dwelling individuals between 60 to 94 years of age. After a mean follow-up of 21 years, there were significant declines in verbal IQ, performance IQ, and performance on visual, but not verbal, memory tasks. The Bonn Longitudinal Study of Aging[29] assessed cohorts of healthy individuals between 60 and 65 years of age and 70 and 75 years of age, during a 12-year period. They found a significant 5-point drop in verbal IQ for the older but not for the younger cohort; similar results were obtained on tests assessing psychomotor and executive functions. The Health and Lifestyle Survey[16] assessed more than 2000 healthy individuals 7 years apart. They found no significant changes in tasks of motor reaction time, visuospatial reasoning, and memory until the fifth decade, but there was a marked decline in all three tasks for individuals above 75 years of age. Snowdon and Lane[30] assessed 146 healthy subjects aged 65 to 95 years, 8 years apart. They found that about 50% of the individuals with a diagnosis of AAMI improved their cognitive performance during the follow-up period. Laursen[31] assessed four successive age cohorts born in 1952, 1942, 1932, and 1922 on two occasions with an interval of about 10 years. There were significant declines in spatial and verbal memory, visuomotor and visuospatial speed, concentration, and motor reaction time, but the overall cognitive decline was mild and of dubious clinical significance. No significant declines were found on tests of visuomotor and visuospatial precision, or visual perception. Laursen[31] also found that cohort, gender, and education accounted for a significant variance of cognitive decline, and suggested that age-related cognitive changes may occur not only as a function of chronological age, but also as a function of cohort differences in education, culture, and lifestyle. Schretlen et al[24] assessed 197 healthy community-dwelling individuals between 20 and 90 years of age with measures of crystallized-verbal and fluid-spatial abilities. Measures of crystalized-verbal abilities showed a significant correlation with education, but not with age, and the opposite pattern was found for measures of fluid-spatial abilities. Most of the age-related variance in fluid-spatial abilities was explained by perceptual comparison speed and working memory.

Before addressing age-related changes on individual cognitive domains, several factors that may influence performance need to be addressed. First, elderly individuals may be slower than younger ones and may be

penalized on timed tasks: given free time, they could eventually prove to be as accurate as younger individuals. Second, elderly individuals may feel less challenged to perform well compared with young people. Third, elderly people have a higher prevalence of visual and auditory acuity problems, which may have an important impact on specific cognitive tasks. Lindenberger and Baltes[32] reported that visual and auditory acuity may together account for 93% of the age-related variance on intelligence, and Grady and Craik[33] suggested that sensory acuity may simply be an "indication of the physiological integrity of the aging brain." Visual resolution,[34] spatial contrast sensitivity,[35] and sensitivity to motor discrimination[36] were all reported to decline with age. Fourth, elderly individuals may become fatigued earlier than younger individuals, which may be an important limitation whenever long testing sessions are used. However, a recent study by Uttl et al[37] could not demonstrate evidence of age-related fatigue effects after a long (3 to 4 hours) neuropsychological evaluation in a sample of healthy individuals between 18 and 91 years of age.

Language functions

Several studies found no significant differences between 40- and 70-year-old healthy individuals on the vocabulary subtest of the WAIS, demonstrating a lack of age-related changes in semantic functions.[38] Verbal naming to confrontation, as assessed with the Boston Naming Test, requires the individual to name objects depicted in line drawings, and this task was consistently reported to be abnormal in the initial stages of dementia.[39] Several studies demonstrated either no or only a mild age effect on the Boston Naming Test,[40,41] suggesting that aging may not impair word-finding abilities.[42] On the other hand, Ramsay et al[43] reported a significant age-related decline on a confrontation naming test for verbs, but not for nouns, in a sample of 66 healthy adults aged 30 to 79 years.

Verbal fluency is the ability to generate words belonging to a specific semantic category (eg, animals, fruits), or beginning with a specific letter (eg, F, A, and S) within a limited amount of time. Cross-sectional and longitudinal studies have demonstrated an age-related decline on this task.[44,45] Huff[42] suggested that the aging effect in verbal fluency, but not in verbal naming, may result from age-related deficits to retrieve words from lexical-semantic memory. He added that the word-retrieval process mediated by automatic mechanisms may not decline with age, but an age-related deficit may become evident whenever a task requires strategic search processing.

Visuospatial abilities

A wide variety of cognitive tasks, such as those assessing visual discrimination, visual recognition, visual attention, spatial memory, and spatial planning, are subsumed under the category of "visuospatial skills." Eslinger and Benton[46] found that elderly individuals performed significantly worse than younger ones on tests of facial discrimination and judgment of line orientation, and Danziger and Salthouse[47] reported more errors on a task of visual perceptual decision in elderly as compared to young individuals. Ogden[48] suggested that the age-related decline in spatial abilities may be primarily related to the specific visual, perceptual, and memory demands of the task, and stressed the importance of assessing visuospatial functions in the elderly using tasks not influenced by sensory deficits or perceptual-motor slowing.

Executive functions

Executive function refers to those processes by which an individual optimizes performance, such as the ability to respond flexibly and appropriately, the efficient scheduling of behavior and attentional resources, the suppression of inappropriate responding, the use of strategies to enhance memory functions, and the formulation of new plans of action.[49] Measurements of executive abilities were reported to predict functional autonomy and functional living skills in older adults.[50,51]

Several cognitive mechanisms, such as planning, concept formation, problem solving, and set shifting, are usually considered to belong to the executive function domain. Set shifting is the ability to initiate a new concept and suppress a previously employed concept that is no longer appropriate to the task. This ability is usually assessed with the Wisconsin Card Sorting Test (WCST), which measures the ability to develop and apply new concepts and subsequently shift sets. Haaland et al[52] assessed the WCST in healthy individuals ranging from 64 to 87 years of age, and found that only those over 80 years of age had deficits on this task. Cronin-Golomb[53] demonstrated mild age-related deficits in concept formation and set-shifting abilities, but stressed that these

deficits could be also related to memory load and task complexity. Similar findings were reported by Fristoe et al,[54] who found that most of the age-related deficits in WCST were significantly correlated with declines in simple perceptual comparison speed and working memory. Problem solving involves the perception of a problem, the generation and testing of ad hoc hypotheses, and the finding of a correct solution.[53] Age-related deficits in problem-solving abilities have been demonstrated on a variety of tasks, such as the understanding of syllogisms,[55] the resolution of abstract problems,[56] and performance on the Tower of Hanoi puzzle (a planning task)[57] and the Stroop Test (which assesses concentration and the ability to ignore distraction).[58] Cronin-Golomb[53] suggested that age-related deficits in problem solving could be also related to both the verbal or visuospatial demands of the task, and the integrity of memory systems.

Robbins et al[49] assessed age-related decline in executive functions in a large sample of healthy individuals ranging in age from 21 to 79 years. They found a significant difference on tests of attentional set shifting between young and old healthy individuals, but there were no significant between-group differences on tests of spatial span, spatial working memory, or spatial planning. On the basis of these findings, Robbins et al[49] suggested that deficits in speed of information processing may not play an important role in age-related cognitive decline. This was further supported by Keys and White's study,[59] which showed that age-related decline in executive performance (as assessed by tests of set shifting) remained significant after controlling for the contribution of psychomotor speed.

Memory functions

In a recent review, Burke and Mackay[60] suggested that highly practiced skills and familiar information, such as procedural learning (ie, the unconscious learning and recall of specific skills) and some aspects of semantic (ie, knowledge about words, ideas, and concepts) and autobiographical memory, are relatively better preserved in old age than memory processes that require new associations, such as recall of recent personal events, the context in which a fact was acquired (ie, source memory), and the use of encoding strategies that enhance the acquisition and retention of information.[61] The recall of an event involves retrieving both contextual information and the source of the event to be recalled. These abilities may decline with age, in parallel with decline in frontal lobe functioning.[62] Recent memory is the ability to identify which of two stimuli presented previously was seen the most recently, and several studies have demonstrated an age-related decline in this ability.[63] Fabiani and Friedman[64] reported an age-related decrement for the recall of both verbal and pictorial stimuli, whereas an age-related decline in recognition memory was found only for verbal stimuli.

Working memory refers to the capacity to hold information in mind for short periods in time, and to use or manipulate this information in thinking and problem-solving tasks. Kirasic et al[65] assessed information-processing speed, working memory capability, and declarative learning in a sample of 477 healthy adults ranging in age from 17 to 86 years. They found significant age-related decrements in all three tasks, and suggested that working memory may be the most important age-related mediator in declarative learning and general processing speed.

Adamowicz and Hudson[66] reported age-related decrements on a visual memory test, and pointed out that errors on this task were significantly related to the complexity of the stimulus. Shelton et al[67] found a significant age-related decrement on a visuospatial paired-associate memory task, which was similar in magnitude to age-related decrements found on a verbal paired-associate memory task. Light and Zelinski[68] reported that healthy elderly individuals had significantly more deficits in encoding and recalling spatial locations than young individuals. Fahle and Daum[69] reported age-related decline in the ability to recall complex geometrical patterns. In a recent study, Jenkins et al[70] assessed groups of healthy young and older adults using visuospatial and verbal processing speed, working memory, and paired-associate learning tasks. They found significant differences between young and old adults on all three tasks, but the differences were relatively greater on visuospatial tests than on verbal tests. On the basis of these findings, Jenkins et al[70] suggested that visuospatial cognition is relatively more affected by aging than verbal cognition.

Raz et al[71] carried out MRI volume measurements of cortical regions and assessments of executive functions, working memory, explicit memory, and priming in a series of healthy individuals ranging from 18 to 77 years of age. They found age-related deficits on all cognitive tasks, although the association was lower for priming

tasks. They also found an age-related loss of prefrontal cortical volume, which was significantly correlated with more severe verbal perseverations. Loss of volume in cortical areas processing visual information was significantly related to lower performance on nonverbal working memory tasks, but the volume of limbic regions was not related to any of the cognitive tasks assessed.

In conclusion, age-related cognitive changes have been reported in several domains such as language (eg, verb naming and verbal fluency), visuospatial functions (eg, face recognition), and executive functions (eg, set shifting, problem solving). Age-related decline in memory functions are substantial in tasks of declarative learning involving free and cued recall, source recall, and prospective memory (ie, remembering to carry out an intention at a future time). On the other hand, age-related declines are relatively milder on tasks of implicit, short-term, and recognition memory.

Age-related brain structural changes

Although both radiological and pathologic studies have demonstrated age-related declines in brain volume, several methodological limitations should be acknowledged. Neuroimaging comparisons between young and elderly healthy individuals may be influenced by subject sample (eg, healthy individuals from the community versus patient samples with normal scans), sample size (studies with small samples have a higher probability of negative findings due to low power), gender and body size (there are gender-related differences in brain size, and there are no accepted methods to correct brain volumes for head or body size), and handedness (differences in brain size or symmetry may be associated with hand dominance).[17]

Coffey et al[72] reported an age-related reduction of brain volume of 2.8 mL/year from ages 65 to 95 years, and also found that age-related brain changes are greater for ventricular volume (about 3% per year) than for brain tissue (about 0.5% per year). On the basis of these findings, Coffey[17] suggested that ventricular enlargement may be a more sensitive marker of the aging process than brain tissue atrophy. Age-related reductions were also reported for total cortical volume[73] and for specific brain structures such as the basal ganglia,[74] the frontal temporal, parietal, and occipital lobes, the amygdala-hippocampal complex, the cerebellum, and the midbrain (see reference 17, for a comprehensive review).

Mueller et al[75] carried out volumetric MRI brain measurements in 11 "young-old" (mean age 70 years), 15 "middle-old" (mean age 81 years), and 20 "oldest-old" (mean age 87 years) healthy individuals. These subjects were scanned twice, 5 years apart. A cross-sectional analysis of brain volumes demonstrated a significant correlation between age and total brain, left hemisphere, right hemisphere, frontal and temporal lobes, hippocampus, and parahippocampal volumes. On the other hand, the longitudinal analysis showed a similar rate of change in brain regional volumes for all three groups, suggesting that the rate of change in brain volume does not differ significantly after age 65.

Whereas no significant age-related changes have been reported for total white matter volume,[76] age-related volume reductions have been reported for specific white matter regions, such as the prefrontal white matter,[77] and the corpus callosum.[78] Age-related changes in brain shape have been recently reported by Magnotta et al,[79] who found sharper cortical gyri and flatter and less curved sulci with increasing age.

White matter hyperintensities have been reported to be more frequent in old as compared to young individuals. Ylikoski et al[80] suggested that white matter hyperintensities could produce specific intellectual impairment in the elderly, such as slowing of motor, attentional, and mental processing functions. In a 10-year follow-up study, Swan et al[81] reported that healthy individuals with relatively larger white matter hyperintensities had a greater decline on measures of planning, sequencing, response, set shifting, psychomotor speed, working memory, selective attention, and response selection as compared with individuals with normal MRI scans, suggesting that some of the age-related cognitive decline may be explained by greater white matter hyperintensities. De Groot et al[82] examined the association between periventricular and subcortical white matter hyperintensities and cognitive deficits in more than 1000 community-dwelling healthy individuals. After adjusting for atrophy, stroke history, educational level, and presence of depression, they found a significant association between neuropsychological deficits (primarily psychomotor speed) and periventricular, but not subcortical, white matter hyperintensities. Inzitari et al[83] suggested that a direct effect of white matter hyperintensities on cognition may be explained by dis-

connection between cortical and subcortical brain regions due to fiber tract demyelination and gliosis.

Schretlen et al[24] assessed a group of 112 healthy young and old adults with high-resolution MRI and tasks of perceptual comparison speed, working memory, and executive functions. One of their main findings was that both age and executive abilities had a significant correlation with frontal lobe volume (ie, older age and more deficits on executive functions were significantly related to smaller frontal lobes). A similar correlation between more perseverations on a set-shifting task and smaller frontal lobe volumes was reported by Raz et al.[71]

Several studies tried to disentangle the neuropathologic changes specific to AD from those related to the aging process. Brains of elderly cognitively normal individuals may show the initial changes of AD, such as senile plaques, neurofibrillary tangles, and Lewy bodies, albeit below the amount required to make a pathologic diagnosis of a specific neuropathologic condition.[84] These changes were considered as either part of the normal aging process, or as incipient AD.[85] In a sample of 10 brains from cognitively normal individuals aged 85 to 105 years at time of death, Hulette et al[86] found a relatively poorer cognitive performance in tasks of memory and executive functions in those individuals with the neuropathological changes of early AD compared with individuals with normal brains. This lack of brain pathological changes in a subgroup of elderly individuals demonstrates that AD is not a final common pathway for the oldest-old.

In conclusion, age-related volume reductions were reported mainly for the frontal lobes and limbic regions. This process is not linear, but may occur at specific stages of life. White matter hyperintensities are related to older age and may explain some of the age-related cognitive decline. The early neuropathological changes of AD may account for mild cognitive deficits in nondemented elderly individuals.

Age-related brain metabolic changes

Age-related changes in brain metabolic activity have been measured with a variety of direct and indirect techniques, but relevant confounding factors, such as reduced visual and auditory acuity and subclinical cerebrovascular disease, have not been adequately controlled. Moreover, most studies on age-related brain metabolic changes have a cross-sectional design.[87]

Several studies using positron emission tomography (PET) report age-related metabolic reductions in cortical association regions, with a linear decrease in cerebral oxygen consumption of about 5% to 6% per decade (see reference 87, for a comprehensive review). Martin et al[88] found a significant age-related decline in cerebral blood flow in frontal, temporal, and parietal association cortices, and in limbic regions. Marchal et al[89] reported a significant age-related decline in frontal cerebral blood flow, as well as widespread cortical decreases in brain oxygen consumption. Eustache et al[90] carried out a comprehensive neuropsychological evaluation and high-resolution PET study in a sample of healthy subjects between 20 and 68 years of age. They found an age-related linear decrease in brain oxygen consumption, most signficant for the neocortex and the left thalamus. Schultz et al[91] used $[^{15}O]H_2O$ PET to map the continuum of normal age-related changes in cerebral blood flow from early to mid-adulthood (19 to 50 years of age). They found a negative correlation between age and cerebral blood flow in mesial frontal cortex, and speculated that this metabolic decline may be associated with changes in memory and executive functions in later life. In a recent study, Garraux et al[92] found an age-related frontal cortical hypometabolism, mainly involving the anterior cingulate and the medial and dorsolateral areas. They suggested this age-related frontal hypometabolism could be related to a decrease in synaptic activity in frontal regions.

Horwitz et al[93] compared correlations between metabolic activity in pairs of brain regions in young (28–32 years old) and elderly (64–83 years old) healthy individuals. The young group showed a higher number of significant correlations primarily in frontal and parietal areas as compared with the older group. On the basis of these findings, Horwitz et al[93] suggested that older individuals may have a relatively lower functional integration among regions of the parietal and frontal lobes than younger individuals.

Several studies used either PET or functional MRI to examine the pattern of brain activation during performance of specific cognitive paradigms in young versus old individuals. Grady et al[94] found significant differences in the pattern of brain activation between healthy young and elderly individuals during the performance of spatial location and object recognition tasks. In a subsequent study, Grady et al[95] reported a stronger activation of hippocampal and frontal regions during memory tasks in

young than older individuals. They suggested that memory decline in the elderly could be related to reduced activation of hippocampal and frontal regions during the encoding of information. Other studies[96,97] demonstrated a pattern of left frontal activation during encoding and right frontal activation during recall in young adults, whereas older individuals showed more bilateral activation of the frontal lobes. Cabeza et al[96] hypothesized that elderly individuals may recruit additional brain areas in order to maintain function. Reuter-Lorenz et al[98] showed that young adults had greater left activation during a verbal task of executive function, and a greater right frontal activation during a spatial task. On the other hand, older adults had bilateral frontal activation during both types of task. Madden et al[97] reported that old adults had increased left prefrontal activation, but worse memory performance than younger adults, suggesting that recruiting additional brain areas does not necessarily improve cognitive function. In a recent study, Cabeza et al[99] found that the right prefrontal cortex in young adults was more activated during temporal-order retrieval than during item retrieval, but this task-related difference was not found in elderly individuals. On the other hand, elderly individuals showed stronger activations than young adults in the left prefrontal cortex, which may be a compensatory effect.

In summary, several studies demonstrated an age-related decline in cerebral blood flow in association cortices and limbic regions, as well as an age-related decline in functional integration of neocortical areas. Activation studies demonstrated a relatively more restricted and lateralized pattern of activation in young than in older healthy individuals, suggesting that older individuals may recruit additional brain areas in order to maintain function.

Conclusion

Age-related cognitive decline is a well-known phenomenon, which was subsumed under a variety of terms, such as age-associated memory impairment (whenever the decline is restricted to memory functions) and age-associated cognitive impairment (whenever the cognitive decline relates to memory and/or other cognitive functions). These deficits may also be coded under the *DSM-IV* category of "age-related cognitive decline." Age-related declines are reported for language functions (such as verb naming and verbal fluency), visuospatial abilities (such as facial discrimination and visual perceptual decision), executive functions (such as set shifting, problem solving, and abstract thinking), and memory functions (such as declarative learning, prospective memory, and source recall). Age-related declines in the above domains are not independent phenomena, but may relate to one another (eg, deficits in executive functions and processing speed may impair performance on other cognitive domains). Neuroimaging studies demonstrated an age-related decline in neocortical gray matter volumes (mainly involving association areas) and limbic-related regions. Age-related metabolic declines were found in similar brain neocortical regions; and activation studies using either functional MRI or PET found a differential pattern of brain activation in old and young healthy individuals on tasks of memory and executive functions. Healthy old subjects were reported to recruit additional brain areas as compared with younger ones, but this functional change is not necessarily associated with improved performance. ❑

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Envejecimiento cerebral: correlatos neuropsicológicos, neurorradiológicos y neurometabólicos

El proceso del envejecimiento se asocia con una progresiva declinación cognitiva, pero tanto la extensión de esta declinación como el perfil de los cambios cognitivos relacionados con la edad deben ser claramente establecidos. Actualmente los déficits cognitivos asociados con el envejecimiento pueden ser diagnosticados bajo las categorías de deterioro de memoria asociado con la edad, deterioro cognitivo asociado con la edad o la categoría de declinación cognitiva relacionada con la edad del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-IV). La declinación relacionada con la edad ha sido comunicada en varias áreas cognitivas tales como el lenguaje (por ej. denominación de verbos, fluidez verbal), habilidades visoespaciales (por ej. discriminación facial), funciones de ejecución (por ej. cambios de escenario, resolución de problemas) y funciones de memoria (por ej. aprendizaje declarativo, memoria de fuente). Hay una declinación relacionada con la edad que se expresa en el volumen cerebral y que primariamente involucra cortezas de asociación y regiones límbicas. Los estudios de la actividad metabólica cerebral demuestran una declinación relacionada con la edad en áreas neocorticales. Los estudios de activación que emplean pruebas cognitivas demuestran que individuos sanos de edad avanzada tienen un patrón de activación diferente de los sujetos más jóvenes, lo que sugiere que los sujetos de mayor edad pueden reclutar áreas cerebrales adicionales para mantener su rendimiento.

Vieillissement cérébral : corrélations neuropsychologiques, neuroradiologiques et neurométaboliques

Le processus de vieillissement est associé à un déclin cognitif progressif, mais l'étendue de ce déclin et le profil des modifications cognitives liées à l'âge restent encore à définir avec précision. Actuellement, les déficits cognitifs associés à l'âge sont regroupés dans les catégories suivantes : troubles mnésiques associés à l'âge, troubles cognitifs associés à l'âge, ou déclin cognitif lié à l'âge, cette dernière catégorie étant celle du DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4e édition). Le déclin cognitif lié à l'âge se manifeste dans plusieurs domaines de la cognition comme le langage, (par ex., reconnaissance sémantique des verbes, fluence verbale), les capacités visuospatiales (par ex., identification des visages), les fonctions exécutives (par ex., capacité d'adaptation des schèmes mentaux, résolution de problèmes) et les fonctions mnésiques (par ex., apprentissage déclaratif, mémoire source). Il existe une diminution du volume cérébral cortical liée à l'âge qui concerne principalement les aires corticales associatives et les régions limbiques. Les études portant sur l'activité métabolique cérébrale mettent en évidence un déclin lié à l'âge des aires néocorticales. Les études d'activation utilisant les tâches cognitives montrent que le schéma d'activation des sujets sains âgés diffère de celui des sujets plus jeunes, suggérant la possibilité d'un recrutement d'aires cérébrales supplémentaires chez les sujets plus âgés pour maintenir un niveau de performance plus élevé.

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