Cognition in aging and age-related disease

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1. Introduction

Aging processes result in changes in cognitive ability, although the magnitude of the changes can vary markedly. At one extreme are individuals who develop dementia and for whom living independently becomes increasingly difficult. At the other end of the spectrum are individuals who note age-related cognitive changes but for whom these cognitive alterations do not interfere significantly with their ability to live independent and enriching lives. Between these two groups are individuals who have cognitive profiles that do not qualify them for dementia but who have cognitive deficits beyond those attributable to normal aging processes. This group of older adults may represent those at risk for developing dementia, or they may be older adults who have always been at the lower end of the normal distribution of cognitive ability. This chapter compares the cognitive performance of individuals with age-related disease (Alzheimer's disease [AD], Section 2; or Parkinson's disease [PD], Section 3), those with mild cognitive impairment (MCI, Section 4), and those who are aging successfully (or "normally," Section 5). We relate the cognitive profiles to the neural changes associated with each condition.

2. Cognitive decline in Alzheimer's disease

Although AD is characterized by multiple brain abnormalities, the neuropathological diagnosis at autopsy depends solely on an abundance of two kinds of abnormal structures: extracellular neuritic plaques and intracellular neurofibrillary tangles. Before death, a diagnosis of "probable AD" can be made, based on the patient's symptoms, and the elimination of other causes of dementia. This diagnosis is accurate in 80% to 95% of cases. In the following sections, we discuss the cognitive symptoms associated with AD.

2.1. Long-term memory deficits

The cognitive profile of AD is distinct from the deficits seen in nonpathological aging. Individuals with mild AD usually manifest deficits in retrieval of information from long-term memory. Recall of recent events and experiences are disproportionately affected, whereas remote memories are often relatively spared. In fact, this inability to remember recently learned information has been found to be the best way to distinguish individuals with AD from other adults who do not have dementia (Locascio et al, 1995).

The deficit in the ability to form new long-term memories (i.e., anterograde amnesia) is thought to result from atrophy to medial temporal-lobe structures. In particular, the hippocampus (so-named because of its seahorse shape) and its surrounding structures (often referred to as the "hippocampal formation") are the most affected, even in mild AD, where the hippocampal formation may show as much as a 25% volumetric reduction. In contrast, a less pronounced volumetric decrease occurs in the hippocampal formation with MCI and nonpathological aging. In fact, volume of the entorhinal cortex serves as one of the best predictors of those who will convert to AD (de Toledo-Morrell et al., 2000)

2.2. Semantic memory deficits

In more advanced stages of AD, the anterograde amnesia worsens, likely due in part to increased atrophy in the hippocampal formation and prefrontal cortex. In addition, cellular abnormalities extend beyond the hippocampal formation to surrounding regions of the temporal neocortex. This region of the brain is thought to be of particular importance for our ability to retrieve semantic information (factual knowledge); thus, patients with advancing AD exhibit increased word-finding difficulties. Patients' performance on tests of verbal fluency and confrontation naming is among the best ways to track the progression of AD (Locascio et al, 1995).

3. Cognitive decline in Parkinson's disease

Although motor symptoms dominate the clinical picture in PD, the disease also results in specific cognitive deficits. In addition, dementia is relatively common in PD; estimates of its prevalence in PD patients range from 4% to 41%. Although researchers have debated whether the dementia typically results from the neuropathological changes that characterize AD (i.e., neuritic plaques and neurofibrillary tangles), or from the presence of Lewy bodies (consisting of deposits of alpha-synuclein protein), recent evidence suggests that diffuse (neocortical and subcortical) or transitional (primarily limbic) Lewy body disease is the most frequent pathologic cause of dementia developing later in PD (Apaydin et al, 2002).

Even in nondemented patients with PD, cognitive alterations commonly occur. These deficits are more subtle than the motor symptoms, and are much less pronounced than the cognitive changes seen in individuals with dementia. They are thought to result from alterations in (and in pathways between) two regions of the brain: the basal ganglia and prefrontal cortex. The basal ganglia are affected because they receive their primary input from dopaminergic cells in the substantia nigra (a pigmented region of the brainstem on which PD exerts its primary effect; Agid, 1989). The prefrontal cortex is affected because of the rich projections that it receives from the basal ganglia (Alexander and Crutcher, 1990). Later we discuss the cognitive symptoms that result from dysfunction in these brain regions in PD.

3.1. Cognitive slowing

One of the most noted cognitive changes in nondemented patients with PD is *bradyphrenia* (cognitive slowing), the counterpart to *bradykinesia* (motor slowing), one of the diagnostic features of the disease. As a result, PD patients often take longer to work through mental problems, and can require more time when trying to learn new information.

3.2. Attention deficits

Another cognitive effect of PD is attentional inflexibility: PD patients find it difficult to shift attention from one item or characteristic to another. This type of attentional flexibility is required in daily life, for example, when we must shift our attention from one conversation to another at a social gathering. In the laboratory, this capacity is often assessed by first asking people to sort items based on one characteristic (e.g., shape), and then by asking them to sort based on another characteristic (e.g., color). PD patients find it difficult to shift their attention from one dimension to another.

PD patients also show deficits in cognitive inhibition (Hasher and Zachs, 1988): The ability to inhibit a dominant or prepotent (but incorrect) response to produce the correct response. For example, if a person is shown the word RED written in green ink, and is asked to say the color of ink in which the word is written, that person must inhibit the tendency to read the word ("red"), and instead name its color ("green"). Patients with PD find these tasks requiring inhibition much more difficult than do age-matched, healthy adults (Kensinger et al, 2003).

4. Cognitive decline in mild cognitive impairment

Some individuals seem to straddle the division between normal aging and dementia. They do not meet the criteria for dementia, yet they have cognitive impairments beyond those associated with normal aging. Interest has focused on these individuals because they may have an increased risk of developing dementia. As symptomatic treatments for AD become available, it will be important to have a method of diagnosing individuals at risk for developing the disease (or identifying individuals in the first stages of the disease). Toward this aim, criteria have been formulated for the diagnosis of MCI by the Mayo clinic Alzheimer's Disease Research Center. They are (1) memory complaint, (2) normal activities of daily living, (3) normal general (overall) cognitive function, (4) impairment in one area of cognitive function, which could include memory (scores must be more than 1.5 SD below age-appropriate norms), (5) a clinical dementia rating score of 0.5, and (6) absence of dementia (Petersen et al, 1995).

A diagnosis of MCI is associated with increased risk of dementia, with some studies showing that as many as half of participants diagnosed with MCI convert to dementia (most frequently AD) in a span of 5 years or fewer. The rate of conversion is still being researched, however, as is the prevalence of this cognitive impairment. The conversion and prevalence rates may also differ depending on the exact criteria used to diagnose an age-related cognitive impairment (Hanninen et al, 2002).

The link between MCI and AD is supported not only by the high conversion rate from MCI to AD but also by genetic and neuropathological similarities between individuals with the two diagnoses. For example, MCI patients often have pronounced medial temporal lobe atrophy, as do patients with AD (see Section 2) . MCI patients also show alterations in the concentration of amyloid-beta protein, associated with the neuritic plaques, one of the hallmarks of AD. A genetic risk factor for AD-

presence of the e4 allele of the apolipoprotein E (ApoE) gene-is also over-represented in individuals with MCI.

5. Cognitive decline in nonpathological aging

Cognitive decline is a normal part of aging and is a result of brain changes that accompany normal aging. Although there is about a 2% reduction in the weight and volume of the brain every decade, this loss is not distributed equally throughout the brain. Rather, two regions of the brain appear disproportionately affected by aging: the medial temporal lobe and prefrontal cortex. Volumetric loss in these regions appears to result primarily from neuronal atrophy (shrinkage), although neuronal loss may also contribute. These brain changes result not in global cognitive deterioration, but rather in specific areas of decline. Below we discuss the areas of cognition that are disproportionately affected by aging, and their relation to age-related brain changes.

5.1. Word-finding difficulties

Aging results in an increased difficulty retrieving information from semantic memory. The ability to retrieve proper names is particularly vulnerable (Burke et al, 1991). Older adults frequently comment on their inability to generate the name of an old acquaintance, a movie star, or a favorite restaurant. Such retrieval attempts are often accompanied by a "feeling-of-knowing" or a "tip-of-the-tongue" state: A word seems just out of reach, that is, a retrieval failure prevents the generation of that word. In these situations, individuals can often correctly choose the name from a list, and if told the name, will usually recognize it as the correct choice. Although tip-of-the-tongue states occur in adults of all ages, their frequency increases with aging. This type of proper name retrieval can be frustrating and embarrassing for many older adults.

Why might this type of retrieval deficit occur with normal aging? Researchers are still investigating the phenomenon, and the critical neural substrates. Recent MRI studies have found that tip-of-the-tongue states are associated with increased activation in regions of the right inferior and middle frontal cortex, anterior cingulate, and right middle temporal cortex (Maril et al, 2002). Age-related abnormalities in these regions, or in parietotemporal regions important for storage of semantic information, may lead to the increased frequency of tip-of-the-tongue effects.

5.2. Episodic memory impairments

As discussed earlier, episodic memory impairments are one of the first symptoms of AD (see Section 2). Older adults without dementia, however, have some difficulties in learning or retrieving episodic memories. The age-related impairment becomes evident when older adults are asked to retrieve detailed information about an episode (e.g., In what magazine did I read that Jennifer Lopez got a divorce?). The memory for this type of detail is often referred to as "source memory"; it is thought to rely on functions of the prefrontal cortex (Johnson, 1997). Older adults' impairments on these types of memory tasks are therefore thought to be related to atrophy in prefrontal cortex.

Older adults also are challenged when they must learn to associate one item with another item (e.g., a face with a name). In the laboratory, this capacity has often been tested by asking people to learn pairs of unrelated words. On these sorts of associative learning tasks, older adults are typically impaired. The deficit likely results from a combination of deficits during the learning phase (e.g., older adults appear less likely to use mnemonic strategies that will help them learn the information) and during retrieval. The hippocampal formation plays a critical role in associative learning. Thus, neuroimaging studies of associative learning have found activation in the medial temporal lobe when participants are asked to associate two types of information together (Sperling et al, 2001), and have found age-related abnormalities in the recruitment of medial temporal lobe structures during this type of task (Mitchell et al, 2000).

6. Risk factors and protection from pathological aging

Many diseases or illnesses can be linked to a specific cause. The age-related diseases discussed in this chapter do not fit this model. The causes of AD, PD, and MCI are not known, and it is likely that disease onset results from many factors, including biological and environmental. Research has, therefore, focused on what factors could increase ("risk factors") or decrease ("protective factors") the likelihood of disease development (Table 1; Cupples et al, 2000; Herman et al, 2002; Selkoe et al., 2001; Vaughan et al., 2001).

The influence of such factors can be assessed in two ways. The first is to follow a group of healthy individuals prospectively over time to determine which people develop a disease. If a larger proportion of individuals with a specific genetic or environmental trait develops the disease (versus those without that trait), this result suggests a "risk factor." If a smaller proportion develops the disease (versus those without that trait), this result suggests a "protective factor." A second approach (which is less rigorous) is to compare individuals who have AD with age-matched individuals who do not. Factors that occur more frequently in the AD group than in the non-AD group are "risk factors," and characteristics that are underrepresented in the AD group are "protective factors." Studies continue to investigate the reliability of these factors in influencing disease development. Additional studies are being conducted to examine whether any of the proposed protective factors can slow or halt disease progression in individuals who already show signs of pathological aging.

7. See also

Aging of the brain
Aging of the brain and Alzheimer's disease
Cognition
Cognitive aging
Parkinsonian syndromes
Death of neurons during development
Learning and memory

8. Further reading

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Table 1. Risk Factors and Protective Factors associated with AD and PD.

Disease	Factor Type	Proposed Risk Factors	Proposed Protective Factors
AD	Biological	Increasing age Female Sex Mutations in *APP* (apolipoprotein), *PS1* (presenilin-1), *PS2* (presenilin-2) genes ApoE ε4 allele Down syndrome	Apo E ε2 allele
	Environmental	Head injury	Anti-inflammatory Drugs Post-menopause hormone replacement therapy Statins (cholesterol lowering drugs) High education level Antioxidants Alcohol
PD	Biological	Increasing age Male sex *SNCA* (alpha-synuclein) and *parkin* genes	
	Environmental	Emotional stress Head injury	Smoking Antioxidants Coffee