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# Normal Cognitive Aging

**Caroline N. Harada**[a,b], **Marissa C. Natelson Love**[c], and **Kristen Triebel**[d]

[a]Investigator, Geriatrics Research, Education, and Clinical Center, Birmingham Veterans Affairs Medical Center, Birmingham, Alabama

[b]Assistant Professor of Medicine, University of Alabama at Birmingham, Birmingham, Alabama

[c]Resident Physician, Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama

[d]Assistant Professor of Neurology, Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama

## INTRODUCTION

The number of Americans over the age of 65 is projected to more than double in the next forty years, increasing from 40.2 million in 2010 to 88.5 million in 2050.[1] It will become increasingly important to understand the cognitive changes that accompany aging, both normal and pathologic. Although dementia and mild cognitive impairment are both common, even those who do not experience these conditions may experience subtle cognitive changes associated with aging. These normal cognitive changes are important to understand because, first, they can affect an older adult's day to day function and, second, they can help us distinguish normal from disease states. In this paper, we first describe the neurocognitive changes observed in normal aging. This is followed by a description of the structural and functional alterations seen in aging brains that may explain observed cognitive changes. We will then discuss some of the practical implications of normal cognitive aging. We will conclude with a discussion of what is known about factors that may mitigate age-associated cognitive decline.

Corresponding Author: [a,b]Caroline N. Harada, M.D. University of Alabama at Birmingham, Division of Gerontology, Geriatrics, and Palliative Care, CH-19-201, 1720 Second Ave S., Birmingham, AL 35294, Phone: (205) 934-3259, Fax: (205) 934-7354, charada@uabmc.edu.
Co-authors:
[c] Marissa C. Natelson Love, M.D., University of Alabama at Birmingham, Sparks Center, Suite 339C, 1720 7th Avenue South, Birmingham, AL 35233, Phone: (205) 975-0447, Fax: (205) 975-6030, mnatelson@uabmc.edu
[d]Kristen Triebel, Psy.D., University of Alabama at Birmingham, Sparks Center, Suite 650, 1720 7th Avenue South, Birmingham, AL 35294-0017, Phone: (205) 934-2334, Fax: (205) 975-3094, ktriebel@uab.edu

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## METHODOLOGICAL ISSUES WITH STUDIES OF BRAIN AGING

Before discussing normal age-related changes, it is necessary to mention a few common methodological challenges that plague the study of normal brain aging. As with all studies of aging, selection bias is a challenge- many potential study participants decline enrollment because they are either too healthy (and busy) or too ill.[2] Additionally, people with limited social or financial support and functional limitations may be less likely to enroll in studies.[3] This results in study findings that may not be generalizable to all older adults.

Because results can be generated more quickly, most studies rely on cross-sectional design, comparing subjects from different age groups.[4] These studies, however, are subject to confounding due to cohort differences. A cohort that was born in the 1920's had a very different life experience than a cohort born in the 1980's. These cohorts may differ greatly in terms of culture, lifestyle, education, and requirements for success in life. Subjects from one age cohort may perform very poorly on any given cognitive or neurological test compared to subjects from a different age cohort irrespective of cognitive capacity, simply because of vastly different life experiences and skill sets.[5] Cohort differences can confound cross-sectional studies by potentially overestimating effects of aging.[6]

Longitudinal studies are likely better, but these studies also are subject to bias. Study populations will undergo attrition over time, and since those subjects who are most likely to remain in the study tend to be the healthiest, best educated, wealthiest, and have the highest scores on cognitive tests at baseline, the study findings may cease to represent the original study group.[7] Longitudinal studies of cognition also are subject to practice effects: because subjects are required to repeat the same tests multiple times, they may be able to improve or maintain their test scores in spite of a cognitive decline.[8,9]

Finally, studies of "normal" aging can be complicated when subjects are misdiagnosed as cognitively normal during study enrollment or when subjects develop cognitive impairment during the course of the study. This is a concerning problem because dementia onset tends to be insidious, and early symptoms can be easily missed.[4,10]

## NEUROCOGNITIVE CHANGES IN AGING

Cognitive change as a normal process of aging has been well documented in the scientific literature. Some cognitive abilities, such as vocabulary, are resilient to brain aging and may even improve with age. Other abilities, such as conceptual reasoning, memory, and processing speed, decline gradually over time. There is significant heterogeneity among older adults in the rate of decline in some abilities, such as measures of perceptual reasoning and processing speed.[11] We will provide a current, brief overview of the neuropsychology of normal cognitive aging. Interested readers are directed to other sources for a more comprehensive review of this topic.[4,12]

### Crystallized and Fluid Intelligence

Concepts of crystallized and fluid intelligence are used to describe patterns of cognitive change over the lifespan. Crystallized intelligence refers to skills, ability, and knowledge

that is overlearned, well-practiced, and familiar.[4] Vocabulary and general knowledge are examples of crystallized abilities. Crystallized abilities remain stable or gradually improve at a rate of 0.02 to 0.003 standard deviations per year through the sixth and seventh decades of life.[13] Because crystallized intelligence is due to accumulation of information based on one's life experiences, older adults tend to perform better at tasks requiring this type of intelligence when compared to younger adults. In contrast, fluid intelligence refers to abilities involving problem-solving and reasoning about things that are less familiar and are independent of what one has learned. Fluid cognition includes a person's innate ability to process and learn new information, solve problems, and attend to and manipulate one's environment.[14] Executive function, processing speed, memory, and psychomotor ability are considered fluid cognitive domains. Many fluid cognitive abilities, especially psychomotor ability and processing speed, peak in the third decade of life and then decline at an estimated rate of −0.02 standard deviations per year.[13]

Cognitive ability can be divided into specific cognitive domains. We will discuss processing speed, attention, memory, language, visuospatial abilities, and executive functioning/ reasoning.

## Processing speed

Processing speed refers to the speed with which cognitive activities are performed as well as the speed of motor responses. This fluid ability begins to decline in the third decade of life and continues throughout the lifespan. [12,15,16] Many of the cognitive changes reported in healthy older adults are the result of slowed processing speed. This "slowing" can negatively impact performance on many neuropsychological tests designed to measure other cognitive domains (e.g., verbal fluency). Thus, a decline in processing speed can have implications across a variety of cognitive domains.

## Attention

Attention refers to the ability to concentrate and focus on specific stimuli. Simple auditory attention span (also known as immediate memory) as measured by repetition of a string of digits shows only a slight decline in late life.[4] A more noticeable age effect is seen on more complex attention tasks, such as selective and divided attention.[15,16] Selective attention is the ability to focus on specific information in the environment while ignoring irrelevant information. Selective attention is important for tasks such as engaging in a conversation in a noisy environment or driving a car. Divided attention is the ability to focus on multiple tasks simultaneously, such as talking on the phone while preparing a meal. Older adults also perform worse than younger adults on tasks involving working memory[17], which refers to the ability to momentarily hold information in memory while simultaneously manipulating that information. For example, older adults may have difficulty ordering a string of letters and numbers in the correct alphanumerical sequence or calculating a tip on a restaurant bill.

## Memory

One of the most common cognitive complaints among older adults is change in memory. Indeed, as a group older adults do not perform as well as younger adults on a variety of learning and memory tests. Age-related memory changes may be related to slowed

processing speed[18], reduced ability to ignore irrelevant information[19], and decreased use of strategies to improve learning and memory.[20–22]

Two major types of memory are declarative and nondeclarative memory. Declarative (explicit) memory is conscious recollection of facts and events. Two types of declarative memory include semantic memory and episodic memory. Semantic memory involves fund of information, language usage, and practical knowledge, for example, knowing the meaning of words. Episodic memory (also known as autobiographical memory) is memory for personally experienced events that occur at a specific place and time. It can be measured by memory of stories, word lists, or figures. While declines in semantic and episodic memory occur with normal aging, the timing of these declines is different. Episodic memory shows lifelong declines while semantic memory shows late life decline[23].

Nondeclarative (implicit) memory is the other major type of memory. This type of memory is outside of a person's awareness. An example of implicit memory is remembering how to sing a familiar song, such as "Happy Birthday." Procedural memory is a type of nondeclarative memory and involves memory for motor and cognitive skills. Examples of procedural memory include remembering how to tie a shoe and how to ride a bicycle. Unlike declarative memory, nondeclarative memory remains unchanged across the lifespan.[4] See Table 1 for a description of the effect of aging on several examples of different types of memory.

Memory can also be broken down into different stages. Acquisition is the ability to encode new information into memory. Rate of acquisition declines across the lifespan.[22,27] However, retention of information that is successfully learned is preserved in cognitively healthy older adults.[28] Declines also occur in memory retrieval, which is the ability to access newly learned information.[24,27,29]

## Language

Language is a complex cognitive domain composed of both crystallized and fluid cognitive abilities. Overall language ability remains intact with aging. Vocabulary remains stable and even improves over time.[30–33] A few exceptions to the general trend of stability with age are worth mentioning. Visual confrontation naming, or the ability to see a common object and name it, remains about the same until age 70, and then declines in subsequent years.[34] Verbal fluency, which is the ability to perform a word search and generate words for a certain category (e.g., letters, animal names) in a certain amount of time, also shows decline with aging.[12,32]

## Visuospatial Abilities/Construction

This group of cognitive functions involves the ability to understand space in two and three dimensions. Visual construction skills, which involves the ability to put together individual parts to make a coherent whole (for example, assembling furniture from a box of parts) declines over time.[35] In contrast, visuospatial abilities remain intact. These abilities include object perception, the ability to recognize familiar objects such as household items or faces, and spatial perception, the ability to appreciate the physical location of objects either alone or in relation to other objects.

### Executive Functioning

Executive functioning refers to capacities that allow a person to successfully engage in independent, appropriate, purposive, and self-serving behavior. This includes a wide range of cognitive abilities such as the ability to self-monitor, plan, organize, reason, be mentally flexible, and problem-solve.[4] Research has shown that concept formation, abstraction, and mental flexibility decline with age, especially after age 70 [4], as older adults tend to think more concretely than younger adults.[12,32,36,37] Aging also negatively affects response inhibition, which is the ability to inhibit an automatic response in favor of producing a novel response.[38] Executive abilities requiring a speeded motor component are particularly susceptible to age effects.[31] The Whitehall II study also found declines in inductive reasoning, as measured by verbal and mathematic reasoning tasks, beginning around age 45.[32] Reasoning with unfamiliar material also declines with age. Other types of executive function, such as the ability to appreciate similarities, describe the meaning of proverbs, and reason about familiar material, remain stable throughout life.

## STRUCTURAL AND FUNCTIONAL BRAIN CHANGES WITH AGING

Promising developments in neuroscience research may help to explain observed age-related cognitive changes. Studies vary significantly in design, including study population and variables examined, and more research in this area is needed. In this section we will describe some of the age-related changes that have been identified and present theories for how these changes may relate to neurocognitive aging.

### Grey matter volume decline

Grey matter volume begins to decrease after age 20.[39] The amount of atrophy is most prominent in the prefrontal cortex.

Age-related changes in the temporal lobes are more moderate and involve decreases in the volume of the hippocampus.[41] The entorhinal cortex, which serves as a relay center between the hippocampus and association areas, has been reported to undergo early decreases in volume in Alzheimer's dementia (AD), but not in normal aging.[42]

**Possible Causes of Grey Matter Volume Loss in Normal Aging—**The death of neurons themselves has been implicated as a possible cause of grey matter volume loss. Neuronal death is particularly detrimental given infrequent cell division and opportunity for mutations to therefore accumulate.[43]

**Beta-amyloid and its contribution to grey matter volume loss in normal aging —**The protein beta-amyloid is found to accumulate in the brains of all patients with Alzheimer's dementia (AD), and has been proposed to cause AD via neuronal death. Its elevated presence in patients with mild cognitive impairment predicts conversion to AD. In recent years, radio-tracers that identify beta-amyloid plaques using positron emission tomography (PET) scanners have allowed study of the protein's presence in cognitively intact elderly individuals. Beta-amyloid is found in the cortex of up to 20–30% of normal adults.[44,45] It has been postulated that the presence of beta-amyloid in cognitively normal individuals indicates those individuals who eventually will develop AD.[46] One study

showed an association between high levels of beta-amyloid and both decreased hippocampal volumes and episodic memory in cognitively normal individuals.[47] This suggests that amyloid may be an early insult and that it is the downstream effects of its presence-cortical volume loss- that leads to clinical change, but this study requires replication with larger sample sizes. Thus, beta-amyloid can accumulate in the brains of people currently classified as cognitively normal, but it may signal high risk for developing cognitive impairment over time.

**Mentalizing**

Mentalizing has been defined as the ability to infer the mental state of others. A recent study using functional MRI (fMRI) confirmed prior studies showing that older adults have decreased mentalizing capacity. [48] Additionally, this decline was also associated with decreases in BOLD response, a marker for metabolic activity, in the dorsomedial prefrontal cortex. This raises the possibility that this area of the brain may be important for mentalizing, and may become less active with advancing age.

**Neuronal Size and Synaptic Density—**Despite the numerous theories explaining neuronal loss, grey matter volume decline in older adults is best explained not by death of the neurons themselves but by decrease in their size and the number of connections between them.[39,49] This reduction in synaptic density is well documented in older adults, and according to the model created by Terry and Katzman, by the age of 130 years a cognitively normal adult will have a synaptic density equivalent to someone with AD.[39] Neurons undergo morphologic changes with aging including a decrease in the complexity of dendrite arborization, decreased dendrite length, and decreased neuritic spines (the major sites for excitatory synapses). These morphologic changes likely contribute directly to the reduction of synaptic density.[50]

## White matter changes

White matter volume decreases are much greater than grey matter volume decreases with increasing age.[51] This white matter loss has been studied with imaging techniques many times but these investigations have been limited by low numbers of “normal” controls.[52] In one study using morphometric methods from autopsy data of neurologically normal subjects, there was a 16–20% decrease in white matter volume in subjects over 70 years old compared to younger subjects. This white matter shrinkage was noted in the precentral gyrus, gyrus rectus, and corpus callosum, areas which demonstrated less than 6% declines in grey matter volume.[53] This study was limited by the small sample size. Nonetheless, these findings have been supported by others, for example, Rogalski et al described that parahippocampal white matter was decreased leading to decreased communication with hippocampal structures and suggesting a possible mechanism for age-associated memory declines.[54]

In addition to changes in white matter structure, a decline in the function of white matter has been studied using diffusion tensor imaging (DTI). DTI has allowed us to observe in vivo that white matter integrity declines with increasing age. O’Sullivan et al showed age-related

declines in white matter tract integrity are most marked in the anterior white matter and are associated with deficits in executive function.[55] Madden et al showed that loss of integrity of the central portion of the corpus callosum may mediate age-related cognitive decline.[56]

## PRACTICAL IMPLICATIONS OF AGE-RELATED COGNITIVE DECLINE

By definition, normal age-related cognitive change does not impair a person's ability to perform daily activities. If an older adult develops functional impairments, even with complicated tasks such as managing finances or medications, it is prudent to pursue a workup for dementia if there is no other obvious explanation for these difficulties, such as a reaction to a medication, a new medical illness, or a vision problem. However, studies show that normal cognitive aging can result in subtle declines in complex functional abilities, such as the ability to drive.[57]

### Driving

Data demonstrate that older adults are at higher risk for motor vehicle accidents compared to younger drivers.[58] In many cases this is due to cognitive impairment (MCI or dementia), other neurologic or musculoskeletal disorders, other medical illnesses, vision problems, or medications. Unfortunately, even older adults who manage to avoid all of these challenges may still become unsafe drivers due to normal cognitive aging, which can cause small decrements in the multiple cognitive domains needed for driving. These domains include visual attention/processing (the ability to select visual stimuli based on spatial location), visual perception (the ability to accurately perceive and interpret what is seen), executive function, and memory.[59] Interestingly, tests of visual processing speed, such as the Useful Field of View® test can predict at-fault motor-vehicle crashes in older adults.[60–62]

In spite of these observations, many older adults with normal cognition do not experience a decline in driving ability or are able to effectively limit their driving to avoid high risk situations.[63] The challenge for clinicians is to determine who is safe to drive, since it has been demonstrated that many older drivers are not able to accurately judge their own driving ability.[64] Unfortunately, many clinicians lack confidence in their ability to assess fitness to drive, and not all clinicians accept that it is their responsibility to do so.[65] Experts recommend that the best way to predict driving fitness is a performance-based road test.[66] This can be performed by the local DMV or by a driver rehabilitation specialist, who is usually an occupational therapist with specialized training in driving services.

In addition to clinical evaluations, some states use licensure renewal laws as an additional safety net to aid in detecting unsafe older drivers. These laws vary widely from state to state, but in 28 states there are additional requirements that apply only to older drivers in an effort to identify unsafe drivers.[67] Older driver retraining may be an effective option for older adults who are known to have impaired driving[68], and older adults suffering only from normal cognitive aging (as opposed to dementia or MCI) seem the most likely to benefit.

#### Professions with Mandatory Retirement

Although it is generally illegal in the United States for employers to discriminate against people based on age, there are certain professions, including pilots, air traffic controllers,

and federal law enforcement officers, where a mandatory retirement age is allowed.[69] The justification for this is that cognitive changes associated with normal cognitive aging, in particular slowing of processing speed, may make it impossible for these professionals to perform their job safely.[70] Unfortunately, these policies are very controversial because they fail to take into account individual variability and often are based on limited scientific data.[71,72]

## AVOIDING COGNITIVE DECLINE: "SUCCESSFUL" COGNITIVE AGING

There is significant variability in age-related cognitive changes from individual to individual. Some of that variability can be attributed to genetic differences, and studies estimate 60% of general cognitive ability can be attributed to genetics.[73] Medical illness, psychological factors, and sensory deficits such as vision and hearing impairment certainly can also accelerate age-related cognitive decline. So the natural question that follows, of course, is whether there are certain environmental factors that can prevent or delay age-associated cognitive declines.

### Lifestyle-Cognition Hypothesis

The lifestyle-cognition hypothesis holds that maintaining an active lifestyle and engaging in certain activities during one's life may help prevent age-associated cognitive decline and dementia. Support for this hypothesis is based on the fact that older adults with high cognitive function seem to participate in certain activities with greater frequency than older adults with low cognitive function.[74,75]

Several longitudinal studies, including the Seattle Longitudinal Study, the Bronx Aging Study, and the Victoria Longitudinal Study have attempted to answer the question of whether or not certain activities may delay or prevent cognitive decline.[76–78] Many of these studies use performance on cognitive testing as the primary outcome, but more recently investigators have also been using brain structure, for example hippocampal volumes, grey matter atrophy, and white matter lesion load as outcome measures.[79,80] The Box below outlines some of the activities that have been associated with these markers of successful "brain aging."

**Activities associated with high cognitive function in older adults**

Intellectually Engaging Activities

- Puzzles, discussion groups, reading, using the computer, playing bridge, playing board games, playing musical instruments [77,81–83]
- Careers that involve high complexity[84–86]
- High educational attainment[85,87]

Physical Activities

- Exercise, especially that which improves cardiovascular health[80]
- Gardening[88]

- Dancing[77]

Social engagement

- Travel, cultural events[81,83]
- Socializing with friends and family[81,82]

Studies of lifestyle factors are limited for several reasons. First, they are often based on observational studies, so there is the potential that known or yet unidentified confounders may bias the data. Second, in the case of activities, there is the "which came first, the chicken or the egg" problem with many studies of this type: did a person engage in a particular activity that *prevented* them from developing cognitive decline, or was the person able to engage in that activity *because* they did not experience cognitive decline?[78] There is now a general consensus that AD pathology likely starts decades before symptoms are recognized[89], so it is entirely possible that study subjects considered cognitively normal could actually be in preclinical stages of dementia. Third, studies lack consistency and detail in their description and categorization of lifestyle activities, as well as consistency and breadth in the cognitive outcomes measured.[78] More, better, and longer-term longitudinal studies are needed.

## Cognitive Reserve

One theory for how certain activities may prevent age-associated cognitive decline is the theory of cognitive reserve. The cognitive reserve hypothesis posits that some individuals have a greater ability to withstand pathologic changes to the brain, such as accumulation of amyloid protein due to greater brain reserve.[90] This hypothesis holds that higher levels of education, participation in certain activities, higher socioeconomic status, and baseline intelligence protect against the clinical manifestations of brain disease.[90–92] Passive reserve refers to genetically determined characteristics such as brain volume and the number of neurons and synapses present. Active reserve refers to the brain's potential for plasticity and reorganization in neural processing, allowing it to compensate for neuropathologic changes. The scaffolding theory of aging and cognition (STAC) proposes that alternative neural circuits are recruited to achieve a cognitive goal.[30] It has been supported by several studies regarding the dedifferentiation theory of neurocognitive aging.[93] In these fMRI studies, aging was correlated with recruitment of more areas within a network in order to perform tasks, especially of working memory and episodic memory, compared to younger controls.[94,95]

## Cognitive Retraining

Researchers have demonstrated that subjects can be trained to do better on cognitive testing, and that these improvements can be maintained for years.[76,96] Even more impressive, in the ACTIVE trial, a randomized, multicenter trial involving cognitively normal older adults, cognitive training resulted in less decline in self-reported ability to perform IADL compared to controls after five years.[96] Cognitive training in this study consisted of ten one-hour sessions teaching subjects strategies to improve memory, reasoning, and speed of processing. A meta-analysis of speed of processing training studies supports the idea that

cognitive training can have real effects on cognitively normal subjects' ability to perform activities of daily living.[97] These promising findings suggest that it may be possible to use cognitive training in the future to allow people to minimize functional decline with advancing age. Cognitive training via home videotape has been shown to be 74% as effective as laboratory-based training, so there may be great potential for making this intervention widely accessible.[98]

## SUMMARY

The normal aging process is associated with declines in certain cognitive abilities, such as processing speed and certain memory, language, visuospatial, and executive function abilities. While these declines are not yet well understood, promising developments in neurology research have identified declines in grey and white matter volume, changes in white matter, and declines in neurotransmitter levels that all may contribute to observed cognitive changes with aging. These changes are small and should not result in impairment in function, nonetheless, driving and certain other activities may be compromised, and it is important to detect safety issues early. Participation in certain activities, building cognitive reserve, and engaging in cognitive retraining may all be approaches to achieving successful cognitive aging. While research in the area of normal cognitive aging may seem less pressing than research in the area of pathologic brain disease, a more complete understanding of normal brain aging may shed light on abnormal brain processes. Additionally, the majority of adults over the age of 65 will not develop dementia or MCI, and more work is needed to better understand how we can maximize cognitive function and quality of life for these individuals.

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### Key Points

1. The normal aging process is associated with declines in certain cognitive abilities, such as processing speed and certain memory, language, visuospatial, and executive function abilities.
2. While these declines are not yet well understood, promising developments in neurology research have identified declines in grey and white matter volume, changes in white matter, and declines in neurotransmitter levels that all may contribute to observed cognitive changes with aging.
3. These changes are small and should not result in impairment in function, nonetheless, driving and certain other activities may be compromised, and it is important to detect safety issues early.
4. Participation in certain activities, building cognitive reserve, and engaging in cognitive retraining may all be approaches to achieving successful cognitive aging.
5. While research in the area of normal cognitive aging may seem less pressing than research in the area of pathologic brain disease, a more complete understanding of normal brain aging may shed light on abnormal brain processes.
6. The majority of adults over the age of 65 will not develop dementia or MCI, and more work is needed to better understand how we can maximize cognitive function and quality of life for these individuals.

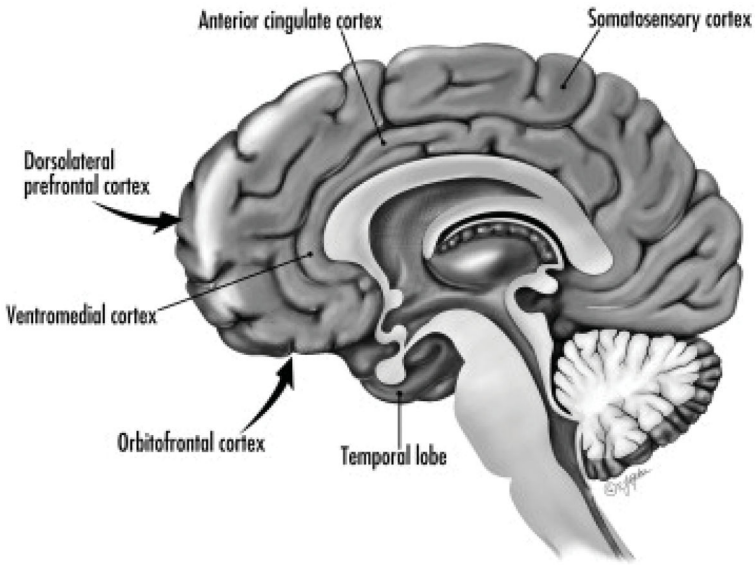


**Figure 1.**

Prefrontal cortex (orbitofrontal, dorsolateral frontal, and frontopolar regions): atrophy is associated with deficits in executive function, working memory and increased perseveration.[40] Keep the arrows and the labels Dorsolatateral prefrontal cortex and Orbitofrontal cortex. On top of the arrows on the left hand side include term: Prefontal Cortex

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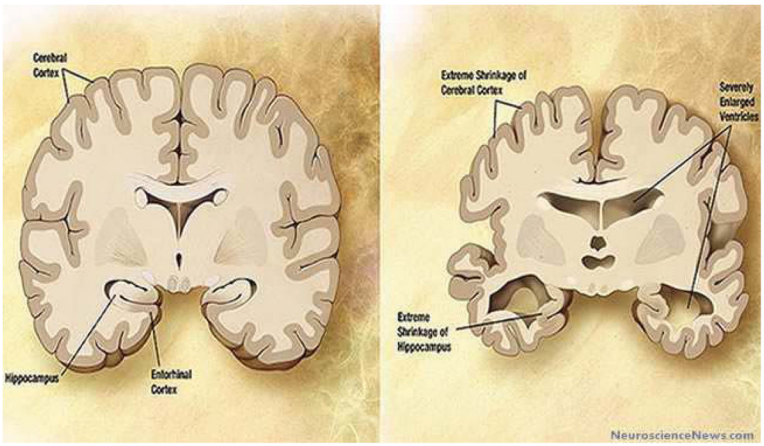


**Figure 2.**

Hippocampus and entorhinal cortex- atrophy has been associated with deficits in episodic memory.[41]

## Table 1

Memory and Aging

| Declines with age | Remains stable with age |
|---|---|
| Delayed free recall: spontaneous retrieval of information from memory without a cue[24,25]<br>Example:<br>Recalling a list of items to purchase at the grocery store without a cue | Recognition memory: ability to retrieve information when given a cue<br>Example:<br>Correctly giving the details of a story when given yes/no questions |
| Source memory: knowing the source of the learned information<br>Example:<br>Remembering if you learned a fact because you saw it on television, read it in the newspaper, or heard it from a friend | Temporal order memory: memory for the correct time or sequence of past events<br>Example:<br>Remembering that last Saturday you went to the grocery store after you ate lunch with your friends |
| Prospective memory: remembering to perform intended actions in the future[26]<br>Example:<br>Remembering to take medicine before going to bed | Procedural memory: memory of how to do things<br>Example:<br>Remembering how to ride a bike |

**Table 2**

Summary of Neurocognitive Changes with Age

| | **Crystallized vs. Fluid** | **Declines with age?** |
|---|---|---|
| Processing speed | Fluid | Yes |
| Attention | Fluid | Simple tasks- no<br>Complex tasks- yes |
| Memory | Fluid | Mixed |
| Language | Crystallized > Fluid | In general- no<br>Visual confrontation naming, verbal fluency- yes |
| Visuospatial | Mixed | Simple tasks- no<br>Complex tasks- yes |
| Executive Function | Fluid | Mixed |