



HHS Public Access

Author manuscript

Curr Behav Neurosci Rep. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Curr Behav Neurosci Rep. 2015 December 1; 2(4): 256–261. doi:10.1007/s40473-015-0058-x.

What is Normal Cognitive Aging? Evidence from Task-Based Functional Neuroimaging

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Abstract

The idea that our cognitive abilities change with age has support from empirical research as well as from anecdotal reports. Cognition has many component processes, some of which are impaired by normal aging like attention and memory as a result of changes in perceptual systems or speed of processing. Other cognitive domains improve in functioning as aging continues such as wisdom and some kinds of decision making. Many years of research in the psychology of cognitive aging has described patterns of age-related changes in cognitive processes with older adults performing worse than younger adults on tests of attention, working memory and episodic memory and better on tests of general knowledge. More recent work in task-related functional neuroimaging has further elucidated the effects of aging on brain circuitry related to these cognitive processes. Generally, studies show that older adults activate regions of the frontal cortex more than younger adults while younger adults activate more posterior cortical areas. This paper describes normal patterns of cognitive change in healthy aging, describes how some of these processes can be explored with functional neuroimaging, and briefly describes the work attempting to describe differences between normal and pathological cognitive aging.

Keywords

geropsychiatry; cognitive disorders; late life; cognitive abilities; pathological cognitive aging; cognitive aging; fMRI; episodic memory; attention; working memory

Introduction

As people age, there are declines in cognition that fall short of dementia but still impact functional abilities and independence¹. The goal of successful aging is to maintain intact cognitive functioning all the way until death. Normal cognitive aging is not dementia and does not result in the loss of neurons. Rather there are changes in brain functioning that may have a financial impact on society. Older adults with normal cognitive changes are more susceptible to financial scams and may have difficulty with financial decisions¹. Moreover,

Conflict of Interest

Julie A Dumas has no relevant conflicts to disclose.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

behaviors which affect health and safety (driving skills, health care decisions, medication adherence) also are impacted by normal variations in cognitive aging. First, it is necessary to understand how cognition changes in healthy older adults and that is the focus of this review. A second step would be to develop interventions that are likely to slow, stop, or reverse normal cognitive aging.

Cognitive Aging

The field of cognitive psychology is concerned with discovering the form of mental representation and the processes that access them. It is the study of how people perceive, learn, remember, and think about information. The study of cognitive aging seeks to examine how these processes change over time and between people. Normal aging has been defined as aging changes that occur in individuals free of overt diseases of the nervous system. Neurological disorders like Alzheimer's disease (AD) and Parkinson's disease (PD) are not normal manifestations of aging fated for everyone who lives long enough to have them. But these diseases do appear in an age-dependent manner and can share some cognitive features with normal aging making it difficult to completely distinguish between signs and symptoms of overt disease and normal aging. As there are decreases in biological functions and mental abilities that are normal and happen with the passage of time, it is helpful to understand these changes in order to understand what happens when there is disease in addition to the normal changes.

Specifically, studies in healthy older adults show declines in some cognitive domains while showing improvements in others. Most commonly, healthy older adults show impairments on tasks of attention, working memory, and episodic memory relative to younger adults (i.e.,²⁻⁴). However, older adults also show improvements on cognitive tasks where they can rely on experience to perform well such as tests assessing wisdom and general knowledge⁴. One way to conceptualize how aging affects cognition is through the model described below.

Model of Information Processing and Aging

Cowan^{5,6} proposed a model of information processing that describes the relationships between attention, working memory, and long term memory storage. In this model, working memory is conceptualized as the activated portion of long-term memory. Working memory contains information both inside and outside the focus of attention which has a very restricted capacity, limited in some cases to as little as one item (e.g.,⁷). In the context of the Cowan^{5,6} information processing model, aging may result in difficulties in controlling the focus of attention. Attentional control impairments imply that older adults allow both relevant and irrelevant information to enter into the focus of attention which will impair performance on any kind of task requiring the ability to differentiate relevant from irrelevant information. Older adults may also fail to suppress attention to irrelevant information that has already entered working memory⁸. Thus, the effect of aging on the focus of attention may be to blur the boundaries or widen the focus of attention such that older adults have less control over the content of what is currently within the focus of attention (see Figure 1).

In the past two decades with the increased access to and availability of MRI scanners, studies have focused on the connection between brain functioning and cognitive processing. The relationship between brain functioning and cognition across the life span is a dynamic one. Understanding how age-related changes in brain functioning affects cognition is important for delimiting differences in normal and pathological aging.

Functional Neuroimaging Studies of Attention, Working Memory, and Episodic Memory in Healthy Older Adults

Older adults show impairments on tasks of attention, working memory and episodic memory relative to younger adults (i.e., ²⁻⁴). Age differences in brain activation in functional imaging studies during performance of attention, working memory and episodic memory tasks have been found in many studies (i.e. ⁹⁻¹¹). These studies show similarities in activation patterns for older adults relative to younger adults across tasks. Generally, older adults show increases in frontal activation (e.g., ⁹) and decreases in occipitotemporal activity (e.g., ¹²) relative to younger adults. While this activation pattern was first described by Grady et al.¹², Davis and colleagues ¹³ labeled the pattern the posterior-anterior shift in aging (PASA). PASA patterns have been seen in a number of different cognitive domains including tests of attention, working memory and episodic memory. Importantly, successful completion of each of these three tasks requires the control of attention. A summary of the prior imaging studies of older and younger adults in these cognitive domains is presented below.

Functional imaging studies of age differences in tasks requiring control of attentional resources show that older adults activate more regions of frontal cortex than younger adults (e.g., ^{10,14-16}). In a study of age differences in Stroop interference, older and younger adults activated similar brain regions during the interference task, but older adults were slower to perform the task and showed more activation in regions of the frontal cortex relative to younger adults¹⁰. Older adults have also shown more frontal activation in tests of sustained, selective, and cross modal shifting attention (from auditory to visual;¹⁶). Thus, across a broad range of attention tasks, age differences in attentional control resulted in differences in brain activation such that older adults required increased frontal cortical activation.

Functional neuroimaging studies of working memory have shown that the age difference in working memory performance may be related to the ability to recruit frontal brain regions to compensate for poor performance. Increases in prefrontal activation for older adults relative to younger adults appear to depend upon successful task performance and suggest a compensatory process is involved in increased activation for older adults ^{17,18}. Three examples across different tasks involving working memory processes support this proposal. First, Rypma and D'Esposito¹¹ found that faster performing younger adults showed less dorsolateral prefrontal cortex activation relative to slower younger adults. However, faster performing older adults showed increased activation relative to slower older adults. Second, Mattay et al. ¹⁹ found that older adults who performed as well as younger adults on the 1-back condition of an N-back working memory task activated more prefrontal cortex bilaterally. However, on the higher working memory load conditions of 2-back and 3-back, older adults performed worse and had less frontal activation than younger adults. Finally,

Grossman et al.²⁰ found that on a sentence comprehension task with a high working memory component, older adults with equivalent comprehension scores as younger adults activated more premotor and inferior frontal cortices. Thus, although older adults performed similarly to younger adults in some working memory tasks, they required more frontal activation to do so.

Research on episodic memory shows that during encoding older adults activated more bilateral frontal areas compared to younger adults. Cabeza and colleagues⁹ have proposed the hemispheric asymmetry reduction for older adults (HAROLD) model of age differences in frontal cortex activation during memory tasks. This is an age-related modification of the hemispheric encoding/retrieval asymmetry (HERA;²¹) pattern of brain activation often seen in younger adults where encoding processes activate left prefrontal cortex while retrieval processes activate right prefrontal cortex. Older adults showed a reduction in this asymmetry such that there was more bilateral activation in both encoding and retrieval tasks. Morcom et al.²² found encoding-related activity was left lateralized in younger adults as predicted by HERA and bilateral in older adults as predicted by HAROLD. Dennis et al.²³ showed that older adults had increased left prefrontal cortex activity compared to younger adults for words that were successfully encoded relative to words that were forgotten. However, conflicting data have been found by Daselaar et al.²⁴. They found that poor performing older adults had increased overall brain activity during episodic memory encoding relative to younger adults and a group of older adults who performed at the level of younger adults on an episodic memory task. Thus, the relationship between increased activation during episodic encoding and age remains to be further elucidated.

Work by Cabeza and colleagues²⁵ emphasized the similarities between age differences in brain activation seen across tests of visual attention, working memory, and episodic memory tasks in one study with the same group of subjects. Older adults showed increased activation in the prefrontal cortex and decreased occipital activations during all three task types. Cabeza et al. interpreted these findings as evidence that there are task-independent age-related changes in brain activity representing sensory decline often seen in older adults, in addition to functional compensation for these sensory changes with recruitment of additional frontal cortical areas during these three tasks. Davis et al.¹³ further explored the PASA effect to examine whether this pattern resulted as an effect of task difficulty, whether it was related to compensation, and whether it generalized to activations on visual perception and episodic retrieval tasks. To investigate the difficulty explanation, Davis et al.¹³ matched older and younger adults on task performance and the PASA pattern was still seen. Frontal increases were positively correlated with improved performance while occipital decreases were negatively correlated with performance thus providing evidence that the additional frontal activation is the result of neural compensation²⁶. Finally, the deactivation pattern mirrored the activation pattern showing more deactivation in frontal regions and less deactivation in posterior cortex. Thus overall, these data patterns support the proposal that the PASA effect reflects age-related neural compensation to maintain adequate task performance.

To summarize the data from functional imaging studies of attention, working memory and episodic memory, age differences in brain activation were found across all tasks such that

older adults recruited more frontal cortical areas to perform at the same accuracy level as younger adults, supporting the proposal that the additional activation is the result of neural compensation¹⁷. Additionally, decreases in posterior cortical areas were seen, potentially indicating a shift toward a frontal cortex-dominated pattern of brain activation. In terms of the Cowan model, older adults may have difficulty controlling the focus of attention^{8,27}. This difficulty may be reflected by an increased need to recruit frontal brain regions²⁵ as well as lessen the ability to suppress activation of irrelevant information²⁸.

Normal versus Pathological Aging: Functional Imaging Evidence

The studies reviewed above detailed differences in brain activation between younger adults and healthy older adults from cross sectional studies. However, understanding how normal aging develops into pathological aging requires additional examination of longitudinal studies as well as cross sectional studies comparing younger adults, healthy older adults, adults with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD). Sperling and colleagues have conducted a number of studies examining normal aging in cross sectional studies^{29,30}, longitudinal studies³¹, and in comparison to patients with age-related pathologies^{30,32}. These studies examined associative encoding during a face-name encoding task in healthy younger and older adults as well as in adults with MCI and AD to examine the age and disease effects on episodic encoding and related brain functioning during the this task^{30,33,34}. The task activates an episodic encoding network that includes the hippocampus, dorsolateral prefrontal cortex, fusiform cortex, and the pulvinar nucleus of the thalamus; decreased activation was found in the posterior cingulate cortex³⁵. One study directly comparing healthy younger and older adults found similar hippocampal activation but different activation patterns in the frontal and parietal cortices³⁴. Both older and younger adults showed increased hippocampal activation during successful encoding of face-name pairs that were successfully remembered³³. When healthy older adults were followed longitudinally and performed the fMRI face-name encoding task two years after a baseline assessment, decreased hippocampal activation was associated with clinical decline³¹, implying that decreased hippocampal activation in healthy older adults may be a biomarker for pathological aging.

To describe differences between normal and pathological cognitive aging, it is necessary to examine differences between those with normal cognition and those with MCI and AD. Cross sectional studies of healthy older adults and those with MCI showed mixed results with some studies showing hyperactivation for the MCI group^{32,36} while other showed hypoactivation for the MCI group^{37,38} compared to the healthy older adults on tests of episodic memory. When task-related activation of those with AD was compared to healthy older adults, generally decreases in task-related activation have been seen in medial temporal regions (i.e., ^{30,36}). However, hypoactivation has also been observed in frontal regions and is interpreted as a compensation response to the inability to engage medial temporal regions³⁰.

Overall, task-based fMRI data showed mixed results for discriminating normal aging from MCI and AD. It appears to depend on the progression of MCI or AD³⁰. Additional information is needed to interpret the fMRI task-based differences between normal and

pathological aging. More recent studies are examining how genetic risk for AD, APOE genotype in particular, and amyloid load contribute to differentiating between normal and pathological cognitive aging^{39–42}. These studies generally show that between 20 – 30% of older adults who show no clinical evidence of cognitive decline have significant amyloid burden. In addition, studies have shown that amyloid plaques have been seen approximately 20–30 years prior to the development of cognitive decline⁴³. As the access to amyloid imaging becomes more widely available, studies are following adults at younger ages before disease begins to fully understand how amyloid and APOE genotype affect the trajectory of the development of pathological cognitive aging. How these processes relate to cognitive performance and affect brain functioning continues to be examined.

Summary

Research on cognitive aging has flourished in recent years detailing how cognitive processes change with increasing age. In addition neuroimaging studies examining the effects of aging on brain circuitry show consistent patterns across a number of cognitive tasks. Recent work is being done to examine biomarkers that differentiate normal and pathological cognitive processes and studies in the near future will be able to describe how these biomarkers relate to patterns of normal cognitive aging shown during fMRI. At this time the data appear to be mixed in terms of the consistent patterns for discriminating normal and pathological aging using task-related fMRI alone. However, the examination of amyloid load and APOE genotype is providing more context with which to interpret the task-based fMRI data. Continued efforts in identifying and defining normal aging and the development of methods to slow or reverse it will be useful in continuing to differentiate normal from pathological cognitive processes.

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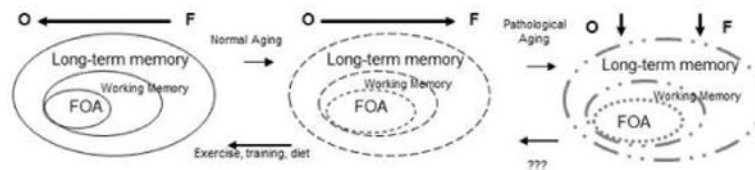


Figure 1. Model of Cognition and Aging

Figure 1 diagrams a model of age-related changes in cognition based on the model of Cowan^{5,6} and includes patterns of brain activation as measured by fMRI. Dotted and grayed lines indicate impairments. When younger adults (left panel) perform attention and memory tests they show brain activation patterns that are balanced between occipital and frontal regions or even have a shift towards greater posterior activation. Normal cognitive aging (middle panel) may degrade the control processes of the focus of attention (FOA) thereby affecting working memory and long-term memory. The functional activation patterns show increased in frontal activation relative to posterior regions. Lifestyle modifications may be effective in slowing or reversing some of the aspects of cognitive aging. Cognitive dysfunction seen in pathological cognitive aging may affect all aspects of cognition. The activation patterns will show decreases in frontal and occipital regions.