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What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus

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ABSTRACT

What can be expected in normal aging, and where does normal aging stop and pathological neurodegeneration begin? With the slow progression of age-related dementias such as Alzheimer's disease (AD), it is difficult to distinguish age-related changes from effects of undetected disease. We review recent research on changes of the cerebral cortex and the hippocampus in aging and the borders between normal aging and AD. We argue that prominent cortical reductions are evident in fronto-temporal regions in elderly even with low probability of AD, including regions overlapping the default mode network. Importantly, these regions show high levels of amyloid deposition in AD, and are both structurally and functionally vulnerable early in the disease. This *normalcy-pathology homology* is critical to understand, since aging itself is the major risk factor for sporadic AD. Thus, rather than necessarily reflecting early signs of disease, these changes may be part of normal aging, and may inform on why the aging brain is so much more susceptible to AD than is the younger brain. We suggest that regions characterized by a high degree of life-long plasticity are vulnerable to detrimental effects of normal aging, and that this age-vulnerability renders them more susceptible to additional, pathological AD-related changes. We conclude that it will be difficult to understand AD without understanding why it preferably affects older brains, and that we need a model that accounts for age-related changes in AD-vulnerable regions independently of AD-pathology.

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1. Introduction

The major risk factor for Alzheimer's disease (AD) is age, with a sharp increase in incidence after 60 years (Kawas et al., 2000). This has inspired many researchers to propose that to understand AD, we must understand its inherent relationship to aging (Herrup, 2010). Why is the aging brain so susceptible to AD, compared to the middle-aged or young brain? What features distinguish normal brain changes from those seen in early AD? How should we understand the fact that three of the major symptoms of AD observed in vivo – disruption of episodic memory function (Koivisto et al., 1995; Nyberg et al., 2012), brain atrophy (Raz et al., 2005; Driscoll et al., 2009; Fjell et al., 2009a) and accumulation of amyloid protein (Morris et al., 2010) – are also found in many presumably healthy elderly? Given these commonalities, it can be argued that AD cannot be understood separately from its major risk factor – age. However, we suggest that this statement can also be reversed: if we understand why the older brain is susceptible to AD, we may have a better chance of understanding brain aging itself. With the aging of the population, a comprehensive understanding of normal, non-demented changes in brain and cognition is arguably as important as understanding AD.

How the link between aging and AD should be understood is thus a major question in contemporary neuroscience. However, it is not obvious that studying the relationship between the two is the best starting point for understanding either phenomenon. Some argue that AD should be viewed as a disease with distinct etiology and neuropathology, separate from normal aging, and that it is less fruitful to view AD in light of normal age changes (Nelson et al., 2011). AD may be driven by factors less related to aging per se, for instance differences in amyloid precursor protein expression (APP) (Nelson et al., 2011), from which the presumably most toxic form of amyloid (Aβ42) originates. However, we have still not understood the role of amyloid in brain atrophy and cognitive decline. Current models of the role of amyloid in AD, as for instance reflected in the proposed diagnostic guidelines from the National Institute of Aging – Alzheimer's Association (NIA-AA) (Jack et al., 2011; Sperling et al., 2011a) and the popular 'dynamic biomarker model' (Jack et al., 2010a, 2013), suggest that the influence of amyloid is greatest in very early phases – at a stage where cognitive and clinical symptoms are not yet detected. When accelerated brain atrophy and cognitive decline become evident, the therapeutic window for anti-amyloid drugs may very well be closed. Thus, it is absolutely necessary to study the relationship between amyloid, brain integrity and memory in healthy elderly if the role of amyloid in neurodegeneration and cognitive decline is to be understood. Animal models of AD are not characterized by the massive brain atrophy that correlates with memory problems in AD patients, and therefore can provide only limited insight into relationships between amyloid, brain integrity and episodic memory decline in non-demented older adults.

In the present paper, we review recent research on cortical and hippocampal changes in normal aging, the relationship between changes in normal aging vs. early AD, and the role played by amyloid. First, we will discuss the characteristics of presumably normal brain aging. What kind of macroscopic brain changes can be expected in older adults without dementia, and what consequences do these brain changes have for cognitive function? We try to identify and evaluate some of the proposed major organizing principles for brain aging, such as the theory of retrogenesis or the principle of "last in, first out". In the cognitive domain, we focus especially on episodic memory, which is of interest because it is affected both in normal aging and very early in AD. Second, we investigate similarities and differences in the pattern of brain atrophy between normal aging and AD, with a special focus on comparisons between AD patients and elderly individuals with low AD-risk. Finally, we discuss the role of amyloid in brain atrophy and cognition, and evaluate current available knowledge related to the question of why brain aging is associated with the dramatic increase in AD-risk.

2. What is normal in normal aging?

2.1. Magnitude, pattern and timing of change

Reductions in specific cognitive abilities like mental speed (Salthouse, 1996), executive function (Connelly et al., 1991; Schretlen et al., 2000; Rabbitt et al., 2001) and episodic memory (Salthouse, 2003; Buckner, 2004; Nyberg et al., 2012) are commonly experienced in aging, while verbal abilities and world knowledge are typically maintained (Park and Reuter-Lorenz, 2009). However, there is disagreement about whether longitudinal changes in older adults reflect continuous ongoing processes starting in young adulthood or whether changes begin in middle age or beyond. Closely related to this is an unsettled discussion about whether changes observed in cross-sectional studies reflect real ongoing change within individuals (Salthouse, 2009) or arise from methodological artifacts (Schaie, 2009; Nyberg et al., 2012). Cross-sectional studies may suffer from cohort effects, and, potentially more seriously, different recruitment bias across age-groups. For instance, most studies are based on convenience samples, and there may be systematic differences in individuals who are recruited for, and agree to participate in, research at younger ages and older ages. For example, young participants are often college students, middle-aged participants may be more likely to be unemployed or under-employed, and older participants may be recruited from senior centers. The older age group may be biased by participants motivated to volunteer due to concerns about their cognitive abilities, or, alternatively, only the superior functioning older adults volunteer or are accepted into the study due to strict exclusion criteria. Thus these three age groups may differ in critical characteristics, which may affect the estimated age-trajectories. This is referred to as covariance between age and sampling bias. Longitudinal studies are, in principle, not affected by this bias and can measure change over time within individuals. However, longitudinal studies too have limitations that can influence the results – such as selective attrition and test–retest effects that may be larger than the change across time points (Salthouse, 2012). Adding to this, few longitudinal studies sample the entire adult age-span, precluding estimations of change rates as a function of age.

Despite the limitations of cross-sectional and longitudinal study designs, there is a consensus that episodic memory, which is of special focus in the present review, declines from about the age of 50–60 years on a population basis (Nyberg et al., 2012), although earlier decrements cannot be ruled out. In a very interesting study, longitudinal trajectories in episodic memory were mapped over