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# Neuroimaging of the Aging Brain: Introduction to the Special Issue of Neuropsychology Review

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Everyone knows what *cognitive aging* is, to borrow from William James' famous definition of attention (James 1890). Cognitive aging is a gradual, late-life decline in cognitive performance, experienced to a degree by most individuals fortunate to reach old age (Grady 2008). Decades of scientific research have shown that there exist age-correlated deficits both in basic cognitive processes (such as speed of processing) and in higher-order cognitive functions, particularly episodic memory (ability to recall events) and cognitive control (ability to control our behaviors). Cognitive aging research also indicates that while some functions decline, others remain relatively intact and may even improve with age (such as semantic knowledge (Grady and Craik 2000; Park and Reuter-Lorenz 2009; Salthouse 2004, 2009)). Still, relatively subtle declines in cognitive performance—for example, in memory and executive functions—are frequently observed in rigorous studies of older adults without clinical conditions. This phenomenon of age-associated cognitive declines, unrelated to detectable clinical processes and distinct from Mild Cognitive Impairment (MCI), is often termed "normal" or "healthy cognitive aging," and these elders are considered "cognitively normal" or "cognitively healthy older adults." Even such mild cognitive declines, however, can affect functionally relevant clinical outcomes related to older age including increasing the rate of hospitalization (Wilson et al. 2014) and predicting poorer medication adherence (Hayes et al. 2009).

Brain structural morphology differs with age (DeCarli et al. 2005; Fjell et al. 2013; Head et al. 2008; Raz et al. 1998; Raz et al. 1997, 2005) and accompanies age-related differences in cognition. These differences are regionally specific with the most consistent and notable


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age-related differences in frontal lobar and medial temporal regions (Buckner 2004; DeCarli et al. 2005; Fjell et al. 2014; Head et al. 2008; Raz et al. 1998). Newer and more technologically sophisticated imaging tools have also identified relevant age-related differences in white matter microstructure which may either underpin gray-matter atrophy differences or accompany such differences (Andrews-Hanna et al. 2007; O'Sullivan et al. 2001; Sullivan et al. 2001; Sullivan and Pfefferbaum 2006, 2007). The notion of age-related dysfunction of specific brain systems has led to the development of a host of theories aimed at integrating these two apparently related processes. The frontal theory of aging, which is consistent with the known age-related differences in frontal gray matter, is one early example (West 1996). Another theory (Salthouse 1988, 1996, 2000; Salthouse and Lichty 1985) invoked the notion of slowed or degraded signal processing, which is finding greater supportive evidence through the study of white matter microstructure. Of course these are only two of the many theories. As our knowledge of cognitive processes expands, more refined hypotheses such as that of separate and dissociable memory processes related to familiarity and recall as discussed in papers by Schoemaker and colleagues and Koen and Yonelinas in this issue (Schoemaker et al. 2014 and Koen and Yonelinas 2014) are being developed. Novel hypotheses incorporate individual differences in cognitive aging through forms of reserve capacity as discussed in this issue by Reuter-Lorenz and Park (Reuter-Lorenz and Park 2014). These relatively recent hypotheses also have recognized discrete anatomical underpinnings that may be further understood by imaging and physiological techniques on the scientific horizon.

Study of the aging brain cannot be fully understood without knowledge of common age-related diseases (DeCarli 2013) and genetic influences (Atwood et al. 2004; Bis et al. 2012; Carmelli et al. 1998; DeStefano et al. 2009; Ikram et al. 2012; Pfefferbaum et al. 2000). Advanced age is associated with multiple overlapping biological processes that adversely affect brain structure and function. Such processes include Alzheimer's disease (AD) and cerebrovascular disease (CVD), which are nearly equally prevalent with advancing age (Seshadri and Wolf 2007). Moreover, both AD and CVD processes are known to have an extended prodromal state during which an individual appears "normal" (Debette et al. 2011; DeCarli et al. 1995; Jack et al. 2013; Pike et al. 2007; Rowe et al. 2010; Sperling et al. 2011; Swan et al. 1998, 2000). *Brain aging* refers to imaging signs of age-related changes absent clinically significant cognitive impairment; however, it remains unclear as to what extent these differences are "normal," and to which biological processes differences in brain structure and function can be attributed. As the brain provides the substrate for cognition, brain aging and cognitive aging are, by definition, closely linked (Grady 2008).

Often age-related biological processes are difficult to disentangle from one another, with the preclinical effects of AD and CVD thought to contribute to and confound the study of normal brain aging (Lockhart et al. 2012, 2014; Mayda et al. 2011). The effects on brain aging of clinically asymptomatic CVD are particularly insidious, as CVD and cardiovascular risk factors are very common (Decarli 2004;Wolf et al. 1991), and vascular risk factor-related brain structural differences (e.g., reduced white matter integrity) are observable as early as mid-life (Maillard et al. 2012). The study of brain aging must therefore examine the

contributions of normal and preclinical disease-related changes to the structure and function of the brain.

This issue of *Neuropsychology Review* presents a series of papers that cogently synthesize and summarize structural and functional brain differences with advancing age including the potential impact of amyloid, cerebrovascular risk factors, and genetic influences on these differences, aspects of cognitive functioning with a specific focus on age-related differences in memory function, and cognitive reserve capacity.

The first section of this issue focuses on biomarkers related to aging. Lockhart and DeCarli provide an overview of structural imaging measures in brain aging including cross-sectional and longitudinal brain imaging studies assessing brain differences in younger versus older adults and the effects of clinically silent CVD risk factors on cognition and behavior in advancing age. Next, Fouquet, Besson, Gonneaud, La Joie, and Chetelat review imaging studies of the effects of ApoE4 on brain structure and function in cognitively normal adults across the lifespan. These authors focus on three main neuroimaging markers associated with AD: cortical beta-amyloid deposition, hypometabolism, and atrophy in Apoe4 carriers versus noncarriers. Factors that influence the association between beta amyloid and cognition in advanced age is next reviewed by Mormino, who makes a strong case for the need of a multimodal approach in determining AD risk.

The second section of this issue focuses on memory processes, specifically recollection and familiarity. Schoemaker, Gautheir, and Pruessner review these memory processes and their neural substrates in older adults with MCI and AD and include remember-know, process dissociation procedure, and receiver operating characteristic paradigms. Next, Koen and Yonelinas provide a meta-analytic review of the effect sizes reported in recollection and familiarity studies in healthy aging, amnestic MCI and AD. Conclusions from both these reviews are consistent with neuroimaging findings suggesting a double dissociation: the hippocampus plays a critical role in recollection, whereas perirhinal regions play a critical role in familiarity.

The last two papers of this issue take a gestalt approach, incorporating what we know about brain and aging to inform interventions to increase level of cognitive functioning and quality of life in older adults. Reuter-Lorenz and Park provide a revision of their previously well-received STAC (Scaffolding Theory of Aging and Cognition) model of cognitive functioning in normal aging. In their conceptual model of cognitive aging, they integrate the influence of biological, environmental, and lifestyle variables and effects level of cognitive functioning and rate of cognitive decline in advancing age. Lastly, the paper by Carmichael reviews what is known and what is not yet known about vascular effects on the brain and cognition in later adulthood. This paper provides strong support for the relevance of therapeutic intervention of vascular risk factors to maintain cognitive health in later life.

Taken together, these timely reviews highlight the need for a better understanding of modifiable factors related to “normal” brain aging so that we may move toward “optimal” brain aging and the retention of strong cognitive abilities even into the ninth decade of life.

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