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Neuropsychology of aging, past, present and future: Contributions of Morris Moscovitch

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ABSTRACT

In this review we provide a broad overview of major trends in the cognitive neuroscience of aging and illustrate their roots in the pioneering ideas and discoveries of Morris Moscovitch and his close collaborators, especially Gordon Winocur. These trends include an on-going focus on the specific and dissociable contributions of medial temporal and frontal lobe processes to cognitive aging, especially in the memory domain, the role of individual variability stemming from different patterns of underlying neural decline, the possibility of compensatory neural and cognitive influences that alter the expression of neurobiological aging, and the investigation of lifestyle and psychosocial factors that affect plasticity and may contribute to the rate and level of neurocognitive decline. These prescient ideas, evident in the early work of Moscovitch and Winocur, continue to drive on-going research efforts in the cognitive neuroscience of aging.

1. . Introduction

The past several decades have brought a tremendous expansion of research on the neural basis of aging cognition. This growth has been made possible by breakthroughs in human neuroscience methodologies that permit new discoveries about how normal age-related alterations in brain structure and function are linked to age-related declines in performance on measures of cognition (Reuter-Lorenz and Park, 2010). In vivo structural imaging measures of cortical volume and morphology, along with white matter tractography and integrity indices, allow for exquisite quantification of neural architecture and delineation of interconnecting neuroanatomical pathways (Lockhart and DeCarli, 2014). Functional imaging methods indicate regions of brain activity during cognitive tasks, patterns of interregional activity correlations or functional connectivity that support cognition, as well as resting state networks that reveal intrinsic communication among brain regions and relate to cognitive abilities outside the scanner. New ligands for imaging deposition of beta amyloid and tau throughout the brain are at the forefront of current efforts to track and identify the development of dementias, especially Alzheimer's disease, and to differentiate pathological from healthy cognitive decline (e.g., Trojanowski et al., 2010). Moreover, increasing availability of lifespan and longitudinal data sets comparing groups across multiple age ranges and characterizing the same individuals over multiple test occasions, respectively, reveals how these measures and their interrelations differ and change over time (cf. Raz and Lindenberger, 2011).

These new types and sources of data provide the wealth of information that has advanced the field now referred to as the cognitive neuroscience of aging. This discipline, like most of contemporary cognitive neuroscience, has its origins in human neuropsychology, the field that began with the pioneering discoveries of Broca (1861). As a basic science discipline, human neuropsychology endeavors to understand the neural bases of psychological processes and to inform psychological theories by investigating how different forms and locations of brain damage selectively alter aspects of cognition and affect. In the latter half of the last century the traditional human neuropsychology approach gained prominence as the primary method for making inferences about *human* brain-behavior relations. Experimental neuropsychology investigates patient populations with localizable brain damage due to stroke, neurosurgery, or other neuropathologies and tests these individuals on standardized psychological test batteries known to tap different domains of cognitive function, and using experimenter-designed cognitive tasks intended to measure the integrity of different cognitive abilities and the processing operations that mediate them. Research using this general approach and for which *Neuropsychologia* has been a long-standing publication outlet, provided foundational knowledge about the neurocognitive organization of such abilities as object recognition through study of the agnosias, language as revealed by the aphasias, memory by studying the amnesias, and many other cognitive

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abilities now more widely investigated using brain imaging methods in neurologically intact individuals.

Until about 1995, the traditional neuropsychological approach was the major means used to make inferences about the neural mechanisms underlying cognitive aging. Morris Moscovitch and his collaborators, especially Gordon Winocur, were at the forefront of theoretical and empirical advances based on this approach. As the decade progressed, a handful of labs began using positron emission tomography to study neurocognitive aging, a functional imaging method replaced by functional magnetic resonance imaging (fMRI) only a few years later. Our intention here is to review the foundational ideas of Moscovitch and his colleagues to illustrate how their neuropsychological approach to cognitive aging set the stage for much of where the field is today. We will draw from several prominent works by Moscovitch and colleagues using relevant quotes to introduce subsequent sections of this paper (Moscovitch, 1982; Moscovitch and Winocur, 1983; Moscovitch and Winocur, 1992, 1995).

2. Neurostructural aging

> *"Our research framework rests on the assumption that cognitive changes with age result primarily from structural changes in the nervous system." (Moscovitch, 1982, Page 75)*

In this quote, Moscovitch makes explicit an assumption that is the bedrock of cognitive neuroscience: psychology is fundamentally linked to biology, and biological approaches can therefore be used to understand cognition. While this idea is hardly newsworthy today, the mind-body link was still debated and by no means universally embraced at that time (e.g., Goleman and Davidson, 1979; Shapiro and Schwartz, 1976; Sirota, Schwartz, and Shapiro, 1976). Aging is arguably one of the earlier frontiers for which "cognitive" psychologists were willing to accept that neural mechanisms play a causal role in cognitive status, with the work of Moscovitch and colleagues being especially influential on this front. This quote expresses a second idea that deserves mention here, which is the notion of "change." Aging is a multifaceted process that unfolds over time. Until only recently, the bulk of the research on *neurocognitive* aging has been cross-sectional, comparing groups of younger and older adults rather than tracking the same individuals over multiple time points. Consequently, most of the neuropsychological and cognitive neuroscience literature to date is based on age *differences* rather than age-related *change*. While this imposes important limitations on our understanding of neurocognitive aging, new evidence is emerging that clarifies how closely conclusions based on differences align with those based on change (e.g., Nyberg et al., 2012). A third aspect of this quote that warrants our attention is that by using the word "change" rather than "decline" or "deterioration", Moscovitch leaves open the possibility that the effects of age are neither uniform nor unidirectional. Both ideas are highly relevant to the current picture of neurocognitive aging where the interplay of positive and negative plasticity (e.g., compensation and decline) influence the cognitive profiles of older adults as well as the wide variability in these profiles and their susceptibility to age-related change (Cabeza and Dennis, 2012; Nyberg et al., 2012; Reuter-Lorenz and Cappell, 2008).

> *"Consistently, disproportionate changes have been found in frontal and medial temporal lobe areas although other regions have been implicated […]. These findings are in general accord with those reported after postmortem examination." (Moscovitch and Winocur, 1995, Page 318)*

Even as early as 1983, Moscovitch and Winocur (Moscovitch and Winocur, 1983; see also Moscovitch, 1982) recognized the non-uniformity of brain aging by calling attention to the disproportionate vulnerability of frontal and medial temporal lobe functions and documenting cognitive parallels with different types of amnesia that result from damage to these brain regions. As we discuss in the subsequent section, frontal and medial temporal processes figure prominently in the study of cognitive aging for the subsequent 30 years and continue to do so today (e.g., Rodrigue and Kennedy, 2011). First evident in post-mortem and histological studies (e.g., Malamud, 1972), medial temporal regions and prefrontal cortices show greater signs of age-related deterioration than other regions of the human brain. In vivo measurements, now made possible by higher resolution MR, have provided volumetric indices that confirm the greater vulnerability of these brain regions to aging, initially in cross-sectional studies (see e.g, Fjell et al., 2009b; Raz, 2000; Raz et al., 1997) and more recently in several longitudinal data sets (Fjell et al., 2014; Pfefferbaum et al., 2013). For the most part, these studies indicate disproportionate atrophy of lateral and medial frontal cortices as well as medial temporal regions, including the hippocampus. Longitudinally, this vulnerability is evident in more rapid rates of volumetric decline in these regions over time (Pfefferbaum et al., 2013), and estimates of average annual volume loss in the range of 1.5% or greater in these regions compared to an overall average loss of 0.5% in adults with a baseline age ranging from 55 to 91 years (Fjell et al., 2009; Fjell et al., 2014). These decline rates obscure a complexity of accompanying patterns, however, including regional variation in the onset and rate of change over time (e.g., nonlinear patterns of acceleration and deceleration – heterochronicity), sex differences, and potential inclusion of individuals with changes in cognitive status that fall outside the normal range (see Raz et al., 2010). That is, despite the consistency of general, population based patterns, individual variation is also broadly evident. Complexities such as these mean that for any given older adult, the extent to which they are accurately characterized by these larger data patterns may differ significantly, thus challenging any attempt to relate individual cognitive abilities with brain status (see Fjell et al., 2014).

Fully appreciating that aging brain tissue will ultimately be characterized by a broad range of physiological, biochemical, and metabolic changes (Moscovitch, 1982; Moscovitch and Winocur, 1983, 1992), Moscovitch and Winocur focused their "neuropsychological approach to cognitive aging" on assessing the cognitive parallels among patients whose loci of brain damage were, similar to age-related morphological change, primarily hippocampal and frontal in nature. Yet, the limitations of this approach were also readily acknowledged. For one thing, while focusing on brain *structure*, Moscovitch (1982) recognized that it is unclear which morphological features are most relevant to cognitive aging, and this uncertainty persists today. Volumetric measurements, which form the bulk of structural characterization of brain aging, include both cortical thickness and surface area, which have somewhat independent phylogenetic and likely ontogenetic determinants (Fjell et al., 2014). Consequently, the same volume loss over time in two different people could result from differential losses of surface and thickness. It is also increasingly evident that age affects white matter volume and white matter integrity, as indexed by such measures as diffusion weighted imaging, diffusion tensor imaging, and T2-FLAIR imaging. By influencing the transmission of neural signals between brain regions, white matter deterioration is likely to affect computation efficiency of neural networks. The application of combined imaging methods to assess white matter, cortical volume, metabolic measures and brain activation is proving to be increasingly important for characterizing the neural bases for age-related cognitive decline as well as variability among older individuals who are