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Research report

Chronological age and its impact on associative learning proficiency and brain structure in middle adulthood

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HIGHLIGHTS

- Neurobiological changes in middle adulthood are relatively understudied.
- Learning proficiency during associative learning appears to decrease through middle adulthood.
- Decreases in gray matter volumes in the hippocampus and the prefrontal cortex.
- Conjoint changes in behavior and brain structures implicate aging related processes.
- Aging in middle adulthood may be more dynamic than previously believed.

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ABSTRACT

Introduction: The rate of biological change in middle-adulthood is relatively under-studied. Here, we used behavioral testing in conjunction with structural magnetic resonance imaging to examine the effects of chronological age on associative learning proficiency and on brain regions that previous functional MRI studies have closely related to the domain of associative learning.
Methods: Participants ($n = 66$) completed a previously established associative learning paradigm, and consented to be scanned using structural magnetic resonance imaging. Age-related effects were investigated both across sub-groups in the sample (younger vs. older) and across the entire sample (using regression approaches).
Results: Chronological age had substantial effects on learning proficiency (independent of IQ and Education Level), with older adults showing a decrement compared to younger adults. In addition, decreases in estimated gray matter volume were observed in multiple brain regions including the hippocampus and the dorsal prefrontal cortex, both of which are strongly implicated in associative learning.
Conclusion: The results suggest that middle adulthood may be a more dynamic period of life-span change than previously believed. The conjunctive application of narrowly focused tasks, with conjointly acquired structural MRI data may allow us to enrich the search for, and the interpretation of, age-related changes in cross-sectional samples.

1. Introduction

Ongoing change is a central characteristic of the life span [1] expressed by continuing changes in behavioral proficiency and complexity, and metrics of brain structure and function [2,3]. The rates of these changes are unequally expressed through the life span. In general, the progressive neurodevelopmental period of

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adolescence evinces rapid expansion in cognitive facility [4] in multiple domains including learning and memory [5,6]. By comparison, aging is characterizing by degenerative changes in brain structure, particularly in regions such as the medial temporal lobe, and these degenerative processes are expressed in functional decrements. Relatively few studies have focused on age-related changes in middle-adulthood. In this investigation we assessed the effects of chronological age in middle adulthood on two dependent variables: (a) proficiency in the domain of associative learning and (b) gray matter volume estimated using a whole brain voxel based morphometry. *In using a task and structural neuroimaging data, it was possible to assess if changes in gray matter were observed in the very brain regions that are known to be strongly implicated in the task itself.*

Longitudinal and cross-sectional life-span studies have assessed subjects in broad age-ranges (typically late adolescence into late senescence). However, and as previously noted, the rates of change across life-stages remain distinct, and assessing the specific break points signifying categorical shifts in the acceleration of age-related changes remains challenging. No single study can be considered definitive in this regard. However, the balance of evidence broadly suggests that middle-adulthood (or middle-age), the period between the chronological age of 20 and 50 years may be relatively stable. For example, using a large corpus of data, Fjell and colleagues [7] recently addressed the viability of parametric regression models for identifying break points in life-span neuroimaging data of hippocampal volumes. The identification of break-points for accelerated aging were highly sensitive to the age-range sampled, but both quadratic regression and smoothing spline functions identified modest changes in hippocampal structure in middle-adulthood.

Though the rate of neurobiological change during middle-adulthood is stable relative to other categorical periods in the life span, this period is characterized by gradual shifts in cognitive proficiency. In a meta-analytic assessment of multiple cross-sectional samples, Verhaeghen and Salthouse [8] investigated age-related effects in multiple domains including response latency, working and episodic memory. Their analyses indicated that even in subgroups under 50 years, age exerted significant negative effects on proficiency, suggesting a gradual decrement in abilities in fundamental domains particularly working and episodic memory.

What remains relatively unclear is whether chronological age in middle adulthood exerts effects on both behavioral proficiency, and on the structure of brain regions that principally sub-serve that behavior. Our study addressed this general question.

To address this we made strategic choices. First, we specifically chose the domain of hippocampal-related associative learning [9], fundamental in the human cognitive economy. Associative learning proficiency was assessed using a paired associate learning paradigm that we have extensively employed to investigate mechanisms of frontal-hippocampal learning in health and disease [10,11]. The behavioral metrics of learning proficiency are relatively well characterized, as is the network of brain regions that are principally involved in task implementation (see below). Learning relies on the central role of the hippocampus in encoding the order of distinct temporal events [12]. This distinct coding of temporal events by hippocampal cells contributes to the creation of unitary memory traces that over time may be distributed in cortical–hippocampal networks [13,14]. In humans during the initial stages of learning (and perhaps throughout), the prefrontal cortex exerts multi-variegated functions including supervisory and attention-related processing [15,16], and retrieval cues during recall [17]. In addition, the parietal and inferior temporal cortices are relatively specialized for spatial encoding, and the encoding of object identity respectively [18], providing focused regional targets for inquiry.

Both the prefrontal cortex and the hippocampus are particularly vulnerable in aging. Therefore the task provides a highly relevant cognitive domain for inquiry in middle-adulthood, to investigate whether gradual decrements in performance are evident. Moreover, behavioral metrics for indexing learning proficiency are straightforward to compute, and well described by negatively accelerated learning functions (observed performance = $1 - e^{-k*\text{time}}$). The single varying parameter k represents learning rate and when derived from this class of functions, provides a very good index of learning proficiency, in animal and human studies [19]. Furthermore, in our study, metrics of structural brain changes with age were estimated using SPM's diffeomorphic image registration algorithm (DARTEL) [20]. DARTEL optimizes the fidelity of shape-based deformations applied to fit native images in stereotactic space, performs well compared to all or most competing non-linear deformation algorithms [21] and is well suited for analyses of large MRI datasets. The task motivates focus on a key behavioral domain that is central to human cognition, and that is relatively well described in terms of functional brain activations. The conjoint analysis of chronological effects of age on learning proficiency and brain structure provides a theoretical focus on age-related changes in middle-adulthood.

2. Methods

2.1. Participants

Sixty six post-adolescent adults ($20 \leq \text{Age} \leq 43$ years; see Table 1) contributed structural MRI and behavioral data to the study. Participants had no current or past history of mental retardation or psychiatric, neurological or general medical illnesses, substance/alcohol abuse or head injuries with significant loss of consciousness. IQ was assessed using the Raven's Progressive Matrices, converted to estimates of Full Scale IQ (WAIS-R) [22]. After a detailed description of the study, each subject gave written informed consent to participate, in accordance with the local ethical committees of the Azienda Ospedaliera Universitaria of Verona, Italy.

2.2. MRI acquisition and processing

MRI data were acquired on a 1.5T Magnetom Allegra Syngo MR 2004A (Siemens), using an axial 3-dimensional magnetization prepared rapid gradient echo (MP-RAGE) sequence (TR = 2060 ms, TE = 3.93 ms, FOV = 256, slice thickness = 1 mm, matrix size = 256 × 192, flip angle = 15°).

All MRI data were processed using DARTEL implemented in SPM8 [20]. By optimizing the fidelity of shape-based deformations applied to fit native images in stereotactic space, DARTEL favorably compares to other non-linear deformation algorithms [21], is ideal for assessing structural changes within a stereotactic framework, and is well suited for analyses of large MRI datasets. For analyses, images were resampled (2 mm^3 isotropic voxels) and segmented to create a rigid gray matter template representing the average shape and size of the sixty-six participants. Segments were warped to the template's coordinate system, with Jacobian modulation used to scale native gray matter volume from native to MNI space. Volume-modulation [23] is extensively used in voxel-based analyses of MRI images within the framework of random field methods [24]. The relatively large sample allowed us to smooth tissue segments with a relatively narrow Gaussian filter (4 mm, FWHM) to increase relative localization of differences in brain structures [25]. In all analyses, tissue clusters of significance that were identified within the random fields approach were interrogated to extract estimated volume for graphical rendering and additional analyses [24]. The extraction