



# Impairment in associative memory in healthy aging is distinct from that in other types of episodic memory

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## ABSTRACT

There is evidence that age related changes in episodic memory are heterogeneous and result from diverse pathologies. To test this, we examined performance of healthy high-functioning younger ( $N = 41$ , ages 18–60 y) and older ( $N = 58$ , ages 61–83 y) individuals in tests of associative memory, logical memory and memory in executive and object-recognition domains. We compared their relationships to each other and to other cognitive functions, including, psychomotor speed and verbal and spatial working memory. Older individuals showed significantly greater reduction in an index of the ability to learn new associations (NAL) than for memory in executive and object-recognition domains. Age-related reduction in NAL and in logical memory was of similar severity, but the two measures showed only moderate correlation when age and other cognitive functions were controlled for. NAL shows an age-related pattern of change distinct from memory in executive and object-recognition domains and from logical (item) memory. We propose that in healthy well-functioning individuals, NAL taps processes which support binding of newly learned association in context of accumulating information, a key function of the hippocampus. NAL may thus serve as a selective marker of complex, hippocampus-based, cognitive functions in studies of normal cognitive aging and of its possible relationship to early dementia.

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## 1. Introduction

Aging is associated with decline in many cognitive functions and one purpose of research is to identify whether this results from single or multiple processes as this knowledge can advance detection of the vulnerable neural systems.

Cognitive aging has been extensively researched providing evidence of generalized and selective changes which different theorists have attributed to mental slowing, declining attentional resources, and inability to inhibit unwanted information, among others (e.g., see Light et al., 2000; Craik and Bialystok, 2006; Prull et al., 2006; Luo and Craik, 2008; Craik et al., 2010; Salthouse, 2010; Gopie et al., 2011). There is consensus that healthy adults improve on measures of processing carried out in the past, such as vocabulary or general information, and show a nearly linear decline from early adulthood in the ability to manipulate or transform abstract or familiar material (Salthouse, 2010), but it is not yet clear, however, how age affects relations between changes in closely related cognitive functions. For example, a recent study reported that well-functioning older individuals show selective

nonlinear deteriorations within the “executive” domain, over and above the more general decline (Silver et al., 2011).

Evidence from behavioral and neuroscience research indicates that age-related episodic memory change is heterogeneous. Indeed, the influential associative deficit hypothesis (Naveh-Benjamin, 2000) originates in the disproportionate decline in associative memory observed in aging individuals. However, despite extensive research (Light, 1991; Naveh-Benjamin, 2000; Luo and Craik, 2008; Stevens et al., 2008; Salthouse, 2010) it is not known how changes in different forms of memory (Squire and Wixted, 2011) relate to each other in normal aging. Such behavioral information can contribute to the understanding of the complex relations between memory types and their neural substrates (e.g., Squire and Wixted, 2011) and inform studies of brain function aiming to clarify whether aging effects result from single or multiple processes.

Several authors proposed that two or more processes are involved in memory decline, although the specific mechanisms proposed differ. One proposal (Shing et al., 2010) is that memory decline involves two processes, one initially in the hippocampus (addressing binding) and the other in the prefrontal cortex (PFC) (addressing strategic encoding and controlled retrieval). A different dual-process model (Yonelinas, 2002; Mayes et al., 2007) distinguishes between recognition memory which is mediated by recollection, cued recall of associated information within a recognition situation, and familiarity, which involves no recall and occurs when exposure to information leads to a ‘feeling’ of memory.

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Recollection is postulated to rely on the hippocampus and prefrontal cortex, and familiarity on para-hippocampal regions. Other models have also been proposed (Bugajska et al., 2007; Luo and Craik, 2008; Stevens et al., 2008; Salthouse, 2010). If memory processes are behaviorally separable, then their neural substrates may be differentially vulnerable to aging. Indeed, imaging studies indicate that age-related cognitive decline may involve distinct hippocampus and PFC-based patterns (Kramer et al., 2007), although some researchers (Wixted and Squire, 2011) believe that distinctions such as between recollection and familiarity are less likely to shed light on functional organization of the medial temporal lobe than the neuroanatomy and neurophysiology findings which indicate that medial temporal lobe structures process different attributes of experience.

Identifying specific patterns of memory decline in aging healthy individuals is difficult since tests often tap several cognitive processes. Further, elderly individuals show decline in many cognitive functions other than memory and use diverse cognitive strategies and compensatory adaptations which impact on test performance. Experimenter constraint too can influence strategy (Rabbitt, 1997) and confound understanding of the relationships between memory functions which occur in “real life” processing.

Research into the evolution of memory decline and the underlying neural changes in aging and illness would benefit from availability of selective measures of specific memory functions which can be related to specific neural systems. In this study we aimed to identify such measures and focused on the ability to learn new associations. Associative learning is sensitive to aging (Naveh-Benjamin, 2000) and linked with hippocampal function. We calculated an index designed to measure the ability to learn new associations with minimum influence of other memory processes and postulated that it can be differentiated from change in memory in executive and object-recognition tasks, which are dependent on prefrontal (Goldman-Rakic, 1996; Wilson et al., 2010) and temporo-parietal (Sergent et al., 1992) regions respectively.

We asked the following questions:

1. Does the effect of aging on associative memory differ from that on logical memory and on memory in executive and object-recognition tasks?
2. What is the relationship between associative and other types of memory in aging?

To minimize interindividual variability in cognitive performance and potential confounds from presence of early dementia, we studied selected well-functioning healthy individuals. We included measures of verbal and spatial working memory and psychomotor speed to enable analysis in a multivariate setting.

## 2. Methods

### 2.1. Population

The elderly healthy group (20 women and 38 men, age range 61–85 y), comprised high-functioning individuals living in the community recruited by personal contact and local community advertisement. They were living independently in their own homes and were socially active. Younger individuals (four women and 37 men, age range 18–60 y) were drawn from the same community or from the professional staff at Sha'ar Menashe Mental Health Center. Extensive questioning relating to health excluded individuals with current medical problems such as cardiac insufficiency, unstable diabetes or epilepsy that could affect cognitive function and those with history of neurological disorders such as stroke or head injury, drugs or alcohol abuse or medication that could significantly affect cognitive performance. Full descriptions of the selection procedures are detailed in Silver et al. (2009, 2011).

The mean age of the younger group was 33.90 (standard deviation (S.D.) 9.51) years and of the older group, 72.36 (S.D. 6.76) years. The mean education level was 11.12 (S.D. 1.82) years in the younger group and 14.64 (S.D. 4.11) years, in the older group ( $p < 0.001$ ). The difference in education (the older group was more educated) did not influence the results of analyses. General cognitive function in the elder group as measured by the Mini-Mental State Examination (MMSE) (Table 1), did not differ significantly from the younger group and showed high consistency with it (95% Confidence interval (CI): 28.81–29.40 older vs. 28.82–29.62 younger, range:

25–30 older vs. 23–30 younger). The one individual with an MMSE score <24 performed comparably to other group members on other tests and was included.

### 2.2. Neuropsychological assessment

Verbal memory was assessed with the Logical Memory and easy and hard Paired Associates subtests from the Wechsler Memory Scale Revised (WMS R) (Wechsler, 1987).

The Logical Memory subtest requires subjects to remember items contained in the story read by the examiner. In the Paired Associates subtest, the subject has to recall pairs of words, some forming easy associations (easy list) and others not readily associated (hard list). To create a measure of the ability to form new associations with minimal influence from other memory processes, we calculated the new associative learning (NAL) index using the formula:  $NAL = (\text{Paired Associates easy list score} - \text{Paired Associates difficult list score}) / (\text{Paired Associates easy list score} + \text{Paired Associates difficult list score})$ . This results in a unitless measure which can be compared with indexes of memory in other domains and across groups. Smaller NAL values indicate better ability to form new associations.

Executive function was tested with the Abstraction, Inhibition, and Working Memory task (AIM) designed as a measure of abstraction and concept formation with and without additional memory load (Glahn et al., 2000). It presents subjects with five shapes: two in the upper right and two in the upper left corner of a computer screen, with a fifth target object appearing in the center of the screen, below the other stimuli. The participants' task is to pair the target object with the objects on either the left or right. In half the trials, an additional requirement for working memory maintenance is superimposed on this basic module by adding a delay between the presentation of the target and other objects. The Executive memory index (CSTAIM) was calculated using the formula:  $CSTAIM = (\text{Abstraction with no memory} - \text{Abstraction with memory}) / (\text{Abstraction with no memory} + \text{Abstraction with memory})$ .

Object recognition was assessed with the Visual Object Learning Test (VOLT, (Glahn et al., 1997)). It uses 20 Euclidean shapes as learning stimuli, which are presented over four learning trials, followed by short- and long-delay test recall. The Object memory index (CSTOBJ) was calculated using the formula:  $CSTOBJ = (\text{Total score with short delay} - \text{Total score with long delay}) / (\text{Total score with short delay} + \text{Total score with long delay})$ .

Verbal working memory (VWM) was tested with the backward digit span tests from the Wechsler Adult Intelligence Scale (WAIS), version 1 (Wechsler, 1955). Spatial working memory (SWM) was tested with the Dot Test (Keefe et al., 1997). In the original test the subject is presented with a card on which a dot is present; to facilitate measurement, we used a cross instead of a dot. After a 10-s interval, the paper is removed and the subject is asked immediately to reproduce the mark on a blank card. The distance between the target mark and that recalled by the subject is measured in millimeters. This procedure was repeated for a total of 10 cards. The sum for all 10 cards was the outcome measure.

Psychomotor speed was tested with Finger Tapping Test (Russell et al., 1970; Reitan and Davison, 1974), which examines the ability to make rapid repetitive movements. The test was modified, and the patients were asked to tap with their index finger on two points set 30 cm apart as rapidly as possible. Each hand was tested separately. The outcome measure was the number of taps per minute with the dominant hand.

The tests were drawn from a battery used previously and are described fully elsewhere (Gur et al., 2001; Silver et al., 2003, 2005).

The tests were administered at the same session or, in some cases, in two sessions not more than 3 days apart. Prior to recruitment, all participants provided written informed consent for participation in the study, after having received a full explanation of the test procedures. The study was approved by the Institutional Review Board of Sha'ar Menashe Mental Health Center.

**Table 1**

Test scores in healthy younger and older individuals.

Test	Health	S.D.	Health	S.D.	<i>r</i>	<i>p</i>
	Old		Young			
	Mean		Mean		( <i>d.f.</i> = 97)	
Logical memory	8.05	2.33	13.00	2.43	–10.22	0.000
Associate memory – Difficult	3.79	3.01	8.63	2.60	–8.33	0.000
Associate Memory – Easy	16.43	1.90	17.22	1.41	–2.25	0.026
Abstraction	23.40	2.04	24.66	1.94	–3.09	0.003
Abstraction with memory	21.67	2.66	23.39	2.97	–3.01	0.003
Object recognition	15.00	2.51	15.98	2.14	–2.02	0.046
Object recognition with memory	14.90	2.14	15.27	2.37	–0.81	0.417
Verbal working memory	7.14	1.71	8.73	2.54	–3.73	0.000
Spatial working memory	138.34	46.82	107.07	25.76	3.88	0.000
General cognition (MMSE)	29.10	1.13	29.22	1.26	–0.48	0.633
Psychomotor speed	95.17	17.00	121.85	22.49	–6.72	0.000

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