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Research report

Pupillary responses and memory-guided visual search reveal age-related and Alzheimer's-related memory decline

Michelle C. Dragan[a], Timothy K. Leonard[b], Andres M. Lozano[c], Mary Pat McAndrews[c], Karen Ng[c], Jennifer D. Ryan[d], David F. Tang-Wai[c], Jordana S. Wynn[d], Kari L. Hoffman[e,*]

[a] Department of Biology, Centre for Vision Research, York University, Toronto, ON, Canada
[b] Department of Psychology, Centre for Vision Research, York University, Toronto, ON, Canada
[c] Toronto Western Hospital, University of Toronto, Toronto, ON, Canada
[d] Rotman Research Institute, Baycrest, University of Toronto, Toronto, ON, Canada
[e] Department of Psychology, Department of Biology, Centre for Vision Research, Toronto, ON, M3J 1P3, Canada

HIGHLIGHTS

- Nonverbal, episodic-like memory shown in a goal-directed natural scene search task.
- Age and AD predict deficits in target detection time and scanpath efficiency.
- Pupil dynamics diminished with aging and further in Alzheimer's disease.
- Memory increased pupil velocity in healthy adults, but less so in at-risk groups.

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ABSTRACT

Episodic memory – composed of memory for unique spatiotemporal experiences – is known to decline with aging, and even more severely in Alzheimer 's disease (AD). Memory for trial-unique objects in spatial scenes depends on the integrity of the hippocampus and interconnected structures that are among the first areas affected in AD. We reasoned that memory for objects-in-scenes would be impaired with aging, and that further impairments would be observed in AD. We asked younger adults, healthy older adults, older adults at-risk for developing cognitive impairments, and older adults with probable early AD to find changing items ('targets') within images of natural scenes, measuring repeated-trial changes in search efficiency and pupil diameter. Compared to younger adults, older adults took longer to detect target objects in repeated scenes, they required more fixations and those fixations were more dispersed. Whereas individuals with AD showed some benefit of memory in this task, they had substantially longer detection times, and more numerous, dispersed fixations on repeated scenes compared to age-matched older adults. Correspondingly, pupillary responses to novel and repeated scenes were diminished with aging and further in AD, and the memory-related changes were weaker with aging and absent in AD. Our results suggest that several nonverbal measures from memory-guided visual search tasks can index aging and Alzheimer's disease status, including pupillary dynamics. The task measurements are sensitive to the integrity of brain structures that are associated with Alzheimer's-related neurodegeneration, the task is well tolerated across a range of abilities, and thus, it may prove useful in early diagnostics and longitudinal tracking of memory decline.

1. Introduction

Episodic memory decline is one of the principal clinical signs of Alzheimer's disease (AD [54]) and amnestic mild cognitive impairment (aMCI [33]), above and beyond the decline observed with healthy aging [19]. This memory decline is thought to be due in large part to pathological changes in the hippocampal formation (HC), its connected fiber tracts, and adjacent entorhinal cortex (EC).

* Corresponding author.
E-mail addresses: mishelle.dr@gmail.com (M.C. Dragan), tsk@yorku.ca (T.K. Leonard), lozano@uhnresearch.ca (A.M. Lozano), Mary.McAndrews@uhn.ca (M.P. McAndrews), karenwy.ng@uhnresearch.ca (K. Ng), jryan@research.baycrest.org (J.D. Ryan), David.Tang-Wai@uhn.ca (D.F. Tang-Wai), jwynn@research.baycrest.org (J.S. Wynn), khoffman@yorku.ca (K.L. Hoffman).

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The best assays of changes in function to this circuit with aging and progressive dementia must optimize task sensitivity and selectivity [9,24,1], accommodate the abilities of impaired individuals to be tested, and maximize ecological validity, here, inasmuch as it would apply to real-world contextual and episodic memory impairments.

Some tests of hippocampal function – e.g. pattern separation, navigation – are difficult to test in impaired populations, who show floor effects or are unable to properly execute the task, though such tests may be ideal for differential early diagnostics in mildly impaired individuals [61,78]. Other tests that are considered to be sensitive to extended hippocampal system integrity are not necessarily linked to episodic memory, e.g. eye blink conditioning, old/new item discrimination, virtual-reality navigation [57,77,9]. The hippocampus is thought to support episodic memory by 'binding' the relations among items within a given spatiotemporal context, and, indeed, rats with hippocampal lesions are impaired on tests of memory for objects ('what') placed at different locations in an environment ('where'), within a given spatial context ('which') [20,41,23,45]. Similarly, disconnection of a major hippocampal fiber tract in monkeys impairs memory for a visual feature embedded in an abstract scene [30]. Moreover, humans with medial-temporal lobe damage and episodic memory deficits are also impaired at remembering the location of objects in photorealistic spatial scenes [65,75,12]. The flicker change detection and learned target detection versions of these object-location-in-context tasks use memory for a concealed or uncued object to speed/enable detection. We predicted that performance in this task would decline with age, with even greater deficits predicted for individuals with Alzheimer's disease.

The primary performance difference expected in this task across populations is speeded target detection time with repetition, which has previously been associated with explicit memory for the scene-embedded target [12]). Among the changes in search underlying rapid target detection are fewer fixations, and a more directed scan path, deviating from the initial, protracted search when the target was concealed and/or unknown [87,14,15]. In addition to changes in visual search, pupillary responses have been linked to memory for scenes [56] objects [40] and objects in scenes [63]. These memory-related pupillary responses were reported for healthy young adults; they have not yet been tested in aging populations. The pupil's size and motility, on the other hand, has been documented to decrease with Alzheimer's disease and in prodromal cognitive impairment, accompanied by hyper-sensitive pupillary responses in the presence of cholinergic antagonists [28,71,72]. We therefore predicted that the pupillary response to natural scenes would weaken as a function of age and additionally with Alzheimer's disease status, and that the greatest effects of scene repetition on the pupillary response would be observed in the populations with the best memory performance.

2. Materials and methods

2.1. Participants

Seventeen university students (5 males, ages 19–32 years, mean(SD) age 22.8(3.1) years), 21 older adults (5 males, mean(SD) age 67.3(8.5) years) and 9 adults diagnosed with probable early AD (5 males, mean(SD) age 69.1(7.8) years), participated in the study (Table 1). All young adults and 14 of the older adults were recruited from the Toronto community; the remaining 7 older adults were recruited from the Rotman Research database. Older adults completed the Montreal Cognitive Assessment (MoCA), a brief neuropsychological test shown to be sensitive to mild cognitive impairment (MCI [18,58,53];) and to conversion from MCI to AD [39] and to individuals at risk for developing MCI [59,58]. Ten older adults scored a 26 or higher (range: 26–31) on the MoCA and therefore were categorized as healthy older adults (HOA); eight scored 24 or lower (range: 21–24) and were categorized as at-risk (ROA) for MCI [18]. Three individuals scored a 25 and could not be placed in either category, thus they were excluded from further analysis. The probable early AD designation was given according to the National Institute of Aging Alzheimer's Association criteria [38,54]. These participants were recruited as part of a clinical trial involving deep brain stimulation (DBS) at Toronto Western Hospital. To enroll in the clinical trial, patients must have scored between 12 and 24 on the Alzheimer's Disease Assessment Scale – cognitive test 11 (ADAS-cog11 [11]), and either 0.5 or 1 on the Clinical Dementia Rating [55]. The main experiment described here took place after device implantation, but before initiation of DBS treatment. See Table 1 for post-admission performance scores that occurred prior to double-blind assignment into treatment or placebo groups. We compared performance in those tested pre-operatively and found no change to post-operative performance on any of the memory measures we tested (see Table 1; entropy: $t = 0.64$ $p = 0.54$; median search time: $t = 0.38$ $p = 0.72$; fixation number: $t = 2.19$ $p = 0.07$).

All participants had normal or corrected- to-normal vision. Participants were informed about the purpose of the experiment and its risks, and written informed consent was obtained. Participants from the younger adult and older AD groups volunteered without monetary compensation; older adults received $10/h in accordance with our ethical guidelines. Experimental procedures for all participants were approved by the York Human Participants Review Subcommittee; older adults who were recruited from the Rotman Research Institute database (N = 7) additionally followed the guidelines approved by the Rotman Research Institute; early AD participants were selected for and participated in a clinical trial in accordance with the ethical guidelines set by the research ethics board (REB) of the University Health Network and the Center for Addiction and Mental Health.

2.2. Stimuli

We selected a range of natural scenes, including wildlife, city, rural, and indoor scenes, that could be displayed at a 1280×1024 pixel resolution (full screen), as described previously [12,36,48]. One object per scene was modified (color change or disappearance, Fig. 1A) using Adobe Photoshop (San Jose, CA). Target sizes i.e. maximal horizontal and vertical extent varied between 40 and 224 pixels horizontally and between 48 and 280 pixels vertically, occupying roughly 5–25% of the scene horizontally or vertically. To discourage bias in search strategies, sets of images were balanced for target location (quadrant on screen) and category (animate/inanimate).

2.3. Experimental apparatus and session design

Participants used a chin rest to minimize head movements throughout the study. A 38.0×30.5 cm monitor displaying the task stimuli was placed 51 cm away from young participants ($41 \times 33^\circ$ visual angle, dva), and 61 cm away from all other participants (35×28 dva). Eye gaze and pupil diameter were tracked using the iView X infrared eye tracking system at a 60 Hz sampling rate (SensoMotoric Instruments, SMI, Berlin, Germany), following a 13-point calibration and validation. Stimulus presentation software (Presentation, Neurobehavioral Systems, CA, USA), received online gaze position information from iView enabling gaze-contingent experimental control and sent event codes to the iView data acquisition stream for alignment of eye position data to trial events. Image selection, presentation timing, and response buttons were also controlled in Presentation. After calibration, three example trials were given to ensure that participants understood the task. Participants

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