Novel strategies for expanding memory's penumbra in aging

David Clewett[1] & Joseph Dunsmoor[2,3]

[1]Department of Psychology, University of California, Los Angeles, CA, USA

[2]Department of Psychiatry and Behavioral Sciences, Dell Medical School, University of Texas at Austin, Austin, TX, USA

[3]Institute for Neuroscience, University of Texas at Austin, Austin, TX, USA

Keywords: memory, arousal, aging, emotion, behavioral tagging, novelty

Acknowledgements: J.E.D. is funded by the National Institutes of Health (NIH; grants R01 MH122387, R00 MG106719) and the National Science Foundation (NSF; CAREER Award 1844792). We thank our co-authors Vishnu Murty, Elizabeth Phelps, and Lila Davachi for helpful conversations and for their significant intellectual contributions to the target article that this commentary is based upon.

The significance of identifying easy and affordable ways to strengthen older adults' memories cannot be overstated. As part of this endeavor, we recently synthesized neurobiological models of memory that could inform new ways to boost weak learning [1]. The core idea of these frameworks is that weakly encoded memories can become strengthened and stabilized in long-term memory when encountered in temporal proximity to a strong event — an effect we referred to as the "penumbra of memory" [1]. In an insightful reply to our review, Schomaker et al. emphasized the need to dissociate which aspects of a strong event facilitate memory, given that salience, novelty, emotion, and arousal differentially engage neuromodulatory systems that decline with age [2]. Here, we briefly respond by outlining key considerations for testing the memory penumbra model across the lifespan. We also highlight innovative strategies for re-engaging neuromodulatory processes to prevent memory loss in both normal and pathological aging.

According to the model we described, there are four factors by which salience creates a window of memory preservation: 1) close temporal proximity between weak and strong events; 2) high spatial overlap in the neural pathways engaged by those events; 3) activation of catecholaminergic systems that trigger the production of plasticity-related proteins needed for memory stabilization; 4) adequate time for consolidation. While the authors cite null results concerning behavioral tagging in older adults [2], the paradigms cited do not satisfy these criteria. One of these studies measured novelty effects on working memory, which is not considered by this model [3]. The other study used a pre-encoding virtual reality (VR) novelty manipulation followed by word learning. Yet free recall was tested immediately after learning, which does not allow sufficient time for putative tag-and-capture processes to induce long-term plasticity [4]. In short, these particular experiments are not strong tests of the behavioral tagging hypothesis we detailed in our review.

We agree that age-related declines in dopaminergic and noradrenergic systems may limit the efficacy of salience exposure interventions. Important structural features of the noradrenergic system, however, remain intact with age. The function of beta-adrenoreceptors is likely maintained in older adults, enabling the synthesis of proteins that stabilize memories. For example, post-encoding exercise has been shown to enhance memory in older adults, but only in individuals not taking beta-adrenoceptor blockers [5]. Notably, this finding also raises the important question of whether certain hypotensive medications impair behavioral tagging processes, especially given that beta blockers are so widely prescribed.

Another consideration is that as locus coeruleus (LC) neurons decline with age and/or Alzheimer's disease (AD), there may be compensatory increase in tonic, or sustained, levels of LC activity [6]. Elevated arousal states block phasic bursts of LC activity that typically mediate the beneficial effects of novelty on memory and also protect against the harmful effects of neuropathological features of AD [7]. Thus, the efficacy of salience inductions on older adults' memory may hinge on whether phasic LC activity can be successfully restored. There may be several ways to accomplish this. Both transcutaneous vague nerve stimulation (tVNS) and administration of atomoxetine boost the phasic-to-tonic ratio of LC activity and improve cognitive abilities in older adults [6,8]. Additionally, isometric handgrip enhances pupil dilation, an index of phasic LC activity, and boosts salience detection by reducing tonic levels of arousal in older adults [9]. Finally, it has been proposed that repeated practice of slow, paced breathing may boost LC phasic activity by reducing sympathetic nervous system activation [10]. Normalizing phasic LC activity might thereby recover its ability to target and rescue weaker memory traces in response to salient events.

Novelty-related inductions of memory consolidation are increasingly being manipulated through VR. Whether older adults enjoy, engage with, or tolerate immersive VR will likely determine the success of these novelty inductions. One alternative to VR could be curiosity interventions, which have been shown to benefit memory in both younger and older adults [11] and activate the dopaminergic system [12]. Thus, the type of "strong" event that is used to enhance nearby memories in older adults is an important consideration.

Looking forward, research on using strong learning events to enhance memory should carefully manipulate all key parameters of this framework, including spatiotemporal overlap between weak and strong events, study-test delay, and types of salience. While neuromodulatory systems may be down with age, they are not necessarily out. Exercise, novelty, and therapeutic tools could be used to restore more youthful patterns of LC activity known to mediate the beneficial effects of arousal and salience on memory. For future interventions to succeed, it will also be important to use strategies that appeal to older adults, such as activities that stimulate curiosity. Discovering how to preserve or even expand memory's penumbra is an exciting and worthy pursuit, because these approaches could improve adaptive memory function in individuals who may need it most.

References

1. Dunsmoor, J.E. *et al.* (2022) Tag and capture: how salient experiences target and rescue nearby events in memory. *Trends in Cognitive Sciences* 26, 782–795
2. Schomaker, J. *et al.* Memory's penumbra in the older or pathological brain. *Trends in Cognitive Sciences*
3. Biel, D. *et al.* (2020) The gains of a 4-week cognitive training are not modulated by novelty. *Hum Brain Mapp* 41, 2596–2610
4. Schomaker, J. *et al.* (2022) Effects of exploring a novel environment on memory across the lifespan. *Sci Rep* 12, 16631
5. Nielson, K.A. and Jensen, R.A. (1994) Beta-adrenergic-receptor antagonist antihypertensive medications impair arousal-induced modulation of working-memory in elderly humans. *Behavioral and Neural Biology* 62, 190–200
6. Janitzky, K. (2020) Impaired Phasic Discharge of Locus Coeruleus Neurons Based on Persistent High Tonic Discharge—A New Hypothesis With Potential Implications for Neurodegenerative Diseases. *Front Neurol* 11, 371
7. Omoluabi, T. *et al.* (2021) Novelty-like activation of locus coeruleus protects against deleterious human pretangle tau effects while stress-inducing activation worsens its effects. *Alzheimers Dement (N Y)* 7, e12231
8. Levey, A.I. *et al.* (2022) A phase II study repurposing atomoxetine for neuroprotection in mild cognitive impairment. *Brain* 145, 1924–1938
9. Mather, M. *et al.* (2020) Isometric exercise facilitates attention to salient events in women via the noradrenergic system. *Neuroimage* 210, 116560
10. Bachman, S.L. *et al.* (2022) Daily heart rate variability biofeedback training decreases locus coeruleus MRI contrast in younger adultsmedRxiv, 2022.02.04.22270468
11. Galli, G. *et al.* (2018) Learning facts during aging: the benefits of curiosity. *Exp Aging Res* 44, 311–328
12. Gruber, M.J. and Ranganath, C. (2019) How Curiosity Enhances Hippocampus-Dependent Memory: The Prediction, Appraisal, Curiosity, and Exploration (PACE) Framework. *Trends in Cognitive Sciences* 23, 1014–1025