Memory's penumbra in the older or pathological brain

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16th of September 2022

Dear Lindsey Drayton,

Herewith we would like to submit a revised version of our letter “Memory’s penumbra in the older and pathological brain” to Trends in Cognitive Sciences. We would like to thank you again for considering our letter for publication.

We received a positive and constructive review. We addressed the points that were raised by the reviewer and tried to stay within the word limits. We are now slightly over the 900-word limit (word count = 910). When addressing the reviewer’s comments, we removed one previously cited article to stay within the limit of 12 references. We would be happy to hear if you have other suggestions to limit the word count.

By addressing the reviewer’s points, we believe our letter improved in terms of clarity and readability, and hope that you will now find the letter suitable for publication in Trends in Cognitive Sciences.

Thank you again for your time and consideration.

Yours sincerely,

Dr. Judith Schomaker, Dr. Marit Ruitenberg & Prof. Tomonori Takeuchi

Letter in reply to: Dunsmoor, J.E., Murty, V.P., Clewett, D., Phelps, E.A., & Davachi, L. (2022).

Tag and capture: how salient experiences target and rescue nearby events in memory,

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Keywords (two to six)

Older individuals; Synaptic tagging-and-capture hypothesis; Behavioral tagging; Novelty; Emotion; Memory ~~re~~consolidation

We thank Dunsmoor *et al.*[1] for their timely and comprehensive examination of how salient events, including novelty and emotion, can save mundane memories from oblivion when encountered in close temporal proximity - an effect sometimes referred to as "memory's penumbra". We specifically applaud their efforts in linking neurobiological mechanisms as identified in rodents to emerging behavioral findings in humans, while explaining these in light of existing memory models. They address the synaptic-tagging-and-capture hypothesis~~model~~ – for which two conditions are indispensable: (1) local setting of "synaptic tags" generated by appropriate synaptic activity, and (2) availability of "plasticity-related proteins (PRPs)" that are synthesised as a result of the activation of neuromodulatory systems in a time-dependent manner[2] – to explain how on a neuronal level an initially *weak* memory trace becomes stable when a salient event is experienced during a critical time window around it. The authors propose that the behavioral counterpart of this phenomenon, i.e., *behavioral tagging*, could be leveraged to improve memory in older individuals, as ~~The authors propose that~~ weaker learning is a hallmark of episodic memory ~~the behavioral counterpart of this phenomenon, i.e., *behavioral tagging*, could be leveraged to improve memory for weakly encoded information~~ in ~~older individuals~~aging. That is, exposure to a *strong, salient* event could save memory for a *weak* event from forgetfulness when the events are presented close in time. Although the authors note that mechanisms underlying behavioral tagging are impaired with age, with both the tagging and capturing aspects being affected, they cite work done in middle-aged rats[3] and postulate that weak memories may be saved in older individuals via reactivation and reconsolidation of memory. As we will argue in this letter, the potential success of such an intervention in an aging or clinical population will depend on several crucial factors, including the integrity of the relevant neuromodulatory systems, the type of salient event, and the timing between the events.

Specifically, work in rodents indicates that the effects of salient events may change over the lifespan. One study observed novelty-induced memory benefits in young but not middle-aged rats[3]. However, post-reactivation exposure to novelty 6h after *strong* encoding had a beneficial effect in the latter group. These results suggest that the tagging mechanism is starting to degrade in middle-aged rats, despite sufficiently intact PRP production. In older age the underlying mechanisms may be further deteriorated[4]: Electrophysiological studies in older rats showed a failure of synaptic-tagging-and-capture due to a decrease of gene expression and associated synthesis of PRPs in CA1 pyramidal neurons of the hippocampus[5]. Reduced synthesis of PRPs could also result from deterioration of the relevant neuromodulatory systems, including

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dopaminergic and noradrenergic pathways (involved in the detection of novelty). Taken together, these neurobiological changes across the lifespan have implications for the applicability of interventions utilizing salience exposure, suggesting that in middle-age either stronger encoding or reactivation is required for novelty-related memory boosts to occur and effects may be further compromised in the (very) old. Furthermore, to determine the applicability of a ~~novelty/~~salience intervention we need to identify the exact time-window of memory's penumbra: What is the most effective interval between encoding and reactivation, and between reactivation and ~~novelty~~ saliency exposure? Another ~~open question~~relevant point that Dunsmoor *et al.* [1]~~,~~ did not consider is whether different types of saliency (i.e., novelty, emotion, and surprise) have the same potential to leverage memory in older age, as they may rely on differential neuromodulatory mechanisms[6], and computational and mathematical models suggest that novelty and surprise should be distinguished~~-~~[7].

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In humans both the dopaminergic and noradrenergic systems have been shown to deteriorate with age as well[8,9~~6,7~~]. As studies in animals suggest that synaptic-tagging-and-capture is less effective in older animals, and integrity of the locus coeruleus or ventral tegmental area are linked to successful PRP production, it is currently unclear if interventions in older individuals will be effective. So far, only two studies in humans including older individuals have been performed, and these did not observe beneficial effects of novelty on memory in older adults[10,11~~8,9~~]. Crucially, these null-results may be explained by different prerequisites for novelty-induced memory benefits in older versus younger individuals. If older individuals only benefit from novelty exposure before or after reactivation of memory traces~~[1210]~~, this should be a critical aspect of intervention protocols. For example, if an older person needs to remember their doctor's appointment, novelty exposure~~information~~ may have to be presented before or after reactivation of memory for the appointment, but this remains to be tested in humans.

The authors[1] discussed salience interventions in older individuals, but potentially clinical populations could benefit as well. Memory impairments are a hallmark of several neurological disorders, including Parkinson's and Alzheimer's disease, but also psychiatric disorders such as obsessive-compulsive disorder and schizophrenia. At the same time, the dopamine system has been implicated in these disorders, thus rendering it unclear if patients' memory could benefit from salience interventions. The feasibility of an intervention likely depends on the disease stage and/or the integrity of the dopaminergic and noradrenergic

systems, and the associated potential for PRP production. As novelty processing is relatively unaffected in an early (prodromal) stage of Alzheimer's disease[1~~3~~2~~11~~], these individuals could arguably benefit from interventions to maintain higher levels of memory functioning in daily life whereas individuals in later stages may not.

In conclusion, it remains to be investigated if *salience* interventions can be used to promote memory in aging and clinical populations, when the integrity of underlying neurobiological systems is compromised. To develop effective interventions, future studies should aim to disentangle the effects of novel, emotional, and surprising ~~and/ or novel~~ events on consolidation and reconsolidation, and to identify the neurobiological mechanisms and specific circumstances under which memory is promoted in humans.

Acknowledgments

This work was funded by a grant from Leiden University Fund Gratama Stichting & Elise Mathilde grant (awarded to J.S.), and Novo Nordisk Foundation Young Investigator Award 2017 (NNF17OC0026774), Lundbeckfonden (DANDRITE-R248-2016-2518) and PROMEMO – Center for Proteins in Memory, a Center of Excellence funded by the Danish National Research Foundation (DNRF133) awarded to T.T.

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Reviewer #1:
Schomaker et al letter highlights the main discussion points from the article of Dunsmoor et al and bring up some critical points. The main point they discuss, is the question if in age salience interventions could work with a potentially compromised system. They cite null-finding studies, which are important to mention. This is a critical and important point, that perhaps was too simply presented in the Dunsmoor article. A second aspect they mention very briefly in the end: that potentially emotional and novelty effects are different mechanisms. This is also a very important critical point. However, in the current form it is too briefly mentioned to be noticed by the naive reader.

We are pleased by the reviewer's positive evaluation of our letter.

We apologize for the unclarity regarding the potentially distinctive effects of novelty and emotion. Taking into account the word limit, we now introduce this point at the end of the first paragraph and further elaborate on it at the end of the second paragraph:

"Another relevant point that Dunsmoor et al.[1] did not consider is whether different types of saliency (i.e., novelty, emotion, and surprise) have the same potential to leverage memory in older age, as they may rely on differential neuromodulatory mechanisms[6], and computational and mathematical models suggest that novelty and surprise should be distinguished[7]."

Overall, the letter brings up important issues, however at times it is not that clear how these topics were discussed in the original article. The format of a letter is very short, but the authors could try to emphasize more how their opinion differs from the original article or which issues were not addressed.

We thank the reviewer for this relevant point of helping readers better understand the differences between the original article and our commentary. In line with the TICS guidelines for a letter, our intent was to complement the work by Dunsmoor et al. (2022). In the revised version of our letter, we clarify what the original authors already discussed and highlight where our letter goes beyond the original article:

"Although the authors note that mechanisms underlying behavioral tagging are impaired with age, with both the tagging and capturing aspects being affected, they cite work done in middle-aged rats[3] and postulate that weak memories may be saved in older individuals via reactivation and reconsolidation of memory. As we will argue in this letter, the potential success of such an intervention in an aging or clinical population will depend on several crucial factors, including the integrity of the relevant neuromodulatory systems, the type of salient event, and the timing between the events."