

# Top-down suppression deficit underlies working memory impairment in normal aging

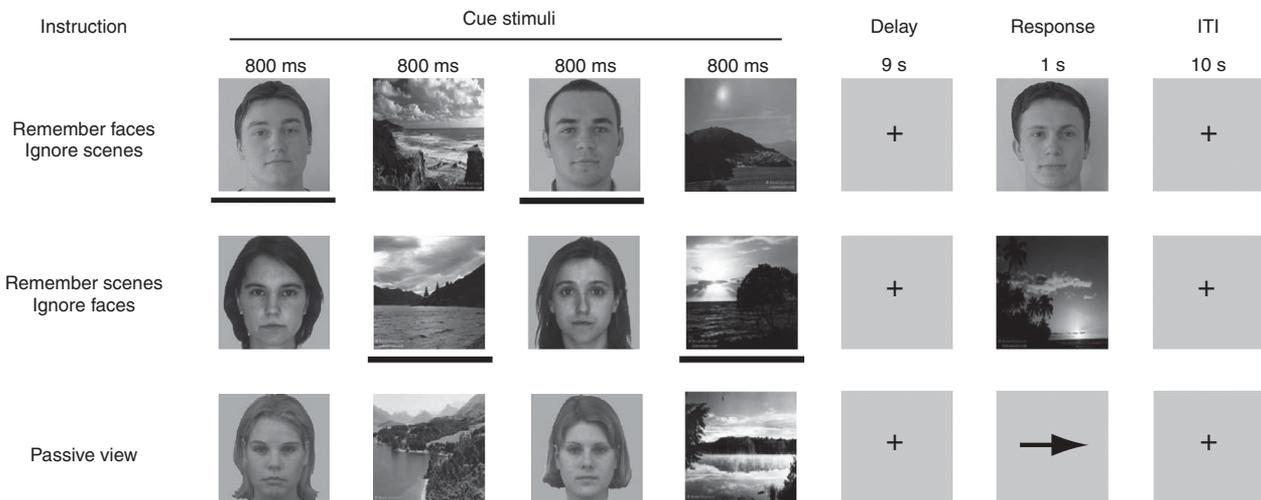
Adam Gazzaley<sup>1,2</sup>, Jeffrey W Cooney<sup>1</sup>, Jesse Rissman<sup>1</sup> & Mark D'Esposito<sup>1</sup>

**In this study, we assess the impact of normal aging on top-down modulation, a cognitive control mechanism that supports both attention and memory by the suppression and enhancement of sensory processing in accordance with task goals. Using fMRI (functional magnetic resonance imaging), we show that healthy older adults demonstrated a prominent deficit in the suppression of cortical activity associated with task-irrelevant representations, whereas enhancement of task-relevant activity was preserved. Moreover, this suppression-specific attention deficit correlated with impaired working memory performance.**

Although it is well established that many aspects of cognition decline with normal aging<sup>1</sup>, the search for an underlying mechanistic theory of cognitive aging is impeded by a tendency to study mutually dependent

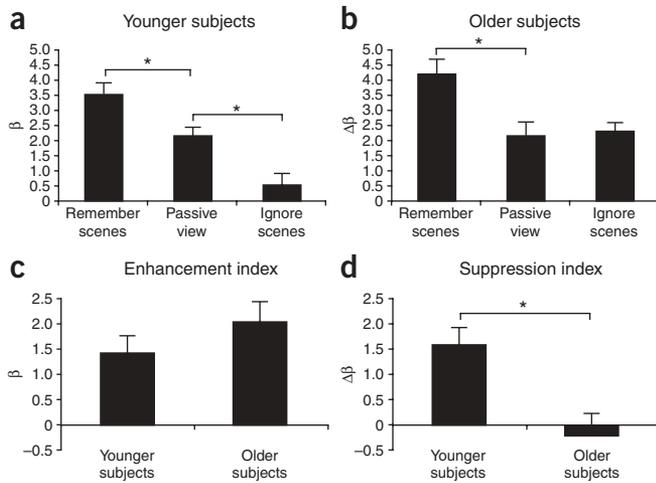
cognitive processes, such as attention and memory<sup>2,3</sup>, in isolation. Evidence suggests that selective attention is necessary to restrict the contents of capacity-limited memory networks to task-relevant representations<sup>4</sup>, thus favoring successful memory performance by limiting interference from task-irrelevant representations<sup>5</sup>. Top-down modulation underlies this selection through both enhancement and suppression of neural activity associated with task-relevant and task-irrelevant information, respectively<sup>6</sup>. Age-related working memory deficits may therefore result from impaired attentional processes<sup>7-9</sup>, specifically an alteration in top-down enhancement or suppression.

We identified distinct measures of top-down enhancement and suppression using a recently developed procedure<sup>6</sup> consisting of three tasks in which aspects of visual information are held constant while task demands are manipulated (Fig. 1). During each trial, participants observed sequences of two faces and two natural scenes presented in a randomized order. The tasks differed in the instructions informing the participants how to process the stimuli: (i) remember faces and ignore scenes ('ignore scenes'), (ii) remember scenes and ignore faces ('remember scenes') or (iii) passively view faces and scenes without attempting to remember them ('passive view'). In each task, the period in which the cue stimuli were presented was balanced for bottom-up visual information, thus allowing us to probe the influence of goal-directed behavior on neural activity (top-down modulation). In the two working memory tasks, the encoding of the task-relevant stimuli



**Figure 1** Experimental framework. The three tasks differ only in the instructions given at the beginning of each run, instructing the participant which, if any, stimuli they should attempt to remember over a 9-s delay, and in the response requirements. In the response period of the two memory tasks, a face or scene stimulus was presented (corresponding to the relevant stimulus class), and participants were required to report with a button press whether the stimulus matched one of the previously presented stimuli. In the 'passive view' response period, an arrow was presented, and participants were required to make a button press indicating the direction of the arrow. The lines below the stimuli are used to highlight task relevance in this illustration and were not present in the actual task.

<sup>1</sup>Henry H. Wheeler, Jr. Brain Imaging Center, Helen Wills Neuroscience Institute & Department of Psychology, University of California Berkeley, Berkeley, California 94720, USA. <sup>2</sup>Present address: University of California San Francisco, 1700 4th Street, Room 102C, San Francisco, California 94143-2512, USA. Correspondence should be addressed to A.G. (adamgazz@comewander.com).



**Figure 2** fMRI data showing a selective deficit of top-down suppression in older adults. **(a,b)** Within-group comparisons of the BOLD signal magnitude in the scene-selective ROI during the ‘remember scenes’, ‘passive view’ and ‘ignore scenes’ conditions for the **(a)** younger and **(b)** older age groups. **(c,d)** Across-group comparisons of **(c)** enhancement (‘remember scenes’ – ‘passive view’) and **(d)** suppression (‘passive view’ – ‘ignore scenes’) indices. Error bars: s.e.m. (\* $P < 0.005$ ).

required selective attention and thus permitted the dissociation of physiological measures of enhancement and suppression relative to the passive view baseline. Also in the memory tasks, after a 9-s delay, the participants were tested on their ability to recognize a probe stimulus as being one of the task-relevant cues, yielding a behavioral measure of working memory performance (see **Supplementary Methods** online).

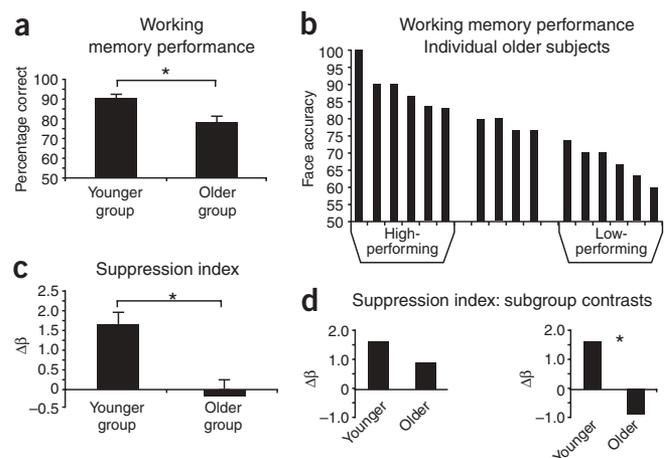
We have recently demonstrated in young adults that during the cue period, modulation of the magnitude of neural activity within scene-selective visual association cortex occurs relative to a perceptual baseline (‘passive view’), with enhancement (above baseline for ‘remember scenes’) and suppression (below baseline for ‘ignore scenes’) manifest depending on task instruction<sup>6</sup>. These top-down influences on posterior cortex may represent neural excitation and inhibition (enhancement and suppression, respectively) or, alternatively, three distinct levels of excitation based on the task relevance of the stimuli. Here we assessed age-related changes in top-down modulation using the most robust marker of modulation identified in the young adults: activity modulation within a scene-selective region of interest (ROI) in the left parahippocampal/lingual gyrus<sup>6,10</sup> (**Supplementary Discussion**).

The fMRI blood oxygen level-dependent (BOLD) signal magnitude was compared between tasks within each group of younger subjects ( $n = 17$ , 19–30 years of age) and older subjects ( $n = 16$ , 60–77 years of age; **Fig. 2**). As recently reported<sup>6</sup>, all younger subjects showed greater activity in this scene-selective ROI during the cue stimuli period when attempting to remember scenes than when ignoring scenes, despite viewing the same number of scenes in both tasks ( $P < 10^{-5}$ ). In addition, 82% of the younger participants showed enhanced activity above the passive view baseline when remembering scenes and 88% demonstrated suppressed activity below the passive view baseline when ignoring scenes (enhancement,  $P < 0.005$ ; suppression,  $P < 0.0005$ ; **Fig. 2a**). The older participants also showed greater activity in the scene-selective ROI when attempting to remember scenes than when attempting to ignore scenes ( $P < 0.0005$ ). However, although 88% of the older participants demonstrated enhanced activity above the passive view baseline (enhancement,  $P < 0.0005$ ), only 44% showed

suppressed activity (suppression,  $P = 0.72$ ), demonstrating an absence of significant suppression of task-irrelevant information in the older population (**Fig. 2b**).

Direct comparisons of BOLD signal across age groups showed a significantly greater signal magnitude within the scene-selective ROI in the older group than in the younger group in the ‘ignore scenes’ condition ( $P < 0.005$ ), whereas there was no age-related difference between the ‘remember scenes’ ( $P = 0.37$ ) or ‘passive view’ conditions ( $P = 0.96$ ). These comparisons demonstrate a selective age-related deficit in the suppression of task-irrelevant information. To further compare across age groups, we calculated three activity modulation indices: overall modulation index (‘remember scenes’ – ‘ignore scenes’), enhancement index (‘remember scenes’ – ‘passive view’) and suppression index (‘passive view’ – ‘ignore scenes’). The use of these indices enabled across-group comparisons without directly contrasting BOLD signal magnitude between populations that might have vascular responsivity differences<sup>11</sup>. This analysis confirmed an age-related decrease in the degree of overall modulation ( $P < 0.05$ ). Critically, this age-related decrease in modulation can be attributed to a selective decrease in the subcomponent process of suppression ( $P < 0.005$ ; **Fig. 2d**), as there was no significant difference in the enhancement subcomponent ( $P = 0.27$ ; **Fig. 2c**).

In addition to showing a decrease in the suppression index during encoding (**Fig. 3c**), older participants were behaviorally impaired on the working memory tasks in terms of both reduced accuracy and a slower reaction time compared to younger participants (accuracy for faces: younger = 90%, older = 78%;  $P = 0.001$ ; **Fig. 3a**; accuracy for scenes: younger = 92%, older = 81%;  $P < 0.001$ ; reaction time for faces: younger = 1,381 ms, older = 1,673 ms;  $P < 0.005$ ; reaction time for scenes: younger = 1,348 ms, older = 1,588 ms;  $P < 0.05$ ). Furthermore, the subgroup of six older participants showing a significant working memory deficit for remembering faces in the ‘ignore scenes’ task ( $Z < -2$  relative to younger adults), the task in which scene-selective ROI activity should have been suppressed, demonstrated a significantly reduced suppression index compared with the young controls ( $P < 0.05$ ), whereas the subgroup of six



**Figure 3** Relationship of suppression deficit and working memory deficit in aging. **(a,c)** Across-group comparisons of **(a)** face working memory accuracy for remembering faces in the ‘ignore scenes’ task (\* $P = 0.001$ ) and **(c)** suppression indices (\* $P < 0.005$ ). **(b)** Subgroups of the six high-performing and the six low-performing older individuals on the ‘ignore scenes’ task. **(d)** A significant suppression deficit is present only in the low-performing older subgroup (\* $P < 0.05$ ). Left graph: high-performing older. Right graph: low-performing older. Error bars: s.e.m.

older participants with preserved working memory performance ( $Z > -1$  relative to younger adults) did not show a reduced suppression index ( $P = 0.38$ ; Fig. 3b,d). This impaired subgroup of six older subjects also rated scenes viewed during the 'ignore scenes' task as significantly more familiar than the younger group rated them on a post-experiment recognition test ( $P < 0.05$ ), demonstrating increased incidental long-term memory of distracting information and supporting our neural data that task-irrelevant scenes were not suppressed (Supplementary Methods). Furthermore, we found neither a difference in the familiarity rating of these irrelevant scenes by the unimpaired older subgroup versus the younger population ( $P = 0.4$ ) nor a difference in correctly rejecting novel scenes for either older subgroup compared with the younger group (impaired,  $P = 0.72$ ; unimpaired,  $P = 0.36$ ). This finding establishes the relationship between an age-related deficit in selective attention (specifically, the suppression of task-irrelevant information), incidental long-term memory encoding and interference during the working memory task.

To more directly evaluate the relationship between top-down modulation during encoding and working memory performance in the older subjects, we computed the correlation between their suppression index and working memory accuracy for remembering faces in the 'ignore scenes' task. The analysis showed that the suppression index significantly correlated with working memory performance ( $r = 0.53$ ,  $P < 0.05$ ) such that the degree of top-down suppression during encoding predicted working memory recognition accuracy. This correlation supports the link between attention and working memory impairments in normal aging with an underlying deficit in top-down suppression. Thus, these data suggest that older individuals are able to focus on pertinent information but are overwhelmed by interference from failure to ignore distracting information, resulting in memory impairment for the relevant information.

Behavioral evidence suggests that age-related working memory impairments are associated with increased sensitivity to interference from task-irrelevant information<sup>9,12</sup>. However, the premise that a specific deficit in inhibitory processes negatively affects cognition—the inhibitory deficit hypothesis of aging<sup>7</sup>—remains controversial because of challenges in dissociating cognitive subcomponent processes (such as enhancement and suppression) using behavioral measures alone<sup>13</sup>. Additionally, recent studies using physiological measures have neither established specificity of an age-related attentional deficit to diminished inhibition nor directly related impaired attentional processing to working memory deficits<sup>8,14,15</sup>. The results of this study serve to resolve the controversy surrounding the inhibitory deficit hypothesis of

aging by demonstrating an attentional deficit specific to the suppression of task-irrelevant information (that is, a suppression deficit occurring in the setting of preserved enhancement) and directly relating this suppression deficit to working memory impairment.

The older individuals that participated in this study were healthy, well-educated and cognitively intact compared with age-matched controls, as measured by extensive neuropsychological testing (Supplementary Methods), allowing us to generalize these findings as a hallmark of normal cognitive aging. Encouragingly, a subgroup of the older population with preserved suppression also demonstrated intact working memory performance, reflecting the variable impact of the aging process and highlighting the importance of top-down suppression in cognition. Future studies should seek to elucidate the factors contributing to successful aging and preserved top-down modulation, as impaired suppression of distraction may underlie the broad spectrum of cognitive deficits experienced by older adults<sup>7</sup>.

Note: Supplementary information is available on the Nature Neuroscience website.

#### ACKNOWLEDGMENTS

This work was supported by the US National Institutes of Health and the American Federation of Aging Research (A.G.) and the NIH (M.D.). We thank D. Pino for helpful discussions and J. Hoffman and A. Rutman for assistance with neuropsychological testing.

#### COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Published online at <http://www.nature.com/natureneuroscience/>  
Reprints and permissions information is available online at <http://npg.nature.com/reprintsandpermissions/>

1. Craik, F.I. & Salthouse, T.A. *Handbook of Aging and Cognition II* (Erlbaum, Mahwah, New Jersey, 2000).
2. Awh, E. & Jonides, J. *Trends Cogn. Sci.* **5**, 119–126 (2001).
3. de Fockert, J.W., Rees, G., Frith, C.D. & Lavie, N. *Science* **291**, 1803–1806 (2001).
4. Rainer, G., Asaad, W.F. & Miller, E.K. *Nature* **393**, 577–579 (1998).
5. Ploner, C.J. *et al. Eur. J. Neurosci.* **13**, 357–363 (2001).
6. Gazzaley, A., Cooney, J.W., McEvoy, K., Knight, R.T. & D'Esposito, M. *J. Cogn. Neurosci.* **17**, 507–517 (2005).
7. Hasher, L. & Zacks, R.T. *The Psychology of Learning and Motivation* Vol. 22 (ed. Bower, G.H.) 193–225 (Academic, New York, 1988).
8. Chao, L.L. & Knight, R.T. *Cereb. Cortex* **7**, 63–69 (1997).
9. West, R. *Mem. Cognit.* **27**, 1064–1072 (1999).
10. Epstein, R., Harris, A., Stanley, D. & Kanwisher, N. *Neuron* **23**, 115–125 (1999).
11. D'Esposito, M., Deouell, L.Y. & Gazzaley, A. *Nat. Rev. Neurosci.* **4**, 863–872 (2003).
12. May, C.P., Hasher, L. & Kane, M.J. *Mem. Cognit.* **27**, 759–767 (1999).
13. McDowd, J.M. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **52**, P265–P273 (1997).
14. Alain, C. & Woods, D.L. *Psychol. Aging* **14**, 507–519 (1999).
15. Millham, M.P. *et al. Brain Cogn.* **49**, 277–296 (2002).