Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see http://www.jneurosci.org/content/jneurosci-journal-club.

A Possible Neural Mechanism of Intentional Forgetting

Madalina Vlasceanu[1,2] **and Michael J. Morais**[2,3]

[1]Department of Psychology, [2]Princeton Neuroscience Institute, and [3]Center for Statistics and Machine Learning, Princeton University, Princeton, New Jersey, 08544

Review of Wang et al.

Directed forgetting is a cognitive-control-dependent process that confers to the brain the flexibility for forgetting undesirable memories (Bjork et al., 1968; for review, see MacLeod, 1999). This process has been proposed to have distinct neural signatures from unintentional forgetting; specifically, frontal cortical processes are thought to play a major role (Wylie et al., 2007) during either encoding (Benoit and Anderson, 2012) or retrieval (Johnson, 1994) of undesirable memories. One neural mechanism by which memories might be intentionally forgotten involves increases in activity of the right dorsolateral prefrontal cortex, which in turn reduces hippocampal activity (Anderson et al., 2004; Benoit and Anderson, 2012), thus decreasing the strength of the targeted memories. This mechanism partially overlaps with the process by which reflexive motor actions are deliberately stopped, thus suggesting that blocking actions and blocking memories may be accomplished by a common inhibitory mechanism (Anderson et al., 2004). Because inhibition-based mechanisms fit smoothly into established models of brain function, the field had long supported them as the main models for intentional forgetting (Anderson et al., 2004). However, more recent proposals suggest effortful processing underlies intentional forgetting (Fawcett and Taylor, 2008).

Wang et al. (2019) propose an unconventional account of intentional forgetting, involving activation rather than inhibition. Their hypothesis builds on the nonmonotonic plasticity hypothesis (Norman et al., 2006), which challenges the positive linear relationship between memory activation and learning, instead proposing a nonmonotonic U-shaped relationship between the two. This idea is supported by extensive neurophysiology research showing that, whereas high postsynaptic depolarization leads to LTP, moderate postsynaptic depolarization leads to LTD (Artola et al., 1990). Thus, the proposed activation-dependent intentional forgetting mechanism suggests that intentional forgetting can be achieved by moderately activating memories represented in sensory cortex (ventral temporal cortex [VTC]). According to the nonmonotonic plasticity hypothesis, this modest activation would lead to memory weakening and thus forgetting.

To test this hypothesis, Wang et al. (2019) showed participants a series of images (faces and scenes), each followed by an instruction to remember or forget the item. Then participants were shown all the images again, this time intermixed with new images, and the participants were asked to indicate which items they had seen before. Brain activity elicited by each image was measured with fMRI during both the preinstruction (perceptual encoding) and postinstruction (mnemonic processing) time intervals, and a pattern classifier applied to data from VTC was used to model subsequent remembering or forgetting using a Bayesian curve-fitting algorithm. The classifier was trained on data collected right before the encoding phase, on a separate set of visual stimuli (faces, scenes, objects, and rest trials).

The main finding supported the authors' hypothesis: there was a nonmonotonic, U-shaped relationship between neural activation and memory, with items that elicited moderate activation in VTC being more likely to be forgotten than items that elicited either higher or lower levels of activation. This was true for both incidental forgetting of the to-be-remembered items and, more importantly, for intentional forgetting of the to-be-forgotten items.

Despite the apparent similarities between the incidental and intentional forgetting curves, the underlying processes were distinct: during intentional forgetting trials, the data show more activity in dorsolateral PFC, posterior cingulate, and precuneus, consistent with prior research showing these areas are involved in intentional forgetting (Rizio and Dennis, 2013). Moreover, processing was stronger for the to-be-forgotten items than for the to-be-remembered items. Representa-

Received April 22, 2019; revised July 22, 2019; accepted Aug. 3, 2019.

This work was supported by National Science Foundation Graduate Research Fellowship to M.J.M.

The authors declare no competing financial interests.

Correspondence should be addressed to Madalina Vlasceanu at mov@princeton.edu.

https://doi.org/10.1523/JNEUROSCI.0908-19.2019

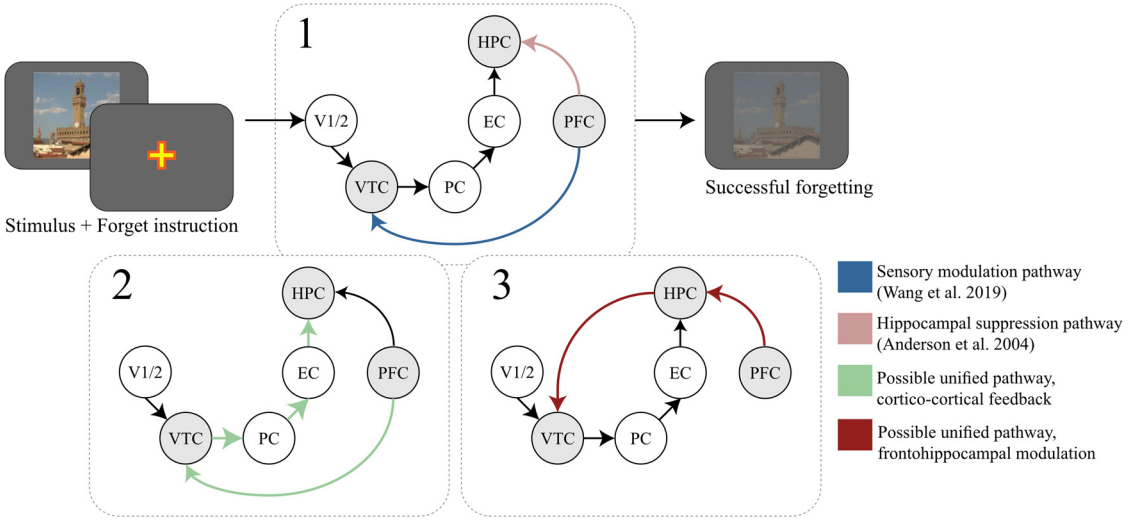

Figure 1. Cognitive control pathways for directed forgetting, as proposed by Wang et al. (2019) and prior work (Anderson et al., 2004). We suggest three pathways by which these two results might co-occur. Visual stimuli enter sensory cortices (V1, V2) and are sent through the ventral stream to VTC, then perirhinal cortex (PC), and entorhinal cortex (EC), before arriving at hippocampus (HPC). ***1***, PFC interprets the "forget" instruction and suppresses HPC (pink) (Anderson et al., 2004), and independently modulates sensory activity in VTC (blue) (Wang et al., 2019). ***2***, Corticocortical feedback projections from PFC to VTC could modulate sensory activity, which could be inherited by HPC through the ordinary feedforward pathway (green). ***3***, Frontohippocampal modulation from PFC could directly suppress HPC (Paz-Alonso et al., 2013), which could then modulate activity in VTC in a strictly feedback pathway (red).

tional similarity analysis indicated that this disparity emerged after the memory instruction (i.e., remember or forget); before the instruction, there was no significant difference in the pattern similarity of the two types of items. After the instruction, the to-be-forgotten items started developing more differentiated representations than the to-be-remembered items. The authors argue that this result provides further support for the activation-based forgetting mechanism proposed.

The authors are agnostic to and did not constrain the strategy of intentional forgetting participants used, and argue that, regardless of the strategy used (e.g., direct suppression, thought substitution, other idiosyncratic strategies), there is a consistent pattern of increased memory processing when attempting to forget compared with when attempting to remember an event, and the degree of this memory processing is predictive of successful forgetting. Thus, Wang et al. (2019) propose a novel neural mechanism that might contribute to intentional forgetting: moderately activating the representations of the undesired memories in sensory cortex weakens them, leading to their subsequent forgetting.

The proposal by Wang et al. (2019) of an automatic, activation-driven mechanism of deliberate forgetting complements prior suppression-driven models (Anderson et al., 2004; Benoit and Anderson, 2012). But how might these two accounts fit together? One possibility is that the two mechanisms are manifestations of a single unitary mechanism of forgetting that elicits different neural signatures (e.g., activation and suppression) in different brain areas (e.g., VTC and hippocampus). For example, a forget instruction might trigger frontal control to modulate VTC activation, which then leads to hippocampal suppression (corticocortical feedback pathway; Fig. 1). This is a possibility because high-order sensory areas in temporal cortex are known to project to entorhinal cortex, from which the hippocampus receives most of its cortical inputs (Anderson et al., 2016). Alternatively, frontal control might modulate hippocampal suppression impairing retention (Paz-Alonso et al., 2013; Anderson et al., 2016), which might then lead to moderate VTC activation (frontohippocampal modulatory pathway; Fig. 1). In support of this, the hippocampus projects to temporal cortex (Blatt and Rosene, 1998) and is involved in concept generalization from category representations (Bowman and Zeithamova, 2018), a main function of the VTC (Grill-Spector and Weiner, 2014). Another possibility is that frontal cortical areas send two signals in parallel, and sensory-activation-based forgetting is an independent process from hippocampal-suppression-based forgetting (Fig. 1). This is a possibility given that studies that found activation or suppression used different tasks and therefore tested different types of memory: Wang et al. (2019) used a paradigm that tests familiarity, whereas Anderson et al. (2004) used a paradigm that tests recollection. This is a meaningful distinction given that familiarity and recollection have been proposed to rely on different brain networks (Ranganath et al., 2004; Yonelinas et al., 2005).

Finally, this work has potentially important implications for treating memory disorders. Future translational work should test whether the activation-based forgetting mechanism unveiled can be used to weaken traumatic memories. Promisingly, intentional forgetting has been documented to be effective in the weakening of autobiographical memories of healthy adults (Noreen and MacLeod, 2013). This translational effort would require a method of triggering the moderate activation needed for successful forgetting, which has been found to be accomplished through directed strategies involving competition (Lewis-Peacock and Norman, 2014) or brief cueing (Poppenk and Norman, 2014), paradigms that could be adapted to weaken traumatic memories. This Goldilocks problem of finding the "just-right" level of activation is ripe for closed-loop experimentation to optimize activations in real time, particularly as online learning tools are becoming tractable and scalable in the machine learning community.

In conclusion, Wang et al. (2019) propose a neural mechanism through which deliberate forgetting can be achieved by moderately activating the representations of the undesired memories in sensory cortex. This hypothesis builds on the nonmonotonic plasticity hypothesis, and

complements suppression-based forgetting accounts. These findings open many directions for future work, including investigating potential connections with the more canonical hippocampal based deliberate forgetting mechanism, as well as investigating its potential implications for memory disorders.

References

Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, Glover GH,Gabrieli JD (2004) Neural systems underlying the suppression of unwanted memories. Science 303:232–235.

Anderson MC, Bunce JG, Barbas H (2016) Prefrontal-hippocampal pathways underlying inhibitory control over memory. Neurobiol Learn Mem 134:145–161.

Artola A, Bröcher S, Singer W (1990) Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature 347:69–72.

Benoit RG, Anderson MC (2012) Opposing mechanisms support the voluntary forgetting of unwanted memories. Neuron 76:450–460.

Bjork RA, Laberge D, Legrand R (1968) The modification of short-term memory through instructions to forget. Psychon Sci 10:55–56.

Blatt GJ, Rosene DL (1998) Organization of direct hippocampal efferent projections to the cerebral cortex of the rhesus monkey: projections from CA1, prosubiculum, and subiculum to the temporal lobe. J Comp Neurol 392:92–114.

Bowman CR, Zeithamova D (2018) Abstract memory representations in the ventromedial prefrontal cortex and hippocampus support concept generalization. J Neurosci 38:2605–2614.

Fawcett JM, Taylor TL (2008) Forgetting is effortful: evidence from reaction time probes in an item-method directed forgetting task. Mem Cognit 36:1168–1181.

Grill-Spector K, Weiner KS (2014) The functional architecture of the ventral temporal cortex and its role in categorization. Nat Rev Neurosci 15:536–548.

Johnson HM (1994) Processes of successful intentional forgetting. Psychol Bull 116:274.

Lewis-Peacock JA, Norman KA (2014) Competition between items in working memory leads to forgetting. Nat Commun 5:5768.

MacLeod CM (1999) The item and list methods of directed forgetting: test differences and the role of demand characteristics. Psychon Bull Rev 6:123–129.

Noreen S, MacLeod MD (2013) It's all in the detail: intentional forgetting of autobiographical memories using the autobiographical think/no-think task. J Exp Psychol Learn Mem Cogn 39:375–393.

Norman KA, Newman E, Detre G, Polyn S (2006) How inhibitory oscillations can train neural networks and punish competitors. Neural Comput 18:1577–1610.

Paz-Alonso PM, Bunge SA, Anderson MC, Ghetti S (2013) Strength of coupling within a mnemonic control network differentiates those who can and cannot suppress memory retrieval. J Neurosci 33:5017–5026.

Poppenk J, Norman KA (2014) Briefly cuing memories leads to suppression of their neural representations. J Neurosci 34:8010–8020.

Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M (2004) Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia 42:2–13.

Rizio AA, Dennis NA (2013) The neural correlates of cognitive control: successful remembering and intentional forgetting. J Cogn Neurosci 25:297–312.

Wang TH, Placek K, Lewis-Peacock JA (2019) More is less: increased processing of unwanted memories facilitates forgetting. J Neurosci 39:3551–3560.

Wylie GR, Foxe JJ, Taylor TL (2007) Forgetting as an active process: An fMRI investigation of item- method-directed forgetting. Cerebral Cortex 18:670–682.

Yonelinas AP, Otten LJ, Shaw KN, Rugg MD (2005) Separating the brain regions involved in recollection and familiarity in recognition memory. J Neurosci 25:3002–3008.