Stimulating memory consolidation

Serra E Favila & Brice A Kuhl

A study in this issue of *Nature Neuroscience* reports that administering caffeine to humans immediately after memory encoding enhances consolidation, as reflected by improved performance in a memory test a day later.

Most readers of this publication are undoubtedly familiar—maybe very familiar—with caffeine, a common CNS stimulant that produces increased wakefulness for several hours after ingestion. Low doses of caffeine have been shown to have positive effects on several measures of cognition in humans, including attention, processing speed and, in some cases, working memory[1]. Although most strategic users of caffeine (including these authors) consume it to increase their alertness during upcoming cognitive tasks, a study in this issue of *Nature Neuroscience* demonstrates a surprising relationship between caffeine and cognition. Borota *et al.*[2] show that caffeine administered to human subjects immediately after learning improves memory 1 d later, a result that suggests caffeine can enhance memory consolidation.

Few studies have been published that attempt to determine whether caffeine affects long-term memory in humans. The results of those studies, all of which administered caffeine before memory encoding, suggest that the effect of caffeine on long-term memory is small, if present at all[1]. Even positive effects produced by pre-encoding caffeine are difficult to interpret as purely mnemonic because of the potential for caffeine to enhance attention or vigilance during learning.

In contrast with the human literature, many animal studies have yielded evidence for caffeine-induced memory enhancement. Honeybees show improved memory after drinking caffeine-laced nectar[3], and multiple studies have provided evidence for caffeine's role in attenuating memory decline in rodent models of aging and neurodegenerative disease[4]. Furthermore, there is long-standing evidence for the positive effect of post-encoding caffeine on memory performance in rodents[5], an effect that seems to depend on caffeine's ability to bind to specific adenosine receptor subtypes[6]. Although the beneficial effects of post-encoding caffeine suggest a positive influence on synaptic consolidation, only recently has a direct link between caffeine and synaptic modification been reported: *in vivo* oral administration of caffeine enhances synaptic potentiation in the CA2 region of the rat hippocampus[7], a structure known to be critical for long-term memory.

Inspired by these findings in animals, Borota *et al.*[2] considered whether caffeine might influence human long-term memory via enhanced consolidation. To test this behaviorally, they used a pharmacological post-encoding design typical of animal consolidation studies. The study was randomized, double-blind, placebo-controlled and recruited only subjects who consumed low amounts of caffeine. On day 1, subjects participated in a learning session in which they were asked to make judgments about everyday items ("Would you find this item indoors or outdoors?") (**Fig. 1**). They were not aware that their memory for these items would later be tested. Immediately after the encoding phase, subjects were given a placebo or 200 mg of caffeine. The next day, subjects returned to the lab for a surprise memory test. During the test, subjects were shown a series of images and asked to decide whether each image was identical to one of the images from day 1 (old), similar to one of the images from day 1 (similar) or entirely novel (new). To monitor for the presence of caffeine and its metabolites over the course of the experiment, subjects were also asked to provide salivary samples before the encoding phase, 1 and 3 h after taking caffeine or placebo, and just before the day 2 memory test. Although caffeine administration resulted in elevated caffeine levels at 1 and 3 h post-administration, caffeine levels fully returned to baseline by the time of the day 2 memory test.

Notably, caffeine administered after the encoding phase—and 24 h before the memory test—improved subjects' abilities to discriminate objects encountered during the encoding phase from highly similar new objects. Specifically, subjects who had been administered caffeine were more likely to correctly label the similar lure items as similar and less

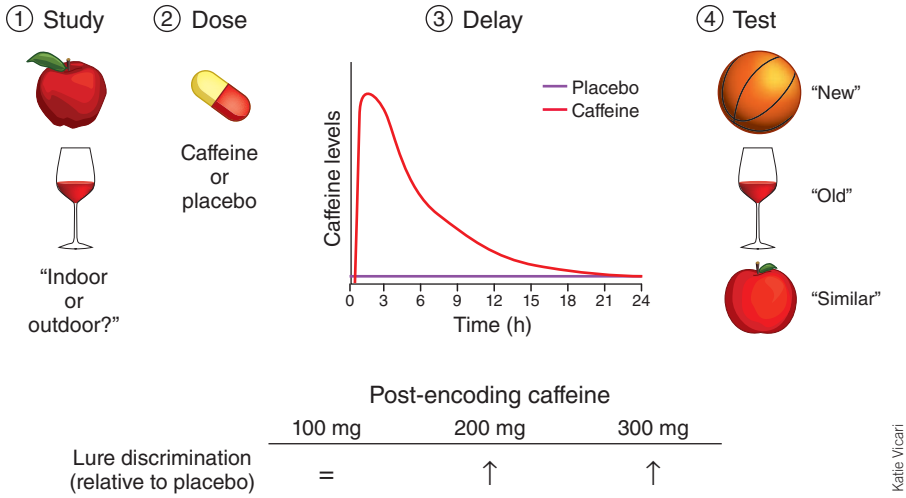

Figure 1 Effect of post-encoding caffeine on memory. On day 1, subjects viewed a series of images of everyday objects and made a judgment about whether each image was likely to be found indoors or outdoors. Immediately after completing this task, they took either caffeine or placebo. Measured caffeine levels fully returned to baseline by the next day. On day 2, subjects were given a surprise memory test. Subjects viewed a series of images and decided whether each image was new (not seen on day 1), old (identical to one of the images from day 1) or similar (a different exemplar of one of the images seen on day 1). The probability of correctly labeling similar images as similar (instead of old) was reflected by a lure discrimination index that corrected for potential response bias. Subjects who received 200 or 300 mg of caffeine after the study period on day 1 showed enhanced lure discrimination on day 2 compared with subjects who received placebo. At 100 mg, caffeine did not enhance test performance, nor did caffeine administered just before the memory test (not shown).

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likely to mistakenly label them as old relative to subjects who were given a placebo. This ability to successfully identify lures ("That's not the apple I saw yesterday!") was quantified by a lure discrimination index, which corrected for potential response biases. Interestingly, performance on old items and new items did not differ between the caffeine and placebo groups, indicating that the observed memory effect is specific to lure discrimination.

Two control experiments provide important information about the timing and dosage of caffeine required to obtain these memory benefits. In the first control experiment, the experimenters delayed caffeine administration to an hour before the memory test on day 2. Although one might expect that caffeine administration just before a memory test would confer some benefit, lure discrimination was equivalent between groups, suggesting that caffeine does not enhance retrieval processes *per se*. In a second experiment, Borota *et al.*[2] explored the dose-response relationship between caffeine and lure discrimination. They found that a lower dose of post-encoding caffeine (100 mg) was insufficient to enhance lure discrimination at day 2. A higher dose of caffeine (300 mg) produced lure discrimination performance that was roughly equivalent to the performance with 200 mg, though when measurements of caffeine metabolites were taken into account, there was some evidence for an inverted-U dose-response function (in case you are wondering: a Starbucks Grande coffee has 330 mg of caffeine).

The findings reported by Borota *et al.*[2] represent an important demonstration of caffeine-related long-term memory enhancement in humans. Given that caffeine was administered after items were encountered and well before they were tested, the results are not easily explained in terms of arousal or attention during either encoding or retrieval. Instead, they suggest a mechanism by which caffeine promotes memory consolidation. Moreover, because the benefit to memory was restricted to lure discrimination, they also suggest a highly specific kind of memory enhancement. Variants of the lure discrimination task used by Borota *et al.*[2] have been used to index pattern separation mechanisms putatively supported by the hippocampus[8,9]—that is, the ability of hippocampal cells to orthogonalize highly similar inputs[10,11].

How might post-encoding caffeine specifically benefit memories that depend on successful pattern separation? Brain-derived neurotrophic factor (BDNF) expression is known to affect synaptic consolidation[12], and a recent study found that post-encoding blockade of BDNF expression in the dentate gyrus region of the rat hippocampus selectively interferes with consolidation when the encoded events are highly similar to one another[13]. Moreover, BDNF expression increases when rats explore an environment that is similar to a prior environment, suggesting that BDNF expression occurs in response to similarity between memories. Interestingly, BDNF blockade at the time of retrieval does not produce similar impairments. There is also evidence that caffeine influences BDNF expression in the rodent hippocampus[14]. Thus, although this is speculative, it is possible that post-encoding caffeine selectively benefits consolidation of pattern-separated memories by influencing levels of BDNF. Furthermore, caffeine may influence memory consolidation via other mechanisms. For example, norepinephrine, whose release can be triggered by caffeine, has been shown to promote memory consolidation for emotional stimuli during sleep[15].

The findings of Borota *et al.*[2] advance our knowledge of pharmacological influences on human memory consolidation and are likely to inspire future research on the neurobiological mechanisms underlying such influences. In the meantime, consider reading their article and following that up with a moderate-sized cup of coffee.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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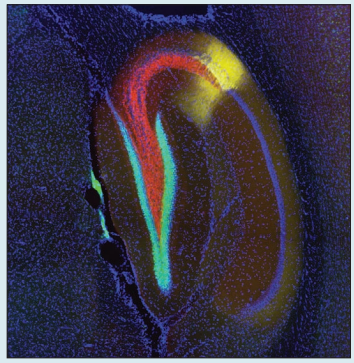
Deciphering CA2 connectivity



The trisynaptic circuit, which is composed of connections from entorhinal cortex to dentate gyrus to CA3 and ultimately to CA1, has long been considered to be the canonical pathway for information flow through the hippocampus and is thought to form the anatomical substrate for learning and memory in this region. Much less is known about the CA2 region, although recent work has suggested that neurons in this area can be uniquely identified by their gene expression patterns, opening up a new avenue for understanding their role in information flow through the hippocampus. On page 269 of this issue, Kohara and colleagues capitalize on these previously unknown molecular markers, using cell type–specific transgenic mouse lines, optogenetics and patch-clamp recordings to identify the unique connectivity patterns of hippocampal CA2 pyramidal neurons.

Although the CA2 region (yellow) has historically been differentiated from CA1 and CA3, in part, on the basis of the absence of input from the dentate gyrus, the authors find that dentate granule cells (cyan) do indeed send abundant functional monosynaptic inputs to CA2 pyramidal cells (red). They also identify a projection from CA2 to CA1, but, unlike the projection from CA3 to CA1, CA2 projects preferentially to the deep rather than to the superficial sublayer of CA1. In addition, in contrast with previous studies using more traditional anatomical techniques, the authors report that neurons in layer III of the entorhinal cortex do not project to CA2.

Although the exact role that these hippocampal connectivity patterns may have in learning and memory processes remains unclear, these findings present exciting opportunities for future research.

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