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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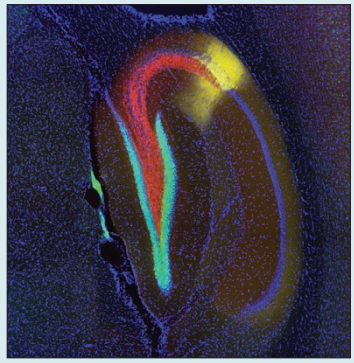
Deciphering CA2 connectivity



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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