In mind and out of phase

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Our ability to hold multiple pieces of information "in mind" relies upon the brain's working memory system. This system temporarily holds a limited amount of information in an active state so that it can be manipulated or quickly accessed. Working memory is thought to play a critical role in many cognitive processes such as language, reasoning, attention, and problem-solving (1). Essentially, any task that requires information to be briefly held in an online state so that it can be operated upon likely depends on working memory as a form of mental workspace. The centrality of this memory system within cognition likely explains why individuals with various neurological and psychiatric disorders such as schizophrenia, clinical depression, and Parkinson's disease generally show substantial deficits in working memory performance (2–4). Indeed, even within a healthy population, differences among individuals in working memory capacity are thought to reflect a core cognitive ability because they strongly predict performance in a wide range of high-level aptitude measures such as reading skills, attentional control, and fluid intelligence (5–7). The importance of this system has strongly motivated many neuroscientists to characterize how working memory is implemented in the brain. In the past four decades, there have been several substantial discoveries that have revealed basic properties of the neural substrates of working memory such as the primary cortical regions involved, as well as how single neurons represent individual memories. Despite this progress, our understanding of how the brain is capable of holding multiple representations simultaneously in memory is still extremely poor. However, a new study by Siegel et al. (8) in this issue of PNAS appears to have made a dramatic and fundamental leap forward in revealing how the brain manages to keep multiple things in mind.

Oscillating Memories

Since the early 1970s, primate neurophysiologists have known that if you record activity from single neurons in areas such as the prefrontal cortex or posterior parietal cortex while a monkey performs a working memory task, many cells show increased and sustained firing while the animal is actively remembering an object or a location (9). This phenomenon is often called *delay activity*, and is thought to reflect that individual neuron's contribution to the memory representation (10). While variations on this general approach have been very productive over the years, it necessarily provides only a tiny window onto how the brain is able to represent multiple complex memories at the same time. More recently, many neuroscientists have begun to examine how the activity from ensembles of many neurons collectively manages to represent information on a much larger scale. The basic approach to doing this is to examine how large groups of neurons rhythmically fire together, which can be measured in the local field potential. These *brain oscillations* are thought to provide a vehicle for coordinating and sharing information within a given cortical region as well as a means of communicating signals between different brain areas. Oscillations can occur across a number of different frequency bands, ranging from very slow cycles (4–7 Hz, theta band) to very fast cycles (25–100 Hz, gamma band). In the context of working memory, oscillations in the gamma band have been proposed to play a fundamental role in linking up the various attributes of the memoranda (e.g., position, shape, color, etc.) across numerous individual neurons into a unified working memory representation (11, 12). However, if working memories are all represented in the same gamma oscillation, how do we manage to keep from blurring all of the active memories together? One solution that has been proposed in a number of computational models has been to keep the memories separated by positioning each one in a different phase within the oscillation. That is, individual memories can be kept segregated, so long as they are "out of phase" with one another in the oscillation.

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How We Keep Them Separated

Such a phase-coding scheme has been proposed in several computational models over the years (12–14). While these models provide a plausible solution to the multiple-memories problem, there has been no empirical evidence to support it. However, the study by Siegel et al. (8) appears to provide the first demonstration of such a phase-coding scheme in the brain for working memory. To do this, they recorded the local field potential over the prefrontal cortex while monkeys performed a sequential short-term memory task. In this task, monkeys are shown two pictures, one at a time, that they had to remember. After a short delay, memory was tested by presenting three pictures simultaneously; two of which were the pictures they had seen earlier in the trial, and one was a novel picture. To perform correctly, the monkey responded by initially looking at the first picture in the original sequence, then looking at the second picture, but not the novel picture. This task requires them to actively remember both of the pictures from the sequence and the order of presentation. By examining the gamma oscillation over prefrontal cortex during the blank delay period while these memories were being maintained in mind, Siegel et al. found that the two remembered objects were represented in distinct phase orientations of the oscillation depending on the order of presentation. That is, the first object of the sequence was preferentially coded in one phase orientation, and the second object was always in a separate phase orientation. Thus, they found direct evidence that the brain kept these two active memories separated by keeping them out of phase. In addition to keeping the memory representations segregated, this phase-coding scheme also provides an easy way for the brain to remember which picture came first in the sequence. In fact, on the trials when the monkey misremembered the order of the two pictures, the brain showed no evidence of adequate phase separation between the two memories.

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The results of this exciting new study provide a great leap forward in our understanding of how information is actively represented in the mind. In addition to this fundamental discovery, these results put us significantly closer to achieving what many consider to be a holy grail in this field: why is working memory capacity limited in the first place? On average, working memory is generally thought to be able to hold a maximum of about four separate representations in memory at the same time (15–17). One clear advantage of a phase-coding scheme for working memory is that it provides a fairly straightforward explanation about what causes capacity limits. Specifically, if each object in memory must be segregated from the others in a different range of phase orientations, then there should be some maximum limit on the number of memories that could be distinctly represented simultaneously. Beyond that number, the representations would become highly confusable and performance would suffer because there is insufficient phase space to keep the memories segregated (12–14). Thus, a core cognitive ability such as working memory capacity might ultimately turn out to be restricted by a biophysical limitation surrounding how information is coded in the brain. While future work will be necessary to test these ideas about capacity limits, the Siegel et al. (8) study has begun to substantially unravel our understanding of what it means for the brain to have more than one thing in mind.

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