

By inspection of the maps in the top row, the responses at position “b” to either black or white stimuli are slightly slower than the responses at “a.” If we take the Hubel-Wiesel model and delay one of the inputs by a few milliseconds (Figure 1, bottom row) we get space-time maps in which the white-stimulus excitation shows space-time slant but the black-stimulus excitation does not, resulting in a cell that should prefer leftward moving white bars as well as leftward moving gratings and would be nondirectional or weakly rightward preferring to black bars. This model is less aesthetic than the Energy model because it does not show the same direction selectivity to both light and dark stimuli, but it may be more realistic; indeed, Conway and I found that many directional simple cells in macaque V1 were direction selective to only one sign of contrast (Conway and Livingstone, 2003).

Priebe and Ferster observed balanced push-pull organization throughout the entire space-time extent of the receptive fields. To achieve this, the Energy model diagrammed in Figure 1 requires at least four simple cell inputs—two excitatory inputs and two complementary inhibitory inputs. But directional simple cells receive direct geniculate inputs and do not lose their direction selectivity when cortical responses are suppressed (Jagadeesh et al., 1993; Ferster et al., 1996), indicating that the spatiotemporal arrangement of geniculate inputs alone is sufficient to generate directionality. To achieve a push-pull organization for the Energy model shown using geniculate inputs would require eight geniculate-like inputs—four excitatory inputs, two fast and two slow, and four matching inhibitory inputs driven by geniculate inputs. One advantage of the model in the bottom row is that it is simpler to wire up, requiring only two excitatory geniculate inputs and two inhibitory inputs driven by geniculate inputs. Another feature is that the timing differences required are smaller.

The mystery remains why one subregion would be delayed relative to the other. It has been suggested that the lagged and nonlagged cells of the geniculate might provide inputs with the necessary timing differences to generate the space-time slant in the Energy model (Saul and Humphrey, 1992). But lagged cells would not look like the slower input in the bottom row because lagged cells are not temporally biphasic. Another possibility is that the envelope of the slower inhibitory inputs might be skewed toward the null side of the receptive field compared to the faster excitatory inputs (Livingstone, 1998). Priebe and Ferster looked at the overall spatial distribution of excitation and inhibition, but they did not account for the increased baseline level of response arising from the continuous presentation of stimuli, so their calculation (inset below Figures 7A and 7B of their text) shows essentially no spatial distribution of either excitatory or inhibitory inputs, which does not make sense. A calculation of the envelope of the summed excitatory inputs compared to the envelope of the summed inhibitory inputs could address this idea. Another possibility is that the timing differences needed to generate space-time slant do not arise from inputs with different temporal properties but are determined by the cortical cell itself, say, by its morphology. Differences in dendritic threshold or differences in distance from the cell body could produce the required small timing differences. Putting this onus on the postsynaptic

cell would automatically generate matching timing differences in corresponding ON and OFF and excitatory and inhibitory inputs, explaining one of the most striking results in the Priebe and Ferster study—the spatiotemporal correspondence among these different inputs.

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DOI 10.1016/j.neuron.2004.12.029

Role of Rhythms in Facilitating Short-Term Memory

Working memory tasks have been associated with the appearance of elevated single unit activity (SUA) in primate studies, and oscillatory activity in the EEG or the local field potential (LFP) in humans. The study by Lee et al. in this issue of *Neuron* provides novel insights regarding the relationship between SUA and LFP rhythmicity in V4 during working memory tasks.

We routinely remember information for short periods, for example, memorizing a string of numbers while placing a call. This rapid, short-term memorization of a small number of items is called short-term or working memory. A typical working memory experiment consists of five stages. The task begins with an eye fixation period, followed by the presentation of a “sample” stimulus.

This is followed by a “delay” period where there is no stimulus and by a “probe” stimulus. The subject has to indicate whether the probe was similar to the sample, say, by pressing a button. Research on working memory has focused on understanding the mechanisms by which information about the sample is maintained in the brain during the delay period. A vast amount of work has revealed two diverse sets of neural phenomena during the delay period. One line of research is carried out by measuring the single unit activity (SUA) in the association areas. In particular, stimulus-specific, persistent SUA of neurons in the prefrontal cortex during the delay period is believed to mediate working memory (Fuster and Alexander, 1971; Asaad et al., 1998; Compte et al., 2003). The other line of research has measured the EEG, mostly in humans, showing the appearance of rhythmicity in the EEG during a working memory task (Gevins et al., 1997; Raghavachari et al., 2001).

Are the two phenomena, persistent activity and rhythmicity, related? Lee et al. (2005 [this issue of *Neuron*]) have addressed this question directly by simultaneously measuring the SUA and the local field potentials (LFP) from several parts of area V4 during a working memory task. The task began with eye fixation at a point on the screen for 1 s, followed successively by a short (350 ms) presentation of a sample, a 1 s delay, and the presentation of the probe. They found a clear increase in theta rhythmic (4–8 Hz) modulation of the LFP during the last 700 ms of the delay period compared to the fixation period. This is reminiscent of the theta rhythmic modulation of the EEG at a variety of sites in humans. Interestingly, while the theta rhythm appeared in several brain regions throughout the working memory task in humans (Raghavachari et al., 2001), the theta rhythm in Lee et al.’s experiments appeared mostly during the delay period and not during the fixation period. More experiments are required to determine whether these differences are due to task differences or because the theta rhythm appears during different epochs of the task in different brain regions.

The appearance of the theta rhythm in the delay period raised an interesting question: could it be induced by the sample stimulus? To address this question, Lee et al. used a clever manipulation: they presented the sample stimuli at a variety of contrasts. The high-contrast stimuli were clearly visible, whereas the low-contrast stimuli were not, as shown by poor performance on these trials. Surprisingly, Lee et al. found that while the high-contrast stimuli led to an increase in theta power, the low-contrast stimuli led to a significant reduction in the theta power during the delay period. Two broad classes of mechanisms could mediate this differential modulation of theta power by contrast. A top-down mechanism would suggest that monkeys pay more attention to high-contrast stimuli and stop paying attention to the task in response to low-contrast stimuli. These differential levels of attention could lead to altered theta power (Fries et al., 2001), perhaps via altered cholinergic levels. Alternatively, a bottom-up mechanism would imply that high-contrast stimuli lead to a strong and synchronous activation of a large number of neurons. This neuronal activity could then generate large recurrent inhibition, thereby setting up theta rhythmic oscillations in the local network of excitatory and inhibitory neurons. Such a

mechanism is supported by Figure 6 of Lee et al., showing a larger increase and decrease of SUA after the sample onset and offset, respectively, after the high-contrast stimuli compared to the low-contrast stimuli.

Lee et al. also recorded the theta rhythm from up to eight electrodes simultaneously. They found that the amplitude and phase of theta was identical on two electrodes that were 1 mm apart, whereas the theta on an electrode 3 mm away was both weaker and phase shifted. Despite this variation in the phase of theta across different electrodes, a majority of the SUA were preferentially active near the troughs of the theta recorded on the same electrode. This suggests that the theta rhythm and SUA were strongly modulated locally by networks of neurons near the electrodes.

Does the theta rhythmic modulation of SUA play a role in working memory? To address this question, Lee et al. analyzed the SUA as a function of both theta phase and the identity of the probe stimulus. They first computed the phase of the theta rhythm where a neuron fired more spikes, called its *preferred phase*. For a vast majority of neurons, the preferred phase was near the trough of the local theta. Lee et al. divided all the spikes fired by each neuron into two classes, spikes near the preferred phase and spikes away from the preferred phase. They made a remarkable discovery: spikes near the preferred phase showed stronger stimulus selectivity than the spikes away from the preferred phase. In fact, stimulus selectivity in the delay period was enhanced when only the spikes near the preferred phase were used, compared to selectivity obtained using all the spikes fired by a neuron. It is possible that the spikes at the nonpreferred phase merely represent noise or spurious activity. On the other hand, it is conceivable that while the majority of spikes, near the troughs of theta, carry information about the stimulus identity, the small number of spikes near the theta peaks convey non-stimulus-specific information, such as context and task. More experiments are required to determine if spikes at different phases of theta in V4 indeed encode diverse information.

Rhythmic modulation of spikes as a function of stimulus has also been observed in other brain structures. Neural activity in the striate (Gray and Singer, 1989) and the parietal cortices (Pesaran et al., 2002) are modulated by the gamma rhythm (~40 Hz) in a stimulus-specific fashion. A vast amount of literature shows that the activity of rodent hippocampal neurons is strongly modulated by the theta rhythm during exploration (Green and Arduini, 1954; Buzsaki, 2002). Furthermore, the phase of the theta rhythm at which a hippocampal neuron fires a spike varies as a function of the position of the rat (O’Keefe and Recce, 1993). The recent work by Lee et al. adds to the growing body of evidence suggesting a critical involvement of rhythmic activity in neural information processing. Their findings also raise several new questions whose answers will bring us closer to understanding the mechanisms of working memory.

Perhaps the most important issue raised by this study concerns the relationship between rhythmic activity and elevated persistent activity in working memory tasks. Lee et al. have clearly demonstrated that neurons in V4 show rhythmic activity during the delay period. However, the mean firing rate of the V4 neurons is not ele-

vated during the delay period. On the other hand, several studies have shown that neurons in the prefrontal cortex fire at elevated rates during the delay period with no clear theta rhythmic modulation of SUA (Compte et al., 2003) or the EEG (Raghavachari et al., 2001). The rhythmic activity in upstream structures such as V4 could generate elevated activity in downstream structures such as the prefrontal cortex, and vice versa, to mediate working memory as follows. Stimuli could induce theta rhythmic activity with weak stimulus selectivity in the balanced excitatory-inhibitory networks within upstream structures such as V4. The synchronized theta rhythmic activity in upstream structures could generate elevated, even ramping activity (Asaad et al., 1998) in the prefrontal cortex via rapid short-term synaptic plasticity (Mehta et al., 2000). Since upstream theta is locally synchronized but is phase shifted at longer distances, the prefrontal activity would show weaker rhythmicity and stronger stimulus selectivity than the upstream structures. When this ramping, elevated activity in the prefrontal cortex is fed back to the upstream structures, it would further tip the balance between local excitation and inhibition to generate more robust theta rhythmic activity. Such a self-sustaining mechanism would have the advantage of keeping multimodal information about the stimulus in the prefrontal cortex while allowing neurons in the upstream structures to respond to sensory stimuli in the delay period. Only simultaneous measurements of LFP and single unit activity in multiple brain regions during working memory tasks will reveal the mechanisms by which rhythmicity and persistent activity mediate working memory. The work of Lee et al. is an important step in this direction.

I thank O. Ahmed and A. Shaikhouni. This work was supported by NSF.

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DOI 10.1016/j.neuron.2004.12.030