

# Polyrhythms of the Brain

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**The mechanism by which multiple brain structures interact to support working memory is not yet fully understood. In this issue of *Neuron*, Fujisawa and Buzsáki report that coordinated oscillatory activities between the hippocampus, prefrontal cortex, and ventral tegmental area (VTA) may be a key neural correlate of working memory.**

Most of today's communication tools utilize waves to carry information. We rely on electromagnetic oscillations with frequencies spanning multiple orders of magnitudes to make phone calls, watch TV, and remotely open our garage door. Waves at different frequencies act as channels, efficiently conveying different kinds of messages without any interference.

Similarly, the brain uses oscillations as a means to link processing ongoing in multiple brain areas. Here as well, a wide variety of frequencies come into play, from the slow oscillations of sleep (starting at a fraction of a Hertz) to gamma oscillations reaching 80–100 Hz. By transiently engaging and disengaging oscillatory coherence, that is, the degree by which oscillations in the two structures keep a constant phase relationship, brain areas can modulate the extent to which their computations interact. Thus, the effective functional network can be reconfigured instant by instant. For example, by shifting the phase relationship between gamma oscillations, a higher visual area such as V4 can “tune in” on a V1 column whose receptive field contains a relevant stimulus, thereby steering visual attention (Womelsdorf et al., 2007). As in radio communication, oscillations at different frequencies may channel information from different sources. This occurs, for example, in the hippocampal subfield CA1, which can selectively “listen” to signals from the CA3 subfield or the entorhinal cortex by resonating at the different characteristic gamma frequency ranges of these structures (Colgin et al., 2009).

The hippocampal and prefrontal cortex (PFC) appear to play special roles as

“hubs” of interstructure communication. As such, both of these structures are capable of orchestrating the activity of many cortical and subcortical areas subserving cognitive functions such as working memory, memory acquisition and consolidation, and decision making (see Benchenane et al., 2011; Schwindel and McNaughton, 2011, for reviews). Both structures receive converging input from the higher sensory/associative areas. Furthermore, the PFC is one of the few neocortical areas that receives direct input from the hippocampus itself. Consistent with this link, activity oscillations in PFC and the hippocampus are coherent (see e.g., Sirota et al., 2008), and the degree of coherence covaries with working memory (Jones and Wilson, 2005) and decision making (Benchenane et al., 2010) demands.

In this issue of *Neuron*, Fujisawa and Buzsáki (2011) aim to extend our understanding of oscillatory coherence in the context of working memory by studying the simultaneous activity of the rat PFC, the hippocampal CA1 subfield and the VTA, a basal ganglia nucleus containing dopaminergic (DA) cells, which sends neuromodulatory signals to much of the brain. The authors analyzed the activity of ensembles of single neurons and local field potentials (which reflect local averages of membrane currents) in these areas while rats performed a working memory task on a T-maze. The animals were trained to choose either the left or right target arm, based either on association with an odor sampled at the departure point, or to alternate between arms. In both cases, while the rat was in transit

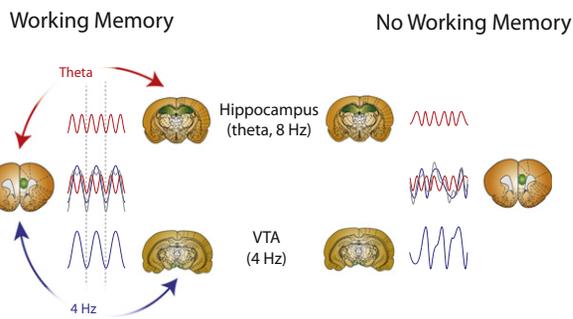
to the choice-point, information about the arm to be chosen (or which arm was most recently chosen) has to be maintained in working memory, a function that, in rats, has been shown to require the integrity of the hippocampal-PFC network (Floresco et al., 1997).

In analyzing the spectral coherence between PFC and VTA, the authors identify a novel slow rhythm centered at 4 Hz. In this frequency range, both regions engage in coherent oscillations that are modulated by behavior, where the strongest and most coherent oscillations are observed on the central arm, or “choice-point,” of the T-maze (i.e., where working memory is necessary for correct decision-making). Those oscillations were not present during performance of a forced-choice control task that did not require working memory (Figure 1). Concurrently, oscillatory coherence at theta frequencies (~8 Hz) was observed between the PFC and the hippocampus, as previously shown during working memory maintenance (Jones and Wilson, 2005), and surprisingly between the hippocampus and VTA as well. Furthermore, the hippocampal theta and 4 Hz PFC-VTA rhythms (with roughly a 2:1 frequency ratio) maintained a fixed cross-frequency relationship, with troughs of the slower and faster oscillations mostly coinciding with each other. In addition to this theta-4Hz oscillatory phase-coupling, the firing of individual neurons in PFC and VTA were also phase-locked to 4 Hz oscillations. Interestingly, CA1 cells also showed a moderate but significant entrainment to the PFC 4 Hz oscillations, implying that the VTA-PFC network coherence may

influence other structures as well. Thus, while we are accustomed to the metaphor of the brain as a symphony “orchestra,” the emerging picture here suggests that brain activity rather resembles the polyrhythmic beats of a jazz drummer effortlessly combining different rhythms played on the snare drum and the hi-hat.

Interestingly, the authors also report a significant task-dependent coherence of fast gamma oscillations (30–80 Hz) between the PFC and VTA. Long-range gamma coherence has previously reported between distant cortical areas in the monkey (see e.g., Gregoriou et al., 2009). To add to the complex polyrhythmic interplay between these structures, gamma power was modulated by the phase of the slow PFC-VTA 4 Hz oscillation, (maximal at the ascending phase). Therefore, the long-range 4Hz interaction between PFC and VTA may affect the local pyramidal/interneuron circuit giving rise to PFC gamma oscillations (similar to what has been shown for hippocampal theta and cortical gamma by Sirota et al., 2008). In support of this conjecture, the authors demonstrate that the interaction between pyramidal cells and interneurons in PFC, as measured by cross-correlations, is modulated by the 4 Hz phase. Thus, the effective strength of prefrontal synaptic connections (in particular those pyramidal/interneuron synapses thought to be important for the generation of gamma oscillations) is regulated by the slow 4 Hz PFC-VTA interaction.

It is enticing to speculate about the functional consequences of this complex dynamic. Fujisawa and Buzsáki’s work provides some hints, showing that working memory demands most markedly affect pyramidal cells in PFC and DA cells in VTA (which also contains GABAergic cells). These cell types are crucial in the classic view of working memory maintenance, in which information is maintained by reverberating activity due to excitatory feedback connections. If the synaptic



**Figure 1. Polyrythmic Interactions among Critical Brain Areas May Facilitate Working Memory**

During working memory maintenance (left), the PFC local field potential has oscillatory components at 4 Hz (blue) and at theta (8 Hz; red) frequencies. PFC theta oscillations are in phase with the hippocampal theta, whereas 4 Hz oscillations in PFC and VTA are in phase. Moreover, troughs of PFC 4 Hz oscillations are in phase with every second peak of theta (dashed vertical lines). When there are no working memory demands, coherence breaks down, and no consistent phase relationship is observed. In phase firing of neurons enables more effective temporal summation and hence greater effectiveness on post-synaptic targets. At higher frequencies such as gamma (~40 Hz), it may also regulate spike-timing-dependent synaptic plasticity. This is interesting because, as the authors show, gamma is modulated by the lower frequency components in VTA (4 Hz) and hippocampus (8 Hz) and so the polyrhythmic interaction between these two structures in PFC may facilitate gamma phase coherence between them as suggested by the authors. Gamma interactions are strongly implicated in numerous cognitive tasks including working memory.

matrix has the appropriate features, many “attractor states,” or stable activity states to which a network is likely to conform when starting from a similar enough configuration, may be possible. Thus, different pieces of information to be held in working memory may correspond to different attractors that may be maintained online even in the absence of a stimulus. DA is known to have an influence on attractor dynamics, with D1 and D2 receptors having opposing effects (Durstewitz and Seamans, 2008); the former making an attractor more stable (and helping working memory maintenance) and the latter lowering the energy barriers between attractors, making it more likely for the network to flip between two states, thus promoting behavioral flexibility. In support of this view, Fujisawa and Buzsáki (2011) found those PFC neurons that are predictive of the animal’s behavioral choice in the working memory task are the cells most robustly modulated by 4 Hz PFC-VTA oscillations and hippocampal theta.

The study by Fujisawa and Buzsáki (2011) raises some interesting challenges to our current views on the role of DA in PFC, which revolve around three im-

portant functions: working memory, decision making, and long-term memory consolidation. As a first consideration, theories tackling all three of these aspects assume tonic DA release. Whether and how this assumption may need to be updated to account for rhythmic DA discharge, taking place in phase with activity fluctuations in PFC, will have to be determined by future work.

Current theories of working memory, based on attractor networks, do not imply any form of rhythmic modulation of activity, at least in their simplest forms. The data in Fujisawa and Buzsáki’s paper hints at a quite different view of working memory where activity is strongly fluctuating, entrained by oscillations at different frequencies. Oscillations may assist in the maintenance of coordinated activity

in multiple attractor modules within and between areas. An alternative model of working memory dependent on transient attractors (Mongillo et al., 2008) could also be envisaged, where activity bouts are terminated by periodic inhibitory inputs related to these polyrhythmic oscillations. In line with this model, neuronal groups in the PFC exhibit transient, synchronous activation during active behavior (Benchenane et al., 2010) and during sleep (Euston et al., 2007). Importantly, the findings by Fujisawa and Buzsáki (2011) raise the possibility that the increased synchrony between PFC and VTA induced by 4 Hz oscillations may be important for spike-timing-dependent plasticity at the PFC to VTA synapses, which is integral to dopamine-dependent reinforcement learning (Liu et al., 2005). Besides working memory, the complex temporal structure of VTA and PFC firing may also have an effect on decision-making by dictating how reward-related information is conveyed by DA. Furthermore, VTA-PFC oscillatory coherence and synchronization may play a role in memory consolidation by potentially influencing expression of plasticity-related proteins and stabilizing memory

traces at the synaptic level (Redondo and Morris, 2011). These new findings represent merely the beginning of a new dimension in research on the manner in which distinct regions integrate information to support optimal working memory.

Another important issue requiring new research is how the coherence between VTA and PFC may arise. The authors speculate that the VTA may be the pacemaker of the 4 Hz oscillation. This hypothesis awaits experimental validation. Moreover, it is not clear how the oscillations can be propagated to the PFC, as second messenger DA receptor signaling is most likely too slow to mediate this function. We can only conjecture that either GABAergic VTA cells, or glutamate corelease from DA cell synapses, may convey the oscillatory input to PFC.

Nonetheless, the study by Fujisawa and Buzsáki (2011) paves the way for future experiments centered on these themes.

#### REFERENCES

- Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P.L., Gioanni, Y., Battaglia, F.P., and Wiener, S.I. (2010). *Neuron* 66, 921–936.
- Benchenane, K., Tiesinga, P.H., and Battaglia, F.P. (2011). *Curr. Opin. Neurobiol.* 21, 475–485.
- Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.B., and Moser, E.I. (2009). *Nature* 462, 353–357.
- Durstewitz, D., and Seamans, J.K. (2008). *Biol. Psychiatry* 64, 739–749.
- Euston, D.R., Tatsuno, M., and McNaughton, B.L. (2007). *Science* 318, 1147–1150.
- Floresco, S.B., Seamans, J.K., and Phillips, A.G. (1997). *J. Neurosci.* 17, 1880–1890.
- Fujisawa, S., and Buzsáki, G. (2011). *Neuron* 72, this issue, 153–165.
- Gregoriou, G.G., Gotts, S.J., Zhou, H., and Desimone, R. (2009). *Science* 324, 1207–1210.
- Jones, M.W., and Wilson, M.A. (2005). *PLoS Biol.* 3, e402. 10.1371/journal.pbio.0030402.
- Liu, Q.S., Pu, L., and Poo, M.M. (2005). *Nature* 437, 1027–1031.
- Mongillo, G., Barak, O., and Tsodyks, M. (2008). *Science* 319, 1543–1546.
- Redondo, R.L., and Morris, R.G. (2011). *Nat. Rev. Neurosci.* 12, 17–30.
- Schwindel, C.D., and McNaughton, B.L. (2011). *Prog. Brain Res.* 193, 163–177.
- Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., and Buzsáki, G. (2008). *Neuron* 60, 683–697.
- Womelsdorf, T., Schoffelen, J.M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., and Fries, P. (2007). *Science* 316, 1609–1612.