domains. This conceptually related gating mechanism in both dimeric Hv1 channels and tetrameric Kv channels, presumably evolved to tune the kinetic behavior of the channels for their functions. Second, Hong et al. (2013) demonstrates that Hv1 can be targeted with small molecule inhibitors, providing a crucial starting point to synthesize derivatives of guanidine compounds for therapeutic applications. The recent demonstration of diminished neuronal death after stroke in Hv1 knockout mice provides a compelling potential application for selective Hv1 inhibitors (Wu et al., 2012). Finally, some of the compounds may be useful for crystallizing the Hv1 channel and stabilizing it in the open state. These pharmacological tools and Hv1 mutations serve as valuable additions to the arsenal of ion channel biophysicists and physiologists, to enable further exploration of these intriguing miniature voltage-activated channels.

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Volitional Control of Cortical Oscillations and Synchrony

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Oscillatory activity in motor cortex has been observed in many experimental contexts, leading to various hypotheses about its possible behavioral function. In this issue of *Neuron*, Engelhard et al. (2013) report that oscillations can be volitionally controlled, opening new directions to explore their function and underlying mechanisms.

Correlating brain activity with behavior has been a tried and true formula for investigating neural mechanism generating behavior. This usually involves training monkeys or asking humans to perform a behavior of interest and documenting the correlated brain activity. The less conventional inverse of this strategy is to get the subject to control a brain activity of interest and observe the correlated behavior. Volitional control of brain activity can be accomplished with biofeedback making some chosen parameters of neural activity explicit and controllable. This neurofeedback paradigm is inherent in the control of brain-machine interfaces, in which the neurally controlled output provides the feedback (Fetz, 2007).

Oscillatory activity in motor cortical neurons has been observed in a number of behavioral situations, leading to a corresponding range of hypotheses about its possible function. Synchronous oscillations have been reported to occur during an instructed delay period prior to movement and then disappear during the overt movement, suggesting a role in motor preparation (Donoghue et al., 1998). In apparent contradiction, oscillations have been observed to appear during a maintained precision grip, where their function could be understood in terms of the enhanced efficacy of a synchronized rhythm in activating motoneurons (Baker et al., 1999). In other studies, robust and widespread oscillatory episodes occurred during free exploratory hand movements, e.g., to retrieve food from unseen locations, but these episodes had no consistent temporal relation to the occurrence of EMG (Murthy and

Fetz, 1996a). These oscillations entrained both task-related and unrelated neurons equally. Coherent oscillations occurred over widespread cortical areas, including both hemispheres, but correlations between different cortical sites did not depend on the sites' relation to the task, indicating that under these free movement conditions coherent oscillations did not seem to be performing any obvious sensorimotor binding function. Thus, task-based experiments have implicated motor cortical oscillations in facilitating motor preparation, amplification of downstream effects, and increased arousal and attention.

The default possibility, that oscillations are merely an epiphenomenon, without any computational function, has remained the plausible position of diehard skeptics. Oscillatory activity could occur when the level of network excitability exceeds some threshold for triggering resonant activity. It may seem remarkable that such robust changes in the temporal structure of neural activity would not somehow affect neural computation. However, the mean firing rates of cells during oscillatory episodes are not changed relative to the rate just prior to the episode (Murthy and Fetz, 1996b). Thus, the oscillations are essentially superimposed on ongoing activity and may have negligible effects on the neural computations performed by more broadly modulated firing rates. Consequently, they could still be an epiphenomenon relative to such rate-based computations. Of course, this notion is anathema to proponents of temporal coding, for whom spike timing and synchrony play critical roles in neural computation.

The study of Engelhard et al. (2013) in this issue of *Neuron* used biofeedback to train monkeys to increase motor cortex low-gamma activity and sheds new light on these issues. They also recorded single-neuron activity and found that the robust operantly conditioned oscillatory episodes were accompanied by a dramatic correlated increase in the synchrony of the entrained neurons. This relation is to be expected, since the local field potentials are produced by postsynaptic potentials and periodicity in spike activity would be associated with periodicity in the fields. The authors noted that oscillatory episodes were not associated with any observed movements or increases in muscle activity. In other studies, in which muscles were simultaneously active, the muscles showed correlated oscillatory modulation (Baker et al., 1999; Murthy and Fetz, 1996a), indicating that the periodic fluctuations were widespread through the motor system. It would be important to investigate the possible behavioral function of the operantly conditioned oscillations in future studies.

The null hypothesis that oscillations are merely an epiphenomenon now has to contend with this new evidence that this phenomenon is under volitional control. In previous studies that observed oscillations with behavior, gamma power is the dependent variable and thus can always be a potential epiphenomenon (Keizer et al., 2010). But with neurofeedback it becomes the independent variable, and its effects on behavior are more compelling evidence of function. Keizer et al. (2010) have shown that volitionally increased gamma activity at occipital and frontal sites in humans improved performance on cognitive tests of sensory binding and memory.

Synchronous neuronal activity can be periodic, as during oscillations, or episodic. Episodic synchrony is detected in cross-correlograms that have a single central peak, without periodic side peaks. It can also be detected during behavior by increases in synchronous spiking beyond that expected by firing rates; such "unitary events" have appeared consistently at particular times in relation to an expected cue, at times unrelated to sensory or motor events (Riehle et al., 1997). Such episodic synchrony could also be trained with biofeedback. For example, humans could learn to increase and decrease above-chance synchrony of forearm motor units with feedback of coincident motor unit potentials (Schmied et al., 1993). However, because synchronized spikes are caused by common synaptic inputs this demonstration is essentially equivalent to demonstrating control of the common input neurons. In contrast, periodic synchrony represents a rhythmic phenomenon involving a different mechanism generating more prolonged circuit resonance.

Oscillatory brain activity has been documented most thoroughly in the visual system, where many experiments have provided evidence that widespread periodicity is involved in top-down perceptual processing (Engel et al., 2001) and plays a role in long-range interactions between cortical areas (Siegel et al., 2012). For example, recent evidence indicates that different visual areas representing a particular stimulus orientation become synchronized in the gamma band specifically when the monkeys attend that stimulus (Bosman et al., 2012). Extrapolating these hypotheses to the motor system would suggest that the motor cortex oscillations could also be involved in attention to aspects of movement (Donoghue et al., 1998; Murthy and Fetz, 1996a). This would mean that in addition to the top-down control of motor cortical activity involved in generating movements, there is an additional and independent top-down mechanism involved in attention to movement control. This hypothesis seems consistent with most of the experimental evidence to date.

This hypothesis also predicts the involvement of other cortical sites during the motor cortex oscillations. Engelhard et al. documented the spatial extent of neurons entrained with the operantly conditioned oscillatory episodes. Over the extent of their 4 × 4 mm electrode grids they found that gamma power in the LFP, phase locking of units, and depth of entrained modulation all decreased as a function of distance from the operant conditioning sites (Engelhard et al., 2013). During task performance the distribution of correlated sites appears to be relatively widespread within sensorimotor cortex, including premotor, postcentral, and contralateral motor cortex (Donoghue et al., 1998; Murthy and Fetz, 1996a).

The demonstration that motor cortical oscillations can be volitionally controlled opens the door to further investigations of underlying mechanism and behavioral correlates. The other cortical regions showing activity correlated with oscillatory episodes in motor cortex could be documented more fully with more widespread electrophysiological recordings or magnetoencephalography (MEG). Human subjects increasing their oscillatory gamma activity with biofeedback should be able to report the effective strategy and any subjective correlates of this activity. Not only the power, but the coherence between oscillations in related cortical sites could be similarly investigated, as in a recent report of volitional control of MEG coherence, associated with motor behavior (Sacchet et al., 2012). Biofeedback could also be used to explore the extent to which the correlated activities in different areas can be volitionally dissociated or independently controlled. Another issue is whether other frequencies in the LFP can be similarly controlled. The same operant conditioning strategies could be used to explore comparable questions in sensory systems. Such neurofeedback studies can be expected to provide further insights into the mechanisms and functional roles of oscillatory activity.

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