

Vandecasteele et al., 2014). Only recently, it was possible to causally link septohippocampal theta activity during REM sleep with successful memory consolidation (Boyce et al., 2016). Having a clearer understanding of the transmission of the theta rhythm from the medial septum to the hippocampus will allow us also to understand how memory-related theta activity and REM sleep-related theta activity are linked.

Comparing ACh with noradrenaline or dopamine reveals that those neuromodulators not only switch between the on and off state, but they also have a tonic and a phasic firing mode. Papouin et al. (2017) have investigated cholinergic modulation of long-term potentiation at the timescale of the circadian rhythm. Whether astrocytic D-serine modulation in the hippocampus is only involved in such a slow, tonic modulation, or whether it can also mediate faster, situation-triggered ACh release, remains to

be investigated. The latter would allow adaptation of NMDAR potentiation based on the demands of the learning situation. Current results leave room for the question of whether wake-dependent modulation already saturates D-serine levels also on a shorter timescale, or whether there is the potential for additional phasic modulation. More broadly speaking, it remains unanswered why D-serine modulation in the hippocampus seems to be coupled with state of consciousness rather than with situational learning demand. A highly speculative answer to this question might relate cholinergic modulation to the continuous demand of moment-to-moment encoding of the stream of consciousness into episodic memory.

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## Ready, Steady, Go! Imaging Cortical Activity during Movement Planning and Execution

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In this issue of *Neuron*, Chen et al. (2017) examine premotor activity representing motor planning, Allen et al. (2017) observe the global representation of goal-directed movement on the cortical network, and Makino et al. (2017) track changes in such dynamics throughout learning.

Imagine Usain Bolt on the track crouched into a four-point stance and waiting for the race to begin. The starting pistol fires, and he springs forth with astonishing speed. In less than 200 ms, the sound of the gunshot is processed by his auditory system and transformed into a series of motor commands that coordinate his skeletal muscles to carry out a behavior that has been shaped by years of practice. We perform

basic versions of this kind of behavior several times every day; for example, turning left in response to a GPS command and nodding in agreement during a conversation with a friend. The capacity to learn, prepare, and command movements in response to sensory information is a fundamental feature of the brain.

Motor engagement likely requires the coordinated activity of many brain regions.

What are these large-scale network dynamics that enable sensorimotor transformations? A primary challenge in addressing this question stems from the difficulty in observing large-scale network changes that accompany a tractable behavior. To address this need, three related studies in this issue of *Neuron* have successfully tracked large-scale neuronal activity patterns during movement acquisition,

planning, and execution using cortex-wide calcium imaging methods at both mesoscopic and cellular scales. In all three studies, mice were taught to respond to a sensory cue (e.g., tone presentation) with a simple motor action (e.g., a controlled tongue movement). Each paper focused on different aspects of the neural response and together begin to form a more complete picture of how the brain generates learned, sensory-driven movements.

At the heart of each investigation is an identified region within the frontal cortex, often referred to as the anterior lateral motor cortex (ALM), which may have functional similarities to the primate premotor cortex. ALM had previously been shown to be a critical node for enabling the transfer of information from sensory to motor regions within the brain (Guo et al., 2014). Further, single neurons within ALM exhibit robust activity that can predict the direction of upcoming movement long before its initiation (Li et al., 2015, 2016). Does motor preparation originate within ALM?

To address this question, the Svoboda lab (Chen et al., 2017) examined the activity of not only ALM, but also a nearby structure—the medial motor cortex (MM)—because it had been shown to exhibit preparatory activity (Erlich et al., 2011). Mice were trained to use their whiskers to discriminate two positions of a pole and to report their perception by licking one of two ports after a substantial delay period. Wide-field imaging during task performance revealed a wave of neural activity that started in contralateral MM during the sensory phase and later emerged in ALM bilaterally during the delay period, peaking just prior to the movement onset.

Chen et al. (2017) used two-photon imaging at cellular resolution, combining imaging planes from multiple locations that span MM and ALM. Neurons within these areas often displayed responses only to specific aspects of the task, namely the sensory percept (anterior or posterior location of the pole), the motor response (direction of licking), or the outcome of the trial (reward or no reward). In order to identify the beginning stages of motor preparation, they examined the relative timing of activity in the neurons that correlated with lick direction, representing the behavioral choice of the animal. They

found that preparatory activity emerges seconds before movement onset in the deep layers of ALM, significantly preceding such neuronal responses in superficial regions or in MM. Because only two identified motor regions were observed, Chen et al. (2017) cannot rule out the involvement of other areas on motor preparation. Regardless, the experimental design with explicit sensory, delay, and response epochs represents a compelling means of delineating the roles of individual neurons in a sensorimotor task. This design is likely to be useful for dissecting the behavioral relevance of other candidate movement planning regions in future studies.

To begin to understand movement representation on a larger spatial scale, a second study in this issue (Allen et al., 2017) examined global responses in most of dorsal cortex while mice performed an olfactory discrimination task. To achieve this, Allen et al. (2017) outfitted mice with a 7-mm window and imaged activity while they licked to indicate the odor identity. During task performance, active neurons were observed across a broad collection of cortical regions, including sensory, motor, and association areas. Neurons that consistently responded during specific points during the trial were found sprinkled throughout the forebrain, with little evidence for spatial clustering.

Motivated to more comprehensively survey this distributed response, the aforementioned group (Allen et al., 2017) directly compared neural responses collected with wide-field and two-photon imaging during optogenetic silencing and activation of ALM. They demonstrate that this approach is strongly biased toward capturing activity occurring in layer 1 rather than layer 2/3, although the precise contribution of different cell types (e.g., layer 5 dendrites) to this response remains unknown. Allen et al. (2017) demonstrate widespread, distributed brain activity during this task, and they find that silencing ALM abolishes this global activity. Surprisingly, they were also able to trigger large-scale patterns of activity, as well as licking movements by optogenetically stimulating ALM, even in the absence of behavior, although it remains unclear whether the evoked patterns directly match the mo-

tor-related firing. These results, nonetheless, suggest that ALM is acting as a ringleader capable of broadly influencing cortical function.

How does this large-scale activity change with motor learning? To address this question, another study (Makino et al., 2017) imaged a large portion of the dorsal cortex in the mouse across successive days while it learned to pull a lever in response to an auditory cue. Over the span of 2 weeks, learning was associated with both a decrease in reaction time and a reconfiguration of network dynamics. To explicitly track cortex-wide changes, Makino et al. (2017) functionally segregated individual brain areas into identified regions (e.g., primary motor cortex) and measured their relative time of activation. Surprising shifts were observed in the sequential order in which individual areas became active. Of particular interest was the secondary motor cortex (M2), which overlaps spatially with ALM. During learning, M2 activity migrated to the beginning of the sequence. This observation was supported by a Granger causality analysis that suggests that activity flowed from M2 to other forebrain areas during late stages of learning. Inactivation experiments support this idea; injection of muscimol into M2 reverses learning-related changes in observed large-scale cortical activity, even in cases where the behavioral output was identical. These results demonstrate that behavioral changes during learning can be associated with large-scale alterations in the flow of activity.

Taken together, these studies deepen our understanding of the forebrain dynamics that underlie movement. Sensory information is routed to ALM from other cortical regions, originating at different points depending on modality (e.g., auditory versus olfaction). Shortly thereafter, within ALM, the upcoming decision is represented by an increase in firing of layer 5 neurons. While we know that premotor neurons projecting out of ALM can drive upcoming movements, ALM also appears to spark a widespread sequence of activation across diverse cortical regions in a manner that is shaped by experience.

Several questions follow from these studies. (1) What are the mechanisms that enable ALM to represent preparatory

activity that anticipates future actions? Of specific interest are the means by which sensory information is integrated by layer 5 ALM neurons and converted into a motor plan, especially with respect to the roles of specific projection classes. Recordings of these neurons and their inputs throughout learning may help to shed light on how this is established. (2) What is the function, if any, of the ALM-dependent global activation of the cortex? It is especially pertinent because inactivation of brain regions other than ALM did not lead to measurable behavioral deficits (Allen et al., 2017; Makino et al., 2017), adding to the growing evidence that neural responses reflecting an animal's decision may not be causally involved in carrying out that decision (Katz et al., 2016). (3) Is ALM a universal hub for learned movement? This is especially pertinent given the fact that ALM activity is both necessary and sufficient for tongue protrusions (Guo et al., 2014; Komiyama et al.,

2010), and all the mice in these studies were required to lick as part of the task. It is possible that other distinct premotor regions may exist for behaviors that do not involve orofacial movements. If this is the case, do all such premotor hubs share a common organizing principle based on their inputs and outputs?

Overall, these studies represent a major step forward toward a detailed understanding of the large-scale dynamics involved in motor preparation. By taking a more global view of activity, as is routine for simpler systems (Ahrens et al., 2012), we can begin to track—and one day to understand—processes that require complex interactions across brain regions.

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## Rat mPFC and M2 Play a Waiting Game (at Different Timescales)

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In this issue of *Neuron*, Murakami et al. (2017) relate neural activity in frontal cortex to stochastic and deterministic components of waiting behavior in rats; they find that mPFC biases waiting time, while M2 is ultimately responsible for trial-to-trial variability in decisions about how long to wait.

Good things come to those who wait—or so the proverb tells us. Yet animals and humans frequently choose to give up waiting for delayed reward, even when patience will ultimately maximize reward over the long run. The predictable (or, *deterministic*) element of the decision to abort waiting is thought to reflect learned expectations regarding the likely timing of outcomes and their value, including an inherent tendency to discount future reward. But like other choice behaviors,

decisions about when to give up waiting are also highly variable, reflecting an apparently random (or, *stochastic*) element in the choice process that limits the ability to control both the selection and timing of actions. While the random element in choice is thought to be adaptive (for example, by promoting the exploration of previously unchosen actions), and comprises a key feature of many theoretical accounts of choice behavior, it remains a challenge to parse out the

neural origin and mechanisms of variability in decisions about when to act.

Frontal regions of the brain, including medial prefrontal cortex (mPFC), are critically important for complex decision making generally (Dalley et al., 2004; Rushworth et al., 2011), including in decisions to wait for delayed reward (Narayanan and Laubach, 2006). Other frontal areas more proximal to primary motor output, such as M2 in rodents (or pre-SMA in primates), are also implicated in