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From Perception to Action: A Spatiotemporal Cortical Map

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In this issue of *Neuron*, Guo et al. (2014) optogenetically probe contributions of different cortical regions to tactile sensory perception, finding that somatosensory cortex is necessary for acquisition of sensory information and frontal cortex is necessary for planning motor output.

Understanding how sensory information is used to elaborate an appropriate behavior is one of the most fundamental questions in neuroscience. The specialization of cortical areas for different functions has emerged as a general organizing principle of the mammalian brain. Thus, cortical areas processing given sensory modalities, specific aspects of motor control, and more complex cognitive functions have been identified based on lesions, neuronal recordings, and microstimulation. However, the simplistic idea of assigning a single function to a given brain area has been challenged by the extent and complexity of interactions between areas. Indeed, sensory information is processed in a highly distributed manner in the mammalian brain (Hernández et al., 2010). For example, about half of the macaque neocortex can be considered as primarily engaged in processing visual information (Felleman and Van Essen, 1991). As another example, a 1 ms deflection of a single whisker in a mouse can evoke depolarization across a large part of sensorimotor cortex (Ferezou et al., 2007). Nonetheless, different cortical areas are known to be specialized for processing distinct aspects of sensory information i.e., the dorsal and ventral streams of the visual system are thought to respectively encode “where” and “what” types of information (Goodale and Milner, 1992). Such large-scale brain activity is probably mediated at least in part by the extensive corticocortical connectivity reported in many mammalian species including mouse, monkey, and man (Van Essen, 2013). As a consequence, the neuronal substrates linking perception to action involve a large number of sensory and motor areas (as well as other brain regions involved in decision making, memory, attention, or motivation) that could be simultaneously or sequentially activated. Deciphering which brain areas are causally involved and when they participate in a given behavior is an important challenge.

Whereas recordings from different cortical areas have provided correlational data supporting possible distinct roles for different brain regions, obtaining causal insight is much more difficult. Perturbation experiments provide the key to investigate causal links between neuronal

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activity and behavior. Pioneering experiments found that it was possible to substitute sensory stimuli with intracortical microstimulation of specific cortical areas to create illusory percepts (Salzman et al., 1990; Romo et al., 1998). More recently, such substitution experiments have been carried out with optogenetic stimulation providing an additional level of specificity (O'Connor et al., 2013; Sachidhanandam et al., 2013). Whereas stimulation experiments probe sufficiency, inactivation experiments are essential to investigate the necessity of cortical activity. Lesion and pharmacological inactivation experiments have provided evidence supporting the necessity of a given region for specific behaviors. However, the timescale of such experiments is typically many minutes and the interventions are likely to affect multiple processes including changes in brain states. Optogenetic inactivation experiments have recently provided further critical information relating to the necessity of cortical activity on the millisecond timescale during specific behaviors (O'Connor et al., 2013; Sachidhanandam et al., 2013). So far these optogenetic inactivation experiments have been limited to the study of one particular region of the neocortex. Until now, we have lacked data resolving when and where activity is necessary in the large-scale cortical network for any given behavior. In this issue of *Neuron*, Guo et al. (2014) make two important advances toward this goal: first, they designed a new behavioral paradigm for mice involving a delay period to separate sensation from action, and second, they developed an optogenetic mapping technique for spatiotemporally precise inactivation, allowing them to probe the necessity of different regions of the dorsal cortex during specific behavioral epochs.

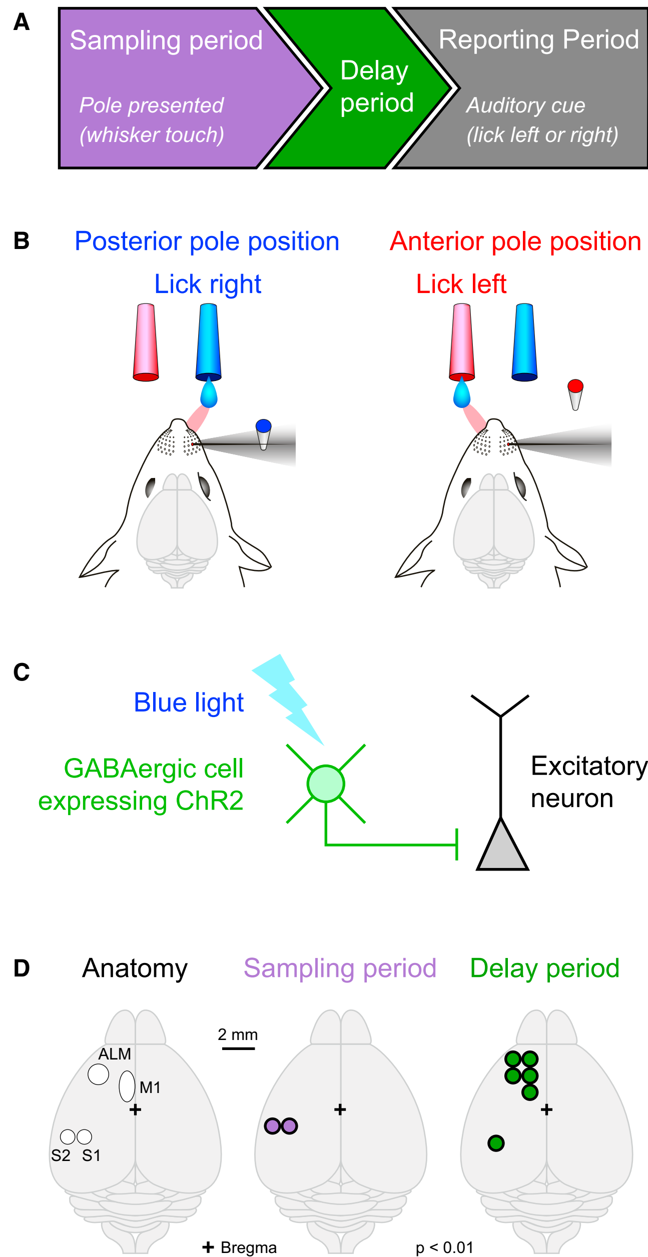

Figure 1. Mapping Cortical Function by Spatiotemporally Controlled Optogenetic Inhibition
Adapted from Guo et al. (2014).

Head-restrained mice were trained to localize an object with a single whisker in a task modified from previous studies (O'Connor et al., 2013) (Figures 1A and 1B). In this new version of the task, mice were trained to report the position of a vertical pole (anterior versus posterior) by licking a right or left lickport. In addition, a delay period was introduced between the sampling period and the response period. During the delay period, the pole was removed from the vicinity of the whiskers and the mouse therefore had to remember the pole location and withhold its response until an auditory cue signaled the reporting period. This delay allowed for a better distinction between sensory and motor components of the task and offered the possibility to perform local cortical inhibition at different phases of the task. In order to inactivate cortical regions with high spatiotemporal resolution, Guo et al. (2014) used transgenic mice in which channelrhodopsin-2 (ChR2) is expressed in GABAergic neurons (Zhao et al., 2011) (Figure 1C). Blue laser light was directed to specific cortical regions to activate the light-gated cation channel encoded by ChR2, causing GABAergic neurons to fire action potentials, thereby inhibiting nearby excitatory neurons. Guo et al. (2014) carefully quantified the spatiotemporal dynamics of their optogenetic inhibition, finding that light at a power of 1.5 mW focused on a 400-μm-diameter spot on the neocortex caused an 87% reduction in action potential firing in presumed excitatory neurons. The inhibition was strongest in the immediate vicinity of the blue light spot, but even a millimeter away from the center there was a halving of the firing rate. Importantly, even though the blue light was only applied to the surface of the brain, electrophysiological measurements indicated a profound suppression across all cortical layers. The time course of the inhibition was fast, with an onset time of 17 ms and offset time of 124 ms. Guo et al. (2014) therefore demonstrate that

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optogenetic stimulation of GABAergic neurons can be used to rapidly and specifically inactivate a local neocortical region.

Optogenetic inactivation was carried out in localized regions spaced across a 1 × 1 mm grid over the entire dorsal neocortex while the mouse was performing the object localization task. Optogenetic inactivation maps during the sampling period revealed the necessity of activity in primary somatosensory barrel cortex (S1) (Petersen, 2007) (Figure 1D). Interestingly, only the trials in which the object was presented at the posterior position were affected by S1 inactivation. This is probably due to the fact that mice actively scanned for the pole only at the posterior location and made very few contacts when the pole was located at the anterior position. The inactivation data agreed well with electrophysiological recordings showing that S1 neurons were most active during the sampling period when the pole was at the posterior position (Guo et al., 2014). However, given the limited spatial resolution of the optogenetic inactivation, it is possible that secondary somatosensory cortex (S2, located ~1 mm lateral to S1) is also involved. Surprisingly, Guo et al. (2014) report that whisker primary motor cortex (M1) is not required during the sampling period, although the behavior is an active task involving motor commands to position the whisker appropriately to sense pole location. During the sampling period, one might therefore have expected the necessity of activity in M1 (Kleinfeld and Deschênes, 2011; Huber et al., 2012). Future experiments should further examine the spatiotemporal interactions of whisker motor and sensory cortex in different behavioral tasks.

Localized optogenetic inactivation across the entire dorsal neocortex was then applied specifically during the delay period rather than during the sampling period. Guo et al. (2014) found necessity for activity in frontal regions of the neocortex during the delay period (Figure 1D), and the authors highlight an important contribution from a region labeled as the anterior lateral motor area (ALM) (Komiyama et al., 2010). The inhibition of right or left ALM impaired licking left or right, respectively, regardless of the pole position associated to each lickport. Electrophysiological recordings showed ramping activity in 23% of ALM neurons during the delay period (Guo et al., 2014). ALM might therefore be necessary for planning the action or holding in memory which lickport to lick (short-term memory). Delay period activity in frontal cortex serving as a short-term tactile memory has previously been reported in monkey experiments (Hernández et al., 2010) and it is of great interest that there may be a related functional organization of the mouse brain. The optogenetic inactivation results also showed significant contributions of activity in S1 during the delay period, and electrophysiological recordings revealed that the activity of 27% of S1 neurons was significantly different between trial types during the delay period. Late activity in S1, persisting beyond the immediate sensory-driven input, may therefore also play a critical role in forming a neural trace of sensory information needed for the later conversion of sensation into goal-directed action (Sachidhanandam et al., 2013). Both S1 and frontal cortex may therefore interact and jointly participate in the encoding a tactile short-term memory.

ALM also played an important role during the reporting period, when the mouse needed to lick a reward spout on the left or right to indicate the anterior or posterior position of the pole. Electrophysiological recordings found that 34% of ALM neurons were activated selectively after the delay during the reporting period, when licking to the contralateral side. The optogenetic inactivation during the delay period may have affected neocortical activity during the reporting period, since the light was kept on during the entire delay period and the offset time for the optogenetic inhibition was 124 ms, therefore within the reporting period. Komiyama et al. (2010) found that stimulation of ALM evoked licking, whereas pharmacological inhibition of ALM suppressed licking. This raises the question of the relative contributions of ALM in motor planning and short-term memory compared to pure motor execution. It should also be noted that electrophysiological recordings were only targeted to ALM (located 2 mm anterior and 2 mm lateral to Bregma), whereas the optogenetic inactivation mapping during the delay period revealed the necessity of a large frontal region extending from 1 to 3 mm anterior and from 1 to 2 mm lateral to Bregma (Figure 1D). Further experiments should therefore investigate whether this entire frontal region is functionally homogeneous or contains subregions differently involved in the task.

Guo et al. (2014) have identified cortical areas lying at the two ends of a sensory discrimination task, i.e., sensory detection in S1 and motor planning in ALM. However, it remains to be determined how the information flows from S1 to ALM and where the decision is made about the behavioral output. Deeper brain areas such as prefrontal cortex, hippocampus, striatum, and midbrain reward areas might be involved and their possible causal participation should be investigated in future studies.

The experimental approach of Guo et al. (2014) provides important new insights into the role of different cortical areas during a specific tactile behavior. The method developed by the authors is of general applicability and could thus be used to examine the necessity of specific spatiotemporal patterns of cortical activity during any behavior in head-restrained mice. Since the transgenic mice expressing ChR2 in GABAergic neurons are available from The Jackson Laboratory (JAX mouse 014548, http://jaxmice.jax.org/strain/014548.html; Zhao et al., 2011), the technique can readily be applied in many laboratories. The spatiotemporal analysis of the necessity of different cortical regions for different specific behaviors in head-restrained mice is sure to provide many valuable clues for advancing our causal understanding of the mouse neocortex.

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