



Neural mechanisms of movement planning: motor cortex and beyond

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Neurons in motor cortex and connected brain regions fire in anticipation of specific movements, long before movement occurs. This neural activity reflects internal processes by which the brain plans and executes volitional movements. The study of motor planning offers an opportunity to understand how the structure and dynamics of neural circuits support persistent internal states and how these states influence behavior. Recent advances in large-scale neural recordings are beginning to decipher the relationship of the dynamics of populations of neurons during motor planning and movements. New behavioral tasks in rodents, together with quantified perturbations, link dynamics in specific nodes of neural circuits to behavior. These studies reveal a neural network distributed across multiple brain regions that collectively supports motor planning. We review recent advances and highlight areas where further work is needed to achieve a deeper understanding of the mechanisms underlying motor planning and related cognitive processes.

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Introduction

During perceptual decision-making, behavior-related information flows from sensory to motor areas. Decisions occur in parts of the brain where correlations between neural activity and future actions first emerge. These correlations are also signatures of ‘motor planning’ (also referred to as ‘movement preparation’). Motor planning has been studied extensively in tasks in which a sensory stimulus instructs an action after an imposed delay. During the delay, neurons in frontal and parietal cortex

and connected structures show persistent and ramping activity related to specific movements, long before movement onset (Figure 1a–d). This neural correlate of future movement is referred to as ‘preparatory activity’ (or ‘anticipatory activity’, ‘build-up activity’).

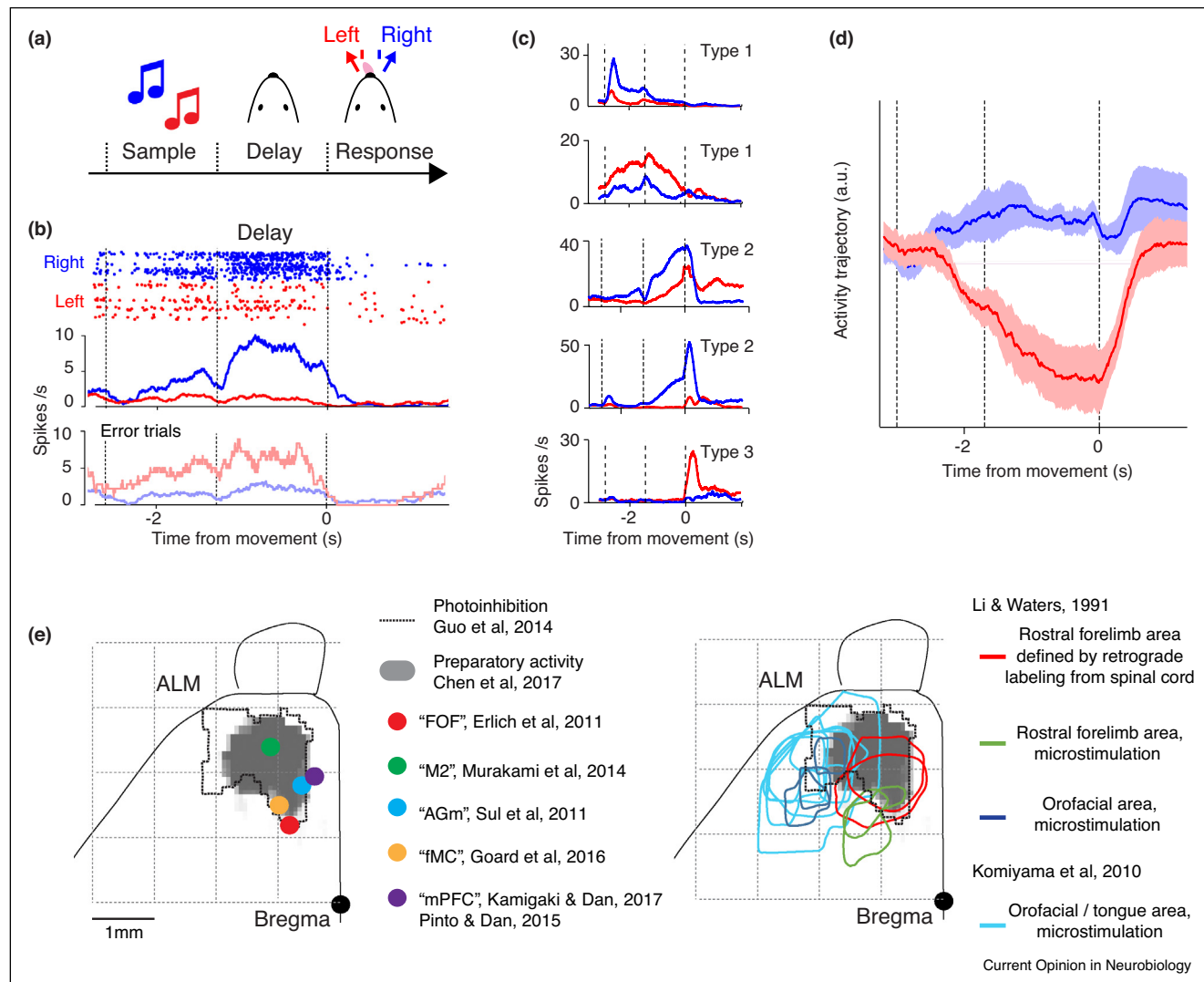
Motor planning and preparatory activity appear in systems neuroscience in three contexts. First, preparatory activity has been studied as part of motor control. Volitional movements are programmed to achieve a specific goal. Many movements are too rapid for online corrections. Movements are therefore preceded by periods of planning, during which parameters are set for specific upcoming movements. Evidence for motor planning comes from behavioral experiments: movements are faster and more accurate when subjects are given time to prepare specific movements [1–3].

Second, motor planning is a link between decision-making and action [4]. In the context of perceptual decision-making, selective ramping activity before a behavioral report (a movement) is often interpreted as a signature of accumulation of evidence [5,6,7]. However, persistent and ramping activity are typically seen in structures that are also associated with motor control [8], and under conditions where evidence accumulation does not occur [9,10]. Conversely, in evidence accumulation tasks, ‘perceptual evidence’ is expressed in motor parameters, which can even be read out in muscle tension [11]. In many cases, perceptual decision-making and motor planning thus appear to be one process [12,13] (but see [14]).

Third, motor planning is a prospective form of short-term memory (STM) that links past events and future movements. STM is often represented by ‘persistent’ changes in spike rates, or slow dynamics in spike rates, that can be maintained internally, in the absence of sensory input [15–18,19,20]. Preparatory activity is an example of such a memory trace. The mechanisms underlying preparatory activity are therefore of broad significance.

Recent years have seen progress in understanding the neural mechanisms underlying preparatory activity and its role in controlling movements in trained behaviors. These advances are driven in part by large-scale neural recordings during behavior, and, in rodent studies, calibrated optogenetic manipulations. Discoveries made about neural dynamics in non-human primates have now been replicated in detail in the rodent brain. Conversely, analyses of neural mechanisms performed in

Figure 1



Preparatory activity in the mouse brain. **(a)** Delayed response task. **(b)** Example neuron. Top, raster plot, correct trials. Each dot corresponds to an action potential. Bottom, average spike rates for different trial types, including error trials. Note that on error trials the activity still predicts movement direction. **(c)** Additional example neurons. **(d)** Population activity projected onto the direction in activity space that best discriminates movements. **(e)** Regions in the motor cortex with various recording locations (left) and microstimulation locations (right) superposed. The outline corresponds to the standard mouse brain from the Allen Mouse Common Coordinate Framework. Note that studies on rats (FOF, M2) were scaled based on Ref. [79] to account for differences in brain size (scaling factor, 1.6, rat:mouse). Data from Refs. [19*,35*,36*,40–43,80–82].

rodents are now stimulating research in primates. Here we review recent work on motor planning with an emphasis on studies that probe how preparatory activity is related to movement and how preparatory activity is generated and maintained.

Localization of preparatory activity

As a neural correlate of motor planning, preparatory activity has to meet three criteria [21]. **First, changes in neural spike rate must precede movement initiation.** **Second, neural activity must be selective for specific movements, such as saccade location, or movement**

direction of the hand, wrist or tongue. Third, details of the neural activity predict aspects of the subsequent movement execution, such as reaction time.

Neural activity consistent with motor planning was first recorded in non-human primates [22]. Monkeys were instructed to pull or push a lever, but only after a delayed go cue. A subset of neurons in the primary motor cortex increased their activity seconds before the go cue. This activity was selective for the movement. On error trials the activity still reflected the future movement rather than the instruction, a key signature of preparatory activity.

Since then motor planning has been studied extensively in tasks involving arm movements and eye movements in non-human primates. Preparatory activity was detected in the primary motor cortex [2,22,23], the premotor and supplemental motor cortex [2,23], frontal eye field (FEF) [9,24–26], parietal cortex [5,10,27], striatum [28,29], superior colliculus [30,31], motor-related thalamus [32], and cerebellum [33]. These studies show that preparatory activity is distributed across interconnected multi-regional networks.

Across these studies, preparatory activity shares certain features. A subset of neurons show gradual ramps of activity that appear to reach a threshold level just before movement onset [5,10,24,34,35*] (Figure 1a–d). However, neurons in the same area show additional diverse activity patterns (Figure 1c). Although the dynamics are distributed on a continuum, selective neurons have been classified into three classes [2]. Some neurons show selectivity only before movement (type 1). Other neurons show selectivity during the delay epoch as well as during the movement (type 2). A third class of neurons do not show preparatory activity, but become selective only after the go cue in the peri-movement epoch (type 3), consistent with activity that might be causally related to movement initiation or execution [36*]. Preparatory activity differs across brain regions. For example, premotor cortex and supplemental motor cortex show a larger proportion of preparatory activity (i.e. type 1 and type 2) compared to primary motor cortex, which shows a larger proportion of command-like responses (type 3) [2,23,37].

More recently, preparatory activity has been studied in rodents. Although rodent motor behaviors are less well controlled compared to non-human primates, rodents allow a more comprehensive analysis of neural activity and a wider range of experimental manipulations.

In a delayed response task in which rats orient to one of two reward ports, preparatory activity was measured in a part of the motor cortex referred to as frontal orienting field (FOF; in analogy with FEF in primates) [19*,38]. A substantial proportion of FOF neurons anticipate the rats choice. Neurons selective for both movement directions are intermingled in one hemisphere.

A conceptually similar experiment was performed in head-restrained mice performing a task in which they report a decision by directional licking [36*,39*]. Here activity was sampled across the motor cortex using calcium imaging and electrophysiology [40]. Preparatory activity for licking direction appeared earliest in the anterior lateral motor cortex (ALM) and remained localized to ALM until movement onset. A large proportion of ALM neurons showed preparatory activity, especially in layer 5, including types 1, 2, and 3 (Figure 1a–d). Similar to FOF, ALM neurons selective for either movement

direction were intermingled in approximately equal proportions in both hemispheres [19*,39*].

Other studies detected preparatory activity in the rodent motor cortex in different behaviors [35*,41–43]. These regions generally overlap with ALM or FOF (Figure 1e). However, in most behavioral contexts the spatial distribution of preparatory activity remains to be determined, which limits possible mechanistic analysis.

Relationship to behavior

A key challenge in systems neuroscience is to link neural dynamics to behavior. One powerful approach is to correlate preparatory activity with parameters of the subsequent movement on a trial-by-trial basis. Neural responses unfold differently across nominally identical trials. At the same time, movements differ in timing and trajectory, even in trained animals. If preparatory activity instructs future movements, then it follows that trial-to-trial variability in neural dynamics should reflect parameters of the movement. Preparatory activity in some neurons predicts movement timing [24,35*], variability [44], and speed [45].

However, the spiking of individual neurons is irregular, and instantaneous estimates of spike rates are therefore noisy [46]. This makes comparisons with movement parameters difficult. In addition, movement parameters may not be explicitly represented in the activity of individual neurons [47]. Simultaneous recordings of multiple neurons have provided a much richer and robust description of the neural dynamics. Over time, the activity of populations of neurons trace out a trajectory in activity space, where each neuron corresponds to one dimension. Dimensionality reduction methods have revealed that these activity trajectories occupy a low-dimensional manifold [48] (Figure 1d). During motor planning, the trajectories in activity space converge to a restricted subspace at the time of movement onset [37,49**]. Behavioral trials in which the trajectories fall outside of these subspaces correspond to slower and less precise movements [49**,50**]. Different convergence points could reflect optimal ‘initial conditions’ for specific planned movements [3].

Perturbation methods have narrowed down the brain areas critical for motor preparation and suggest mechanisms underlying preparatory activity. Electrical microstimulation in motor cortex delayed subsequent arm movements, but only when the stimulus was applied immediately before movement onset, but not earlier [45]. This suggests that preparatory activity can recover from perturbations to recover the appropriate initial condition for the execution of the movement. Moreover, microstimulation perturbed behavior when applied to the premotor cortex, but not to the primary motor cortex. Together with the preponderance of preparatory activity

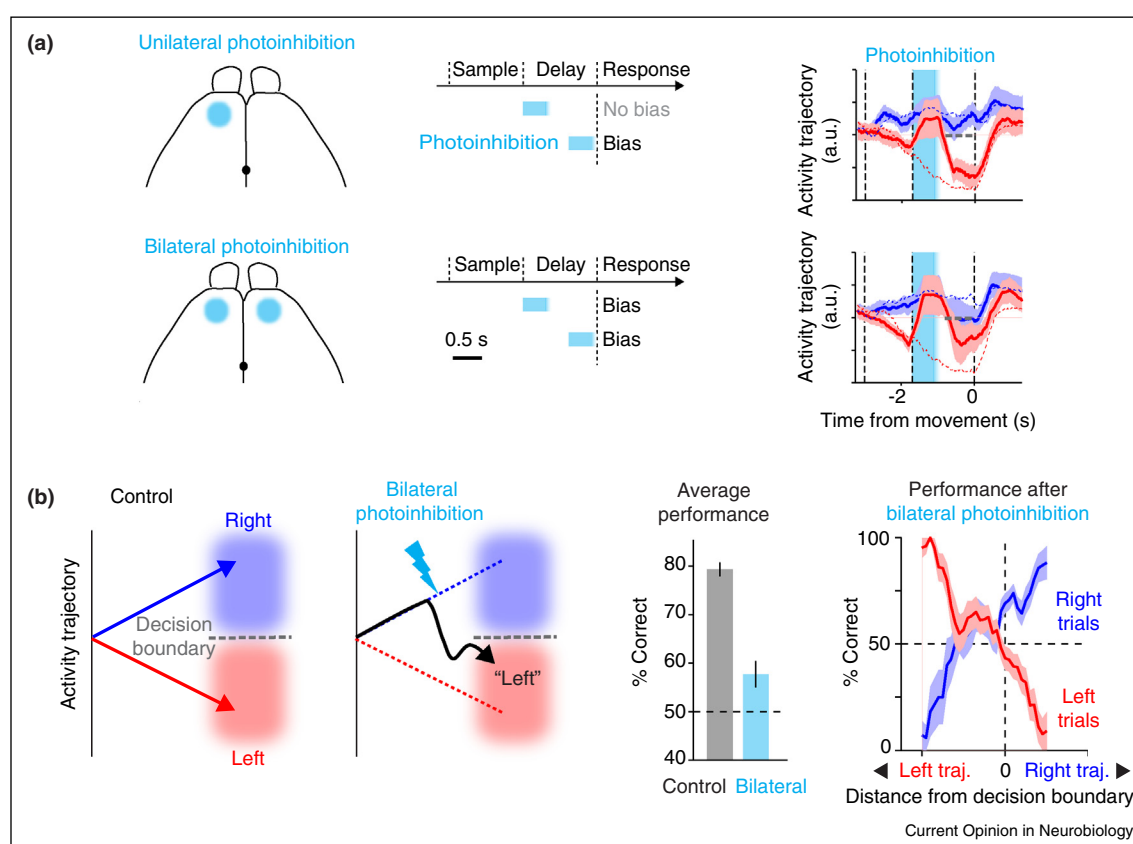
in premotor cortex [2,23,37], these findings have given rise to the notion that premotor cortex plays a privileged role in motor planning, whereas primary motor cortex is closer to movement execution [51]. Consistent with this view, patients and non-human primates with lesions in premotor areas have an inability to plan movements in the contralesional space, without overt effects on the ability to make movements themselves [52,53].

In mice, transient *unilateral* inactivation during motor planning in ALM, but not surrounding cortical regions, caused an *ipsiversive bias* in future licking direction. In fact, ALM was first defined in an optogenetic inactivation screen [36^{*}]. Inactivation of ALM biased the future movement only when applied right before movement onset, but was ineffective if it terminated more than several hundred milliseconds earlier [50^{**}], similar to the microstimulation experiments in primates [45] (Figure 2a). Electrophysiological analysis of the network response to perturbation revealed a remarkable robustness of ALM activity. In these experiments inactivation

completely silenced more than 60% of ALM (one cubic millimeter of cortical tissue; >100 000 neurons), for hundreds of milliseconds. After inactivation offset, neural activity and selectivity recovered rapidly (Figure 2a). Individual neurons regained the spike rates that they would have reached in the absence of inactivation, thus catching up to the appropriate initial condition for movement onset. This robustness of ALM preparatory activity is the result of redundancy, in this case across hemispheres (see Circuit Mechanisms for further discussion) [50^{**}].

Transient *bilateral* inactivation of ALM perturbed preparatory activity and randomized licking direction (Figure 2b). After inactivation, activity recovered on average, but selectivity did not. Instead activity meandered along seemingly random trajectories. Remarkably, at movement onset, the distance of the perturbed trajectories to the normal trajectories still predicted movement direction [50^{**}]. These perturbation experiments together implicate ALM as a critical hub in the network

Figure 2



Effects of perturbing ALM activity during motor planning. The perturbation used here eliminates (>80% reduction) activity in a 1 mm² cortical area. (a) Top, unilateral inactivation causes a transient change in the activity trajectory, after which preparatory activity recovers. A behavioral change is only seen when the perturbation occurs within approximately 300 ms of movement onset. Bottom, bilateral transient inactivation destroys preparatory activity and reduces behavioral performance. (b) Even after bilateral inactivation, activity trajectories still predict movement direction.

that maintains preparatory activity. Moreover, the location of the trajectory in activity space at the time of movement onset determines the direction and timing of specific movements.

Transient inactivation of rat FOF produced complex behavioral effects. In a task that required integration of sensory stimuli, late but not early inactivation caused an ipsiversive bias [6[•]], consistent with a premotor role of FOF and also consistent with the perturbation experiments discussed before. However, in a delayed response task, early but not late inactivation caused the bias [38]. One interpretation is that the FOF network is only sensitive to perturbation before decision commitment, and this commitment occurs early in the delayed response task. It is also possible that different multi-regional networks mediate behavior in these different tasks.

The finding of robust preparatory activity in ALM presents challenges for the interpretation of perturbation experiments in general. A lack of behavioral effect does not imply that the perturbed brain area is not involved in the behavior. In many situations information is likely to be encoded in a redundant fashion in the cortex and coupled brain regions. Perturbation experiments have to be interpreted in the context of measurements that characterize the primary effects of the perturbation and, equally importantly, the effects on dynamics in 'downstream' brain areas.

Multi-regional interactions

Recent studies using wide-field imaging of neural activity and neural inactivation revealed ALM to be a network hub that regulates cortex-wide activity related to motor planning and movement initiation, beyond the control of orofacial movements [54,55]. However, preparatory activity is not maintained by cortex in isolation. In the context of eye movements, silencing thalamic regions that project to parietal cortex and FEF delays memory-guided saccades [56] and thalamus also show preparatory activity [32]. These findings suggest that thalamocortical loops might help maintain preparatory activity for memory-guided movements.

This issue was addressed directly in behaving mice [57^{••}]. ALM is connected in a bidirectional manner with parts of several thalamic nuclei, including the ventromedial and ventral anterior-lateral nuclei. Thalamic neurons exhibit preparatory activity, similar to ALM. Also similar to ALM, unilateral inactivation of thalamus during the delay epoch caused an ipsiversive bias. Importantly, inactivation of thalamus caused a near total collapse of ALM activity. Conversely, inactivation of ALM diminished activity in the thalamus. These experiments show that persistent preparatory activity is maintained in a cortico-thalamocortical loop (see [58,59] for related studies in the context of studies of working memory).

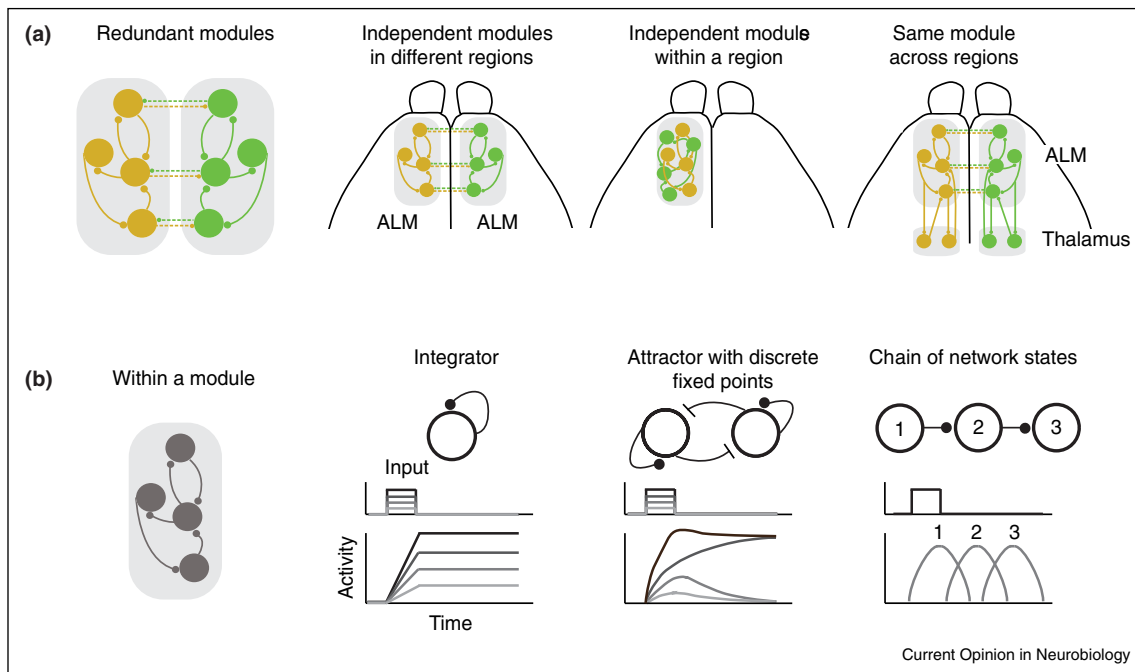
Other manipulation experiments also point to multi-regional interactions involving subcortical areas. ALM projection neurons include two major classes: intratelencephalic (IT) neurons that project to other cortical areas; pyramidal tract (PT) neurons that project out of the cortex, including thalamus, various motor-related areas in the midbrain and brainstem [60]. IT neurons excite PT neurons, but not vice versa. Optogenetic activation of IT neurons causes only transient changes in preparatory activity, similar to transient inactivation [50^{••}]. However, stimulation of PT neurons produces changes in preparatory activity over seconds, together with changes in future movements [39[•]]. It is possible that stimulation of PT neurons activates the thalamocortical loop and loops involving other targets. ALM PT neurons send axon collaterals to multiple subcortical structures that exhibit preparatory activity. ALM projects to the superior colliculus, similar to FEF in primates. ALM also projects to the cerebellum via the basal pontine nucleus. Perturbations in the superior colliculus [38] and the cerebellum [33] appear to change the direction and timing of upcoming movements. Elucidating the precise roles of various subcortical areas in motor planning would be helped by a finer dissection of motor cortex projection neurons.

Circuit mechanisms

Preparatory activity is an example of persistent activity encoding an STM [61]. Isolated neurons have intrinsic time constants on the order of ten milliseconds. Slow dynamics over seconds is therefore an emergent property of the circuit (but see [62]). In particular, long time-constants are thought to arise through positive feedback [63]. Network models based on positive feedback can produce persistent and ramping activity. For example, preparatory activity has been modeled as an integrator of transient input [35[•]]. However, the amplification that prolongs the model network response causes fragility to perturbations of activity. By contrast, after optogenetic perturbations, ALM network dynamics recovers quickly, showing remarkable robustness to external perturbations [50^{••}].

What could be the circuit principles underlying robust preparatory activity in ALM? Controlled transient perturbations together with neurophysiological measurements and modeling suggest that preparatory activity is redundant, modular and coupled through feedback connections [50^{••}] (Figure 3a). 'Modules' correspond to circuits that can maintain preparatory activity independent of other modules. 'Redundancy' means that multiple modules show preparatory activity at the same time. Feedback connections implement interactions between modules, so that individual modules retain preparatory activity when other modules are perturbed, and help the perturbed modules recover. Each module can consist of circuits distributed across multiple brain regions. Redundancy and modularity underlie robustness in

Figure 3



Neural circuit mechanisms. **(a)** Preparatory activity is maintained by redundant modules. Each module can maintain preparatory activity independently. Modules are coupled so that perturbations to one module can be corrected by feedback from another module. ALM modules are distributed across the two hemispheres, but modules could also consist of intermingled subnetworks within a brain region, across different brain regions (i.e. cortico-thalamocortical loops). **(b)** Cartoons representing models for persistent or ramping activity within a module [63].

other biological systems [64]. Interestingly, redundancy and modularity are also design principles in systems engineering.

This leaves open the question of maintenance of preparatory activity within an ALM module [63]. Multiple circuit mechanisms could underlie preparatory activity (Figure 3b). Integrators produce persistent activity with a continuum of fixed points [65,66]. Other attractor networks have discrete fixed points [67], where each fixed point might correspond to one action [38]. Memories can also be maintained by a purely feedforward mechanism in which activity is passed sequentially through a network [68]. To distinguish between these models it will be necessary to observe neural dynamics, infer specific model predictions, and then perturb dynamics in a controlled way to test the model. For example, it may be possible to infer the boundary between two attractors in activity space and produce a specific perturbation to cross it, or only get near it.

From preparatory activity to movement execution

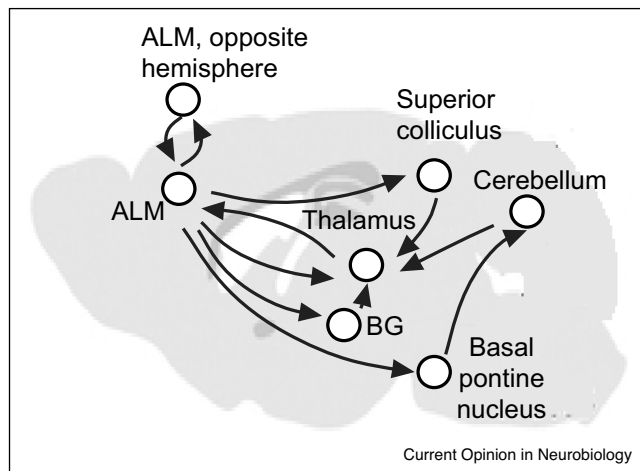
Preparatory activity is prominent in motor cortex where microstimulation can evoke specific movements. Preparatory activity has even been observed in identified PT neurons that project directly to spinal cord and brainstem

motor centers [22,39*,69,70]. Paradoxically, preparatory activity does not trigger movements. How is preparatory activity converted to movements?

Recent analysis of neuronal populations in motor cortex in monkeys offers an algorithmic account of movement initiation [71**]. During movement, activity trajectories traverse directions in the activity space that carry little weight during planning ('movement-potent' direction). In contrast, during planning activity trajectories traverse orthogonal directions that carry little activity during movement ('movement-null'). Thus motor cortex could prepare and gate movement by rotating activity from one subspace into another [72].

This view of population activity is a compact description of the data, but does not inform how movement-null and movement-potent activity are distributed within, and produced by, neural circuits. The circuit mechanisms linking movement preparation and initiation are beginning to be worked out in the mouse. ALM is involved both in preparation and execution of directional licking [39*]. ALM PT neurons project to a brainstem center controlling directional licking (IRt) and related areas in the superior colliculus [73]. Optogenetic activation of ALM outputs evokes rhythmic contralateral licking. Projection-specific recordings show that activity consistent

Figure 4



Multi-regional circuit underlying motor planning.

with a movement command arises in PT neurons, but not IT neurons, around the time of movement. ALM preparatory activity is converted to a ‘movement-potent’ command signal, mainly in PT neurons, late during planning.

What triggers the ‘movement-potent’ activity to execute a movement? A population analysis of motor cortex during the transition from planning to movement revealed a ‘timing’ signal that likely originates outside of motor cortex [74•]. Initiation of movement likely involves coordination of multiple brain systems, including the basal ganglia, midbrain and brainstem motor centers (Figure 4). The prototypical example is the movement initiation circuit underlying voluntary saccades [75]. Saccades are controlled by the superior colliculus, which receives descending input from cortex. The initiation of saccades also relies on pauses in SNr activity, which transiently disinhibits activity in the superior colliculus. A similar disinhibitory pathway operates for orofacial behaviors in rodents [73,76]. SNr projects to and inhibits lateral regions of superior colliculus, which regulates rhythmic licking. Lateral superior colliculus also receives prominent input from ALM. In addition, SNr also shows preparatory activity and projects to the ALM-projecting motor thalamus [57••]. A future line of inquiry is to resolve how these brain structures work collectively to convert preparatory activity into movement and how these distributed processes are coordinated on a millisecond time scale.

Conclusions and outlook

Preparatory activity is widely distributed across brain areas involved in decision-making and motor control. Recordings and manipulations are beginning to pin down the loci of motor preparation in several behavioral tasks in non-human primates and rodents. Within each brain

region, intermingled neurons show activity anticipating specific movements with diverse selectivity and temporal profiles. Recordings from large populations of neurons, together with dimensionality reduction methods, can extract the key features of preparatory activity and their relationship to behavior. These studies suggest that preparatory activity moves the network to an initial condition that is matched to specific movements.

Perturbation methods provide a complex picture of multi-regional interactions during motor planning. Activity in a brain region can be robust to perturbation of one strong input, whereas perturbation of other inputs can have a dramatic effect. The biophysical basis underlying these differences in coupling is not understood. A major outstanding question is if interactions between brain areas are dynamically gated. Simultaneous recordings across coupled multi-regional networks, in combination with perturbations, might help reveal the mechanisms of gating.

Localized and transient optogenetic activation and inactivation have allowed testing algorithmic models of preparatory activity. These experiments have rejected the simplest models of persistent activity, such as monolithic integrators and attractors. Instead, redundant modules, each maintaining preparatory activity independently, interact to produce robust motor planning. The mechanisms underlying persistent activity within a module remain to be delineated.

The competing algorithmic models of preparatory activity are embodiments of a hypothesis of how the dynamics is generated. These models do not make reference to defined cell types and the actual circuit diagram, or to specific biophysical features that are necessary to generate ramping activity. For example, the correspondence between units in the model and specific neuron types or groups of neurons has not been established. On the other hand, our understanding of cell types and their connections is undergoing a revolution, based on transcriptomic [77] and anatomic profiling of single neurons [78]. Studies linking defined cell types and behaviorally relevant responses will be particularly powerful. Actual neural circuits can then be incorporated into biophysically constrained models. Refined manipulations of neural ensembles in defined cell types will allow testing of model predictions.

Conflict of interest statement

Nothing declared.

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