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Annual Review of Neuroscience Neural Algorithms and Circuits for Motor Planning

Hidehiko K. Inagaki,¹ Susu Chen,² Kayvon Daie,^{2,3} Arseny Finkelstein,^{2,4} Lorenzo Fontolan,² Sandro Romani,² and Karel Svoboda^{2,3}

¹Max Planck Florida Institute for Neuroscience, Jupiter, Florida, USA; email: hidehiko.inagaki@mpfi.org

²Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, Virginia, USA

³Allen Institute for Neural Dynamics, Seattle, Washington, USA; email: karel.svoboda@alleninstitute.org

⁴Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel

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Keywords

ALM, motor cortex, motor control, licking, dimensionality reduction, mice

Abstract

The brain plans and executes volitional movements. The underlying patterns of neural population activity have been explored in the context of movements of the eyes, limbs, tongue, and head in nonhuman primates and rodents. How do networks of neurons produce the slow neural dynamics that prepare specific movements and the fast dynamics that ultimately initiate these movements? Recent work exploits rapid and calibrated perturbations of neural activity to test specific dynamical systems models that are capable of producing the observed neural activity. These joint experimental and computational studies show that cortical dynamics during motor planning reflect fixed points of neural activity (attractors). Subcortical control signals reshape and move attractors over multiple timescales, causing commitment to specific actions and rapid transitions to movement execution. Experiments in rodents are beginning to reveal how these algorithms are implemented at the level of brain-wide neural circuits.

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INTRODUCTION

Movement is a fundamental building block of behavior. We move our eyes to explore visual scenes, our hands to manipulate objects and tools, and our facial muscles to vocalize and express emotions. Injuries and neurological disorders that impair our motor system have devastating consequences for our daily lives and well-being.

Volitional movements involve a series of distinct computations. Consider an orchestra preparing to play Beethoven's Symphony no. 5. Based on the conductor's hand signals, the violinist prepares to play the famous opening four-note motif at a specific speed and timbre. This information is then stored in the violinist's head. Another signal from the conductor releases the movement of the violinist's bow, in perfect synchrony with other strings, to create music. Motor planning (or movement preparation) begins with the deliberation of multiple actions (decision-making), followed by a commitment to a particular choice, and is terminated by movement execution (Cisek & Kalaska 2010, Thura & Cisek 2014). Movements are more rapid and accurate when subjects have time to plan (Rosenbaum 1980, Riehle & Requin 1989, Duan et al. 2021).

Motor planning has been studied extensively in memory-guided response tasks, in which a sensory stimulus instructs an action that is executed after a delay (**Figure 1***a*). Perturbation experiments have revealed causal roles for the frontal cortex in motor planning: dorsal premotor cortex (PMd) in reaching behaviors (Churchland & Shenoy 2007) and frontal eye field (FEF) for eye movement (Acker et al. 2016) in nonhuman primates, secondary motor cortex in orienting behaviors [frontal orienting field (FOF)] (Erlich et al. 2011, Kopec et al. 2015) and directional licking [anterior lateral motor cortex (ALM)] (Komiyama et al. 2010, Guo et al. 2014) in rodents. During the delay, neurons in these cortical areas and many connected brain areas show slowly varying neural activity that predicts specific future movements (Svoboda & Li 2018) (**Figure 1***b*). This neural correlate of motor planning is referred to as preparatory activity. Preparatory activity is thought to set the state of neural activity to initial conditions that favor accurate and rapid movements, with different initial conditions corresponding to different movements (Vyas et al. 2020) (but see the sidebar titled Motor Planning and Uninstructed Movements).

Computation: what problem does the system (e.g., brain) solve (e.g., behavioral goal)?—as in Marr's three levels of analysis



Neural dynamics in a memory-guided movement task. (*a*) During the sample epoch, sensory cues (e.g., sound, touch) instruct action types (e.g., direction of lick, saccade, limb movement). During the delay (or memory) epoch, animals remember the instruction and develop a motor plan. After the delay epoch, animals execute a movement. In this example, a Go cue releases directional licking. (*b*) Example ALM neurons during the memory-guided movement task showing preparatory activity selective for lick direction during the delay epoch (*left, middle*) and a transient response to the Go cue (*rigbt*). Spike rasters are shown on top and mean spike rates on bottom. Blue indicates correct lick-right trials, and red correct lick-left trials. Time is aligned to the timing of the Go cue. Dashed lines separate behavioral epochs. (*c*) Schematic showing activity trajectories in activity space. (*d*) ALM activity modes. Planning (selective) and ramping (nonselective) modes explain ALM activity during the delay epoch. Execution (selective) and Go cue (nonselective) modes explain activity during the response epoch. Abbreviations: ALM, anterior lateral motor cortex; D, delay epoch; R, response epoch; S, sample epoch. Panels *a*, *b*, and *d* adapted from Inagaki et al. (2022).

MOTOR PLANNING AND UNINSTRUCTED MOVEMENTS

Decision-making and motor planning are often viewed as separated from the execution of actions. However, it has been known for decades that cognitive processes are reflected in an ongoing manner in posture and movement. For example, cognitive signals descend to brainstem nuclei that control pupil size (Kahneman & Beatty 1966, Joshi & Gold 2020), and in perceptual decision-making tasks, decision variables are reflected in the reflex gains in skeletal muscles (Selen et al. 2012). Neural dynamics in cortex causes muscle tension, and sensory feedback modulates cortical activity in turn.

With the advent of high-speed videography, it has become routine to track fine-scale movements during behavior (Huber et al. 2012, Musall et al. 2019, Stringer et al. 2019). Uninstructed movements are observed during motor planning and correlate with preparatory activity. It is unknown whether preparatory activity causes idiosyncratic micromovements, movement contributes to preparatory activity, or preparatory activity and movement are modulated by a common input. These micromovements could be part of an embodied loop underlying motor planning and have to be considered when dissecting the neural circuits producing preparatory activity.

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Working memory:

retrospective short-term memory that allows manipulation of stored information; for example, remembering an object and comparing with a second object

Algorithm: neural

representation of information (e.g., neural dynamics) and the mechanisms that create and manipulate these representations to perform computation Short-term memory (STM) is a data buffer critical to maintaining and processing information over times of seconds. Motor planning is a form of STM, linking decision-making and movement execution. STM often correlates with persistent changes in spike rates, or slow dynamics in spike rates, that are maintained in the absence of sensory input. Preparatory activity is an example of such a memory trace. The network mechanisms underlying preparatory activity and the transition to another state (e.g., movement initiation) are of great interest because similar mechanisms might underlie diverse cognitive functions, including working memory and integration of evidence for sensory decision-making.

The neural dynamics underlying motor planning have recently been reviewed (Svoboda & Li 2018, Vyas et al. 2020). Here we focus on two related questions: How do networks of neurons produce preparatory activity, and how do neural dynamics switch from decision-making to movement execution? We highlight recent work exploring these algorithms and sketch out the multiregional neuronal circuits that may implement them.

COMPUTATION WITH NEURAL DYNAMICS

Preparatory activity is maintained over many seconds in the absence of sensory instruction. After a transient input, isolated neurons sustain activity for only tens of milliseconds, limited by membrane biophysics (Abbott & Dayan 2005) (see the sidebar titled Single-Cell Versus Network Mechanisms of Memory-Related Activity). Preparatory activity, and other memory-related neural processes with seconds-scale dynamics, therefore arises from network interactions between neurons with short time constants.

Dynamical systems theory provides a mechanistic framework for explaining population neuronal activity (Amari 1972, Wilson & Cowan 1972, Hopfield 1982, Sompolinsky et al. 1988, Kleinfeld et al. 1990, Amit & Brunel 1997, Laurent 2002, Brody et al. 2003b, Stopfer et al. 2003, Sussillo & Abbott 2009, Druckmann & Chklovskii 2012, Gallego et al. 2017, Vyas et al. 2020, Ebitz & Hayden 2021). A dynamical system is defined by differential equations that govern how a point (referred to as a state) evolves in a space that spans the dynamical variables of the equations. For example, Newton's equations describe the physical motion of a pendulum and determine how the pendulum state evolves in the two-dimensional (position, speed) state space. Neuronal activity is also often treated in a dynamical systems framework. Depending on the problem, different state variables are modeled, ranging from the microscopic membrane conductances of individual neurons (Markram et al. 2015) to the mesoscopic functional MRI signals measured across brain areas (Ryali et al. 2011). In this review, we treat an intermediate level, in which the activity of populations of individual neurons is described, as a state in a high-dimensional space, where each

SINGLE-CELL VERSUS NETWORK MECHANISMS OF MEMORY-RELATED ACTIVITY

Intracellular recordings of membrane potential during short-term memory in behaving animals find no evidence for cell-autonomous mechanisms (Aksay et al. 2001, Inagaki et al. 2019, Kim et al. 2021). First, neurons with very short membrane time constants sustain persistent activity. Second, membrane potential manipulations that are expected to perturb voltage-dependent conductances that could sustain persistent activity do not affect persistent activity. These experiments suggest that network mechanisms play a key role in sustaining persistent activity. Nevertheless, cell-autonomous mechanisms for maintaining persistent activity may exist in some cell types and conditions (Zylberberg & Strowbridge 2017, Deemyad et al. 2018).

dimension corresponds to the spike rate of one neuron (or a group of neurons with similar inputs). The population activity trajectory, r(t), evolves as

$$\frac{\mathrm{d}r}{\mathrm{d}t} = f(r(t), W, I(t)),$$

where the function (f) is an abstraction of cellular biophysics, W describes the structure of the network, and I(t) describes the external inputs to the network. Because of constraints imposed by the connectivity matrix W, activity trajectories propagate only through certain subspaces of the activity space.

This model ignores multiple biological processes that may be critical for signal propagation through neural networks, including millisecond-timescale synchrony across neurons (Kremkow et al. 2010, Yu et al. 2016) and cell type–specific biophysics such as short-term synaptic plasticity (Pouille & Scanziani 2004). Nevertheless, this simplified framework can reveal the network constraints that produce particular activity trajectories and test possible algorithms underlying decision-making (Mante et al. 2013, Hunt & Hayden 2017), motor control (Sussillo et al. 2015), and STM (Druckmann & Chklovskii 2012).

The Attractor Hypothesis

Some states in activity space can be stable, and nearby states relax into these stable states. The activity near such attractors thus recovers in response to small perturbations (Strogatz 1994). Because activity can linger near attractors for much longer than neuronal membrane time constants, attractors have been hypothesized as a mechanism of memory (Amari 1972, Hopfield 1982, Chaudhuri & Fiete 2016).

An attractor memory system resembles a ball rolling in a hilly landscape. The bottom of each valley (the attractor) is attractive in that a ball (the state) will roll down the side of the hill to the bottom. The memory is resistant to small inputs or perturbations, but a sufficiently large kick can move the ball across a ridge into another valley, corresponding to another memory. An attractor could correspond to a point in activity space (referred to as a fixed point, or a point attractor) or a set of contiguous states forming a line or ring (continuous attractors). Point attractors can store discrete memories (Amari 1972, Amit & Brunel 1997, Hopfield 1982), whereas continuous attractors allow integration and storage of continuous variables (Cannon et al. 1983, Ben-Yishai et al. 1995, Seung 1996, Samsonovich & McNaughton 1997, Lim & Goldman 2013). In the context of motor planning, a point attractor could correspond to a specific state of preparatory activity leading to a specific future movement, with different point attractors corresponding to different movements (Shenoy et al. 2013).

Dimensionality Reduction in Search of Attractors

Large-scale neurophysiological recordings (Jun et al. 2017, Paninski & Cunningham 2018) enable analysis of population activity at the level of single trials (Churchland et al. 2007, Cunningham & Yu 2014, Peixoto et al. 2021). The art of dimensionality reduction is to extract the dimensions in activity space that contain the computations performed by the network. Neural trajectories r(t) occupy low-dimensional subspaces (manifolds; i.e., the surface of the hilly landscape). Modes are particular directions in these subspaces and are typically chosen to reveal interpretable features of the data. For example, in a licking task, projections along a vector in activity space that maximally distinguish movement directions contain nearly all licking direction-selective activity (**Figure 1c**,*d*). This projection also helps reveal attractor dynamics related to motor planning. Trajectories projected to these modes can be interpreted as multineuron peristimulus time histograms, with each

Implementation:

how neurons and connections physically realize the algorithm neuron contributing a specific amount of information. Projections of population trajectories along modes combine activity across neurons, providing statistical power for moment-by-moment analysis of behavior in terms of neural activity (Cunningham & Yu 2014).

New methods for dimensionality reduction provide increasingly refined windows into population dynamics (Kobak et al. 2016, Low et al. 2018, Pandarinath et al. 2018, Williams et al. 2018, Aoi et al. 2020). Low-dimensional representations of population data enable comparisons of dynamics and neural network models, which have led to insights into the mechanisms underlying decision-making (Mante et al. 2013), motor control in cortical (Hennequin et al. 2014, Sussillo et al. 2015) and subcortical (Aksay et al. 2007) networks, and gating of information flow across brain regions (Finkelstein et al. 2021). Below we focus on experimental tests of the attractor hypothesis as a mechanism for motor planning and initiation, which rely on large-scale recordings and trial-by-trial analysis of neural activity aided by dimensionality reduction.

Tests of the Attractor Hypothesis

During motor planning, activity trajectories converge to discrete locations in activity space, consistent with relaxation into point attractors (Churchland et al. 2006, 2010b; Afshar et al. 2011; Inagaki et al. 2019). But measuring neural activity alone is insufficient to test the attractor hypothesis and distinguish between specific implementations because multiple dynamical systems can produce identical low-dimensional neural dynamics (Prinz et al. 2004, Fisher et al. 2013, Li et al. 2016). For example, discrete states in preparatory activity could reflect point attractors or continuous attractors driven by discrete inputs. Perturbation experiments are required to distinguish between these models (see the sidebar titled Limitation of Perturbation Experiments).

Behavioral effects of the perturbations have been used to test algorithmic models. For example, silencing FOF biases choice in a perceptual decision-making task (Erlich et al. 2011, Piet et al. 2017), consistent with models in which FOF maintains the binary choice (motor plan) with point attractors but not with FOF making decisions with continuous attractors.

Directly monitoring neural dynamics and behavior after temporally precise perturbations provides even stronger constraints on models (**Figure 2**). Following a perturbation, a continuous attractor will maintain a trace of the perturbation, corresponding to a displacement in activity

LIMITATION OF PERTURBATION EXPERIMENTS

Optogenetic perturbations can reveal the causal relationships between activity in different brain regions and behavior. However, optogenetic perturbations have to be considered in the context of complex circuit responses to perturbations. First, because of nonlinear feedback loops, unexpected effects of optogenetic perturbations, such as rebound excitation after inhibition, are the rule rather than the exception. Second, manipulating activity in one area inevitably modulates activity in connected areas, making it difficult to ascribe behavioral effects to perturbations of one brain area. Third, the impact of a manipulation could be permissive instead of instructive, in the sense that baseline activity in one brain area may simply be required to fuel a connected area for computation. Fourth, the brain adapts to optogenetic perturbations by plasticity and learning so that the physiological and behavioral effects can attenuate over trials. Fifth, optogenetic perturbations can bring the population activity to an unnatural state. For some questions, more targeted two-photon perturbations may be required. Given these caveats it is essential to invest in extensive measurement of neuronal activity during manipulation and interpret the effects of the manipulations in the context of these measurements (for further discussions, see Jazayeri & Afraz 2017, Wolff & Ölveczky 2018, Li et al. 2019).



Figure 2

Tests of attractor hypotheses. Models explaining preparatory activity in a memory-guided movement task. Projections of population activity along planning mode (*left*) and corresponding energy landscapes (*right*; time points T1, T2, and T3). In both models, instruction initiates movement type–selective preparatory activity (*blue or red dotted lines*). Perturbations are applied on blue trials. (*a*) In the continuous attractor model, optogenetic perturbation (*left, cyan bar; right, cyan arrow*) shifts activity. The shift outlasts the perturbation (*blue solid line*; a ball stays there because of the flat landscape). (*b*) In the point attractors model, activity either recovers (*dark blue solid line*; the ball does not clear the ridge) or switches (*light blue solid line*; the ball goes over the ridge) to the other attractor.

space. In contrast, in point attractors, activity will relax back to the same fixed point (rolling back to the same valley). For strong perturbations, activity may occasionally switch to other attractors (kicked across a hill into a different valley). The network response after perturbations tests the attractor hypothesis and distinguishes between continuous and point attractors.

This approach has been applied to ALM in a memory-guided licking task. Dimensionality reduction methods identify a mode of population activity that best separates direction-selective activity; this mode reveals attractor dynamics because it transects two valleys and the ridge separating them. Transient optogenetic inactivation of ALM during the memory (or delay) epoch results in a binary (left/right) outcome: The activity state either recovers to the previous activity trajectory or switches to the alternative trajectory, followed by the movement predicted by the trajectory measured after the perturbation (Inagaki et al. 2019). Similarly, stimulation of input to ALM in the memory epoch causes bistable dynamics: either recovery to the initiated trajectory or switching to the trajectory corresponding to the other choice (Finkelstein et al. 2021). These results provide direct support for the point attractors hypothesis.

This view of motor planning is likely an oversimplification. Additional mechanisms such as hidden feed-forward connectivity (Goldman 2009, Murphy & Miller 2009) and short-term synaptic plasticity (Mongillo et al. 2008) likely also play roles in decision-making and motor planning. Exploring these mechanisms will require highly specific manipulations of activity modes during different phases of behavior.

The behavioral tasks used in the experiments mentioned above have two behavioral choices, which likely explains two fixed points in neural dynamics. What happens in tasks with multiple choices? Attractor networks can accommodate a large number of fixed points (Hopfield 1982, Amit et al. 1985). Continuous variables could be stored in continuous attractors or approximated by closely spaced point attractors (Brody et al. 2003b, Wimmer et al. 2014, Panichello et al. 2019). Other fundamental questions remain to be answered. For example, can a single network multiplex multiple attractor landscapes to perform multiple tasks (Gallego et al. 2018, Yang et al. 2019)? How is the attractor landscape shaped by learning (Sadtler et al. 2014, Sun et al. 2022)? And how does the sensory information feed into the attractor landscape? Probing attractor landscapes in tasks with multiple movements and during training is an important area for future investigation.

Control Signals Shaping the Attractor Landscape

The standard implementation of point attractors produces dynamics as activity trajectories approach fixed points and stationary activity once the fixed points are reached (Amit & Brunel 1997). Importantly, attractor landscapes are modifiable by external input (Machens et al. 2005, Wong & Wang 2006, Vyas et al. 2020). Nonselective inputs can change the number and locations of attractors in activity space, altering the computation performed in response to selective input, including transitions from decision-making to memory (Machens et al. 2005, Wong & Wang 2006) and resetting of memories. The external inputs can change gradually or abruptly and thus cause rich changes in neural population dynamics. The same network can thus participate in multiple computations that require distinct attractor landscapes.

The attractor framework can model behaviors that require multiple computations in sequence (Heeger & Mackey 2019). Changes in inputs to the attractor network trigger changes in the sequence. For example, in memory-guided movement tasks, subjects make a decision based on sensory information during the sample epoch, maintain a memory of the choice during the delay epoch, and execute the movement during the response epoch. ALM is involved in all of these processes (Guo et al. 2014, Xu et al. 2022, Inagaki et al. 2022). Below we discuss examples in the context of memory-guided movement tasks where external signals reshape attractor landscapes to implement different computations.

Ramping Activity

In general, memory-related neural activity is not stationary but changes predictably over time, even in tasks without an explicit need to estimate time (Funahashi et al. 1989; Brody et al. 2003a,b; Maimon & Assad 2006; Machens et al. 2010; Erlich et al. 2011; Shenoy et al. 2013; Thura & Cisek 2014; Kobak et al. 2016; Cueva et al. 2020). For example, in typical memory-guided movement tasks, a Go cue instructs the timing of the action, sparing the subject the need to keep track of time. Still, activity of many ALM neurons ramps up or down until the time of movement (Li et al. 2016, Inagaki et al. 2018) (**Figure 1**). When the delay is short/long, the ramp is steep/shallow, which is referred to as temporal scaling (Wang et al. 2018). When the delay duration is unpredictable, ramping is rapid, commensurate with the earliest possible Go cue, followed by persistent activity (Tanaka 2007, Inagaki et al. 2019).

These ramping activity trajectories could be the result of two different dynamical processes. First, the activity trajectory could reflect relaxation of the system toward a fixed point (the ball slowly rolls down the sides of a shallow hill in a static landscape) (**Figure 3***a*). Second, the system could remain near a point attractor for the duration of the memory, but the attractor moves over time as the landscape is deformed (dynamic attractor, **Figure 3***b*).

Rapid perturbations of activity shift the activity state. The rate of recovery after perturbation distinguishes between models. The first model implies shallow attractors and thus slow recovery of the activity trajectory, similar to the dynamics of the unperturbed trajectories (**Figure 3***a*). Optogenetic perturbation experiments in ALM instead reveal rapid recovery after perturbation, much faster than the normal dynamics of activity trajectories, consistent with rapid decay into attractors and gradual deformation of the attractor landscape to produce ramping (Li et al. 2016, Inagaki et al. 2019, Finkelstein et al. 2021) (**Figure 3***b*).

Several lines of evidence suggest that the ramping signal originates outside of ALM. First, the nonselective ramping activity recovers after bilateral perturbation of ALM, while selective activity does not (Li et al. 2016). A parsimonious explanation is that ALM is required to maintain motor planning (what to do) but the ramping signal (when to act) is provided by an external source.



Figure 3

Models explaining ramping activity. Projections of population activity along the planning mode (*left*) and corresponding energy landscapes (*right*) are shown for both models. (*a*) In the internal ramping model, the attractor landscape is shallow. A ball (activity state) rolls down the valley slowly to produce ramping (compare the ball location in the landscape and preparatory activity in the trajectory). Relaxation after a perturbation has similar dynamics as ramping (*dashed cyan line*). (*b*) In the external ramping model, the energy landscape is reshaped over time by an external ramping input. The ball is always near the bottom of the valley. When attractors are still shallow early in the delay epoch (*middle landscape*), distractors/perturbations can kick the ball above the ridge to move it into another attractor (*light blue ball* and *purple dotted line*). When attractors are deep prior to action (*right landscape*), the same kick cannot move the ball out of the valley.

Second, training a recurrent neural network to mimic ALM activity patterns and their response to perturbations requires an external ramping input (Finkelstein et al. 2021).

The ramping appears to signal increasing commitment to the selected action (Cisek & Kalaska 2010, Thura & Cisek 2014). In a memory-guided movement task in mice, distractors early in the memory epoch, or on trials with low ramping, biased choices by shifting ALM dynamics, whereas distractors late in the delay, or on trials with high ramping, did not affect choice or ALM dynamics (Finkelstein et al. 2021). Similarly, in rat, transient unilateral silencing of FOF and superior colliculus (SC; receiving input from FOF) biased choices early but not late in the memory epoch (Kopec et al. 2015). These results imply that a nonselective ramping signal gradually reshapes the landscape from shallow point attractors (or a continuous attractor) to deeper point attractors (**Figure 3b**). In the shallow attractor regime, input can easily shift the dynamics (a ball can readily move from valley to valley over the low ridge). In the deeper point attractors regime, the dynamics becomes more robust to distractors (a ball cannot cross the high ridge). This gradual shift may help the motor system to prepare actions seconds before movement initiation, while retaining flexibility to alter decisions, with benefits for survival in uncertain environments (Cisek & Kalaska 2010).

From Planning to Execution

Movement initiation is preceded by dramatic changes in cortical activity (Churchland et al. 2012; Kaufman et al. 2014, 2016) (**Figure 1**). In directional licking tasks, ALM activity is causally related to movement initiation (Komiyama et al. 2010, Li et al. 2015, Xu et al. 2022, Inagaki et al. 2022, Bollu et al. 2021, Takahashi et al. 2021) in addition to planning. Given the dual roles of ALM in planning and execution, key questions include how is motor planning maintained without triggering actions and what mechanisms cause the transition to movement initiation?

An early hypothesis suggested that preparatory activity is a subthreshold version of the activity that later causes movement (Tanji & Evarts 1976, Hanes & Schall 1996). However, the tuning of individual neurons (**Figure 1***b*) and the state of population activity (**Figure 1***d*) differ greatly between planning and execution, arguing against this simple notion (Guo et al. 2014, Kaufman et al. 2014, Li et al. 2015, Elsayed et al. 2016, Inagaki et al. 2018).

Population activity encoding future movement during the memory epoch can be decomposed into a few activity patterns (planning modes) (**Figure 1***d*). Following the Go cue, the activity along planning modes collapses, and a new activity pattern with multiphasic dynamics emerges, which presumably controls movement (Churchland et al. 2012, Kaufman et al. 2014, Elsayed et al. 2016, Economo et al. 2018, Inagaki et al. 2022). These execution modes (**Figure 1***d*) occupy different, near-orthogonal subspaces from the planning modes in both primate primary motor cortex and PMd (Kaufman et al. 2014, Elsayed et al. 2016) and mouse ALM (Economo et al. 2018, Inagaki et al. 2022). In other words, preparatory activity remains in a separate subspace from activity that executes movement. This has been used as a geometrical explanation for why movements may not be triggered during planning (Kaufman et al. 2014) (**Figure 4**). A mechanistic explanation requires an analysis of the neuron types that contribute to motor planning versus execution and a mechanism coupling motor cortex activity and movement (see the section titled Cell Types).

Although planning and execution modes are orthogonal, information is transferred between these modes (Elsayed et al. 2016, Wei et al. 2019, Inagaki et al. 2022). At the level of single trials, activity projected to these modes is correlated so that trials with strong preparatory activity for one movement direction have strong execution activity for the same direction. This explains



Figure 4

Activity trajectories and attractors. (*a*) Activity trajectories projected to the planning (*top*) and execution (*bottom*) modes. (*b*) Evolution of anterior lateral motor cortex activity in the activity space defined by planning and execution modes. During the delay epoch, activity evolves along the planning mode. After the Go cue (*dark blue/red circles*), activity moves along the execution mode, followed by recovery to baseline (*gray circle*).

the correlation between preparatory activity before movement and the fine-scale parameters of upcoming movement (Churchland et al. 2006, 2010a; Li et al. 2016; Even-Chen et al. 2019). Networks with a hidden feedforward structure (Ganguli et al. 2008, Goldman 2009) could underlie this transfer of information from one mode to another.

The Go cue triggers transient nonselective activity in both primate primary motor cortex/PMd (Kaufman et al. 2016) and mouse ALM (Guo et al. 2014, Inagaki et al. 2022). This Go cue mode (**Figure 1***d*) is the most prominent activity mode during the memory-guided movement tasks and is transduced to cortex via thalamus to initiate the transformation from planning to execution (discussed in the section titled Ascending Multiregional Circuits).

Distinct planning, Go cue (referred to as condition-invariant signal), and execution modes appear across behavioral tasks (Lara et al. 2018, Zimnik & Churchland 2021). The near-orthogonal relationships across all activity modes may allow simultaneous processing without interference. For example, when animals plan an action while executing another action, an execution mode of the current action and a planning mode of the following action can coincide in motor cortex. This enables multiplexed processing of multiple movement primitives during natural behavior.

MULTIREGIONAL NEURAL CIRCUITS

Although most neurophysiological studies of motor planning have focused on frontal cortex (ALM, FEF, FOF, PMd, etc.) or SC, one brain area at a time, preparatory activity is generated and maintained in multiregional neural circuits (Alexander & Crutcher 1990, Kopec et al. 2015, Kunimatsu et al. 2018, Svoboda & Li 2018, Wang et al. 2018). In neural networks, attractors are maintained by positive feedback: Excitatory feedback compensates activity dissipated in each neuron, which slows network dynamics beyond the time constant of individual neurons. This feedback could be local or arise via long-range loops involving multiple brain regions (**Figure 5***a*). Moreover, the inputs shaping attractor landscapes, such as ramping and Go cue signals, ascend from subcortical structures via the thalamus. Large-scale recordings together with optogenetic manipulations are beginning to reveal how brain regions interact during motor planning and movement initiation.

The multiregional circuits involved in planning and initiating movements have been studied extensively in licking tasks in mice (**Figure 5***a*). Key results have been reproduced in multiple laboratories across three continents (e.g., Guo et al. 2014, Chen et al. 2021, Duan et al. 2021, Esmaeili et al. 2021, Wang et al. 2021) and have provided general insights. First, preparatory activity is maintained in multiregional neural circuits with multiple obligatory partners. Second, different brain regions have distinct roles in shaping preparatory activity. Third, the strength of functional coupling between brain regions can be gated in a time-dependent manner, which can be implemented via dynamic attractors. We focus on these insights and highlight parallels to other behaviors and brain regions in rats and primates.

Cortico-Cortical Loops

A striking feature of the neocortex is the complex matrix of connections linking any one cortical area with many other cortical areas (Markov et al. 2014, Oh et al. 2014, Harris et al. 2019). ALM is interconnected with primary motor cortex, somatosensory cortex, and multiple parietal cortical areas, mostly in a bidirectional manner. Information from the sensory cortex is the basis of decision-making and ultimately initiates preparatory activity in ALM (Guo et al. 2014, Esmaeili et al. 2020). During the memory epoch, the same input from the sensory cortex that drives decision-making and preparatory activity in ALM loses influence (Finkelstein et al. 2021). This temporal gating of information flow between sensory cortex and motor cortex is based on attractor dynamics: During



Figure 5

Multiregional neural circuits implicated in memory-guided licking behavior in mice. (a) Major brain regions and their interconnections, including the isocortex (green), Str (blue), Thal (red), midbrain nuclei (purple), PN (orange), Cb (yellow), medulla (magenta). Not all of the shown brain regions and interconnections are discussed in this review. This circuit diagram is based on mesoscale anatomy (https://connectivity.brain-map.org/) and single-cell reconstructions (http://ml-neuronbrowser.janelia.org/). Arrowheads signify excitatory connections, and circles inhibitory connections. ALM is part of multiple closed loops involving several brain regions each (e.g., $ALM \rightarrow PN \rightarrow Cb$ cortex \rightarrow deep Cb nuclei \rightarrow Thal \rightarrow ALM). Note that this diagram hides additional complexity and specificity. For example, ALM projects to, and receives input from, parts of multiple distinct thalamic nuclei (not shown). These ALM-projecting thalamic regions are in turn differentially innervated by SNr, PPN/MRN, SCm, and Cb (Inagaki et al. 2022). Other parts of the rodent frontal cortex, such as FOF, have similar long-range connectivity (Erlich et al. 2011), as do cortical regions in primates that are involved in reaching and eye movements (Strick 1976, Alexander & Crutcher 1990, Tanaka 2007, Kunimatsu et al. 2018, Wang et al. 2018). (b) Two types of ALM PT neurons in layer 5. The Thal-projecting PT neurons (black) maintain planning-related activity during the memory epoch, presumably by forming a loop with thalamocortical neurons (red). In contrast, the medulla-projecting neurons (pink) develop execution-related activity (motor command) after the Go cue. Abbreviations: ALM, anterior lateral motor cortex; ALMc, contralateral anterior lateral motor cortex; Cb, cerebellum; Ctx, somatosensory and motor cortex interconnected with ALM; FOF, frontal orienting field; Med, medulla; MRN, midbrain reticular nucleus; PN, pontine nuclei; PPN, pedunculopontine nucleus; PT, pyramidal tract; SCm, motor-related superior colliculus; SNr, substantia nigra reticulata; Str, striatum; Thal, ALM-projecting thalamus.

the memory epoch, ALM preparatory activity enters a fixed point that moves away from other fixed points in activity space and thus becomes more resistant to sensory input (Finkelstein et al. 2021).

Remarkably, bilateral silencing of large regions of cortex posterior to ALM, including primary motor cortex, sensory cortex, and parietal cortex, has little effect on preparatory activity and subsequent behavior (Guo et al. 2014). During motor planning, ALM appears to be functionally uncoupled from connected cortical regions.

The robustness of preparatory activity is in part enabled by coordination between ALM hemispheres, which are connected via the corpus callosum. Silencing or activation of neurons in one ALM hemisphere has often little effect on preparatory activity in the other hemisphere, implying that each hemisphere can maintain preparatory activity independently (Li et al. 2016, Chen et al. 2021). Moreover, after the perturbation, the perturbed hemisphere recovers selectivity, with precision at the level of individual neurons. This recovery is produced by information flow from the unperturbed hemisphere via the corpus callosum. These experiments reveal modular organization (modules have strong within-module connectivity and relatively weak intermodule connectivity), where one brain region (here, an ALM hemisphere) can maintain preparatory activity independently and help the perturbed brain region recover preparatory activity after perturbations.

Modular intracortical connectivity also appears on finer spatial scales. Two-photon-mediated optogenetic stimulation of a small number (<10) of ALM neurons revealed sparse subnetworks that independently maintain activity and are only weakly coupled to other subnetworks (Daie

Selectivity: difference in neural activity between behavioral conditions such as sensory stimuli, trial types, or movements et al. 2021). This fine-scale modular organization may provide higher memory capacity than standard point attractors models while maintaining robustness. How such architectures and dynamics are shaped during learning and/or development and how such modules map onto specific cell types are not yet known.

Cortico-Thalamocortical Loops

Frontal cortical areas connect bidirectionally to nonsensory thalamus. For example, ALM is connected bidirectionally with parts of the ventromedial and ventral anterior-lateral nuclei, intralaminar nuclei, and the mediodorsal nuclei (Guo et al. 2017, 2018; Collins et al. 2018; Economo et al. 2018; Inagaki et al. 2022). Thalamus is a key hub of multiregional connectivity because subcortical inputs enter the frontal cortex via the thalamus (Shepherd & Yamawaki 2021). ALM also projects to the striatum, multiple regions in the midbrain, and the cerebellum (via the pons). Most of these regions in turn send information back to ALM via the thalamus in closed multiregional loops. Similar multiregional loops via the thalamus have been documented in the context of reaching (Strick 1976, Sauerbrei et al. 2020) and eye movements (Tanaka 2007).

Thalamic neurons show preparatory activity, similar to the frontal cortex (Tanaka 2007, Guo et al. 2017, Catanese & Jaeger 2021). The connections between frontal cortex and thalamus are strong (driving) in both directions (Guo et al. 2017). Preparatory activity is therefore maintained in an obligatory cortico-thalamocortical loop. These anatomical and functional features suggest that the thalamus is operationally an extension of cortex, specialized for processing input from multiple subcortical structures. What kind of information is conveyed by these diverse inputs to thalamus and how they are parsed and combined in thalamus before transmission to the cortex are major questions that have yet to be answered.

Cortico-Basal Ganglia-Thalamocortical Loops

Most ALM projection neurons send collaterals to the lateral striatum (Hintiryan et al. 2016, Hunnicutt et al. 2016). Striatum in turn directly/indirectly projects to basal ganglia outputs, including substantia nigra reticulata (SNr), which inhibits parts of thalamus (for example, ventromedial and mediodorsal thalamus). Thalamocortical projections close the loop by projecting back to ALM (Lee et al. 2020).

The roles of cortico-basal ganglia circuits have been explored in the context of action selection/ initiation (Mink 1996, Hikosaka et al. 2000, Klaus et al. 2019) and movement vigor (Turner & Desmurget 2010). Recent experiments show that basal ganglia circuits also play critical roles in motor planning (Wang et al. 2021) and action timing (Thura & Cisek 2017, Kunimatsu et al. 2018, Paton & Buonomano 2018, Wang et al. 2018, Catanese & Jaeger 2021). Neurons in SNr show preparatory activity that depends on input from ALM (Wang et al. 2021). Similar to ALM, activity in the basal ganglia ramps in a timing-dependent manner (Thura & Cisek 2017, Kunimatsu et al. 2018). Interestingly, optogenetic modulation of activity in SNr axons projecting to thalamus (ventromedial) causes a dramatic reduction of selectivity in ALM (a collapse of the planning mode; **Figure 1***d*) (Wang et al. 2021). These experiments suggest that the basal ganglia could be a source of the external ramping signal that shapes the attractor landscape in the ALM cortico-thalamocortical loop.

Additional timing signals may arise in the cerebellum (Ohyama et al. 2003, Chabrol et al. 2019). Further investigations are required to probe the neural basis of signals that shape preparatory activity. Identification and manipulation of the relevant neural substrates will facilitate direct tests of the hypothesis that an external signal shapes the attractor landscape and computations in ALM.

Other ALM-Subcortical Loops

ALM projects to the motor segment of the superior colliculus (SCm). During the memory epoch, ALM projections to the SCm carry preparatory activity (Li et al. 2015, Chen et al. 2017, Duan et al. 2021). Downstream, SCm neurons also show preparatory activity, and silencing SCm unilaterally during the memory epoch causes a response bias toward the silenced side (Kopec et al. 2015, Duan et al. 2021). However, SCm projects back to ALM via the thalamus, as well as directly to premotor areas in the medulla (Rossi et al. 2016). It is unclear whether the behavioral effects of SCm inactivation are caused by effects on ALM preparatory activity, direct effects on medulla circuits, or other SCm targets. Strong coupling between the frontal cortex and the SC has also been revealed in studies of eye movements in primates (Wurtz & Goldberg 1972) and orienting behaviors in rats (Kopec et al. 2015).

ALM also connects to the cerebellum via the pontine nuclei (Gao et al. 2018, Li & Mrsic-Flogel 2020). Output from the deep cerebellar nuclei (DCN) projects back to ALM via the thalamus. Preparatory activity in the cerebellum depends on ALM activity. Optogenetic manipulation of DCN in turn changes activity patterns in ALM. Activation of DCN rotates the direction in ALM activity space that contains movement direction–selective activity, suggesting that cerebellum shapes the attractor landscape in the cortico-thalamocortical loop (Li & Mrsic-Flogel 2020).

Ascending Multiregional Circuits

The neural mechanisms that terminate preparatory activity and trigger a movement also involve multiregional neural circuits (Hikosaka et al. 2000, Inagaki et al. 2022, Dacre et al. 2021). Recent work has revealed key roles for ascending signals from midbrain structures, including the pedunculopontine nucleus (PPN) and midbrain reticular nucleus (MRN), in movement initiation in directional licking tasks (Inagaki et al. 2022). PPN/MRN neurons show short latency (~5 ms) and transient responses to the auditory Go cue triggering movement (Figure 1a), caused by input from midbrain auditory centers. Optogenetic stimulation of thalamus-projecting PPN/MRN neurons triggers correct movements. Importantly, the optogenetic stimulus also triggers the precisely choreographed sequence of neuronal dynamics associated with movement initiation: collapse of the planning mode, initiation of the Go cue mode, and the execution mode (Figure 1d). These results show that an ascending PPN/MRN to thalamus to ALM pathway provides Go cue information to ALM, which triggers mode switching from preparatory activity to execution mode that releases planned movement. Similarly, in a cued reaching task, DCN activity is necessary and sufficient for the Go cue signal in MCx and movement initiation (Dacre et al. 2021). PPN/MRN and DCN project to partially overlapping thalamic nuclei and frontal cortical areas. It remains to be answered whether PPN/MRN and DCN are redundant, serving as parallel Go cue pathways for different sectors of MCx, or are recruited differently depending on task requirements.

Cell Types

So far we have considered neural representations and dynamics in brain regions and connections between brain regions, all with anonymous populations of neurons. Inputs to any brain region connect to defined cell types (Hooks et al. 2013, Collins et al. 2018, Anastasiades et al. 2020), each with specific local connections (Pouille & Scanziani 2004, Kiritani et al. 2012, Pfeffer et al. 2013, Yu et al. 2019). Computation mediated by such local circuits propagates to other brain regions via diverse projection neurons (Hooks et al. 2013, Shepherd 2013, Winnubst et al. 2019, Muñoz-Castañeda et al. 2021). Understanding the logic of multiregional communication requires measurement of neural dynamics in these defined cell types. The diversity of cell types is being mapped in mice using single-cell genomics (Tasic et al. 2018). For example, ALM alone contains

potentially up to 100 cell types, including more than a dozen glutamatergic projection neurons. Classically, projection neurons have been grouped into intratelencephalic (IT) neurons, which project to other cortical areas and extensively to the striatum, pyramidal tract (PT) neurons project to the midbrain and brainstem but have few intracortical axons and small arborizations in the striatum, and corticothalamic neurons project mainly to the thalamus. These cell types form structured intracortical areas (Hooks et al. 2013). IT neurons in the motor cortex receive input from sensory cortical areas (Hooks et al. 2013). IT neurons connect to PT neurons, whereas PT neurons do not connect back to IT neurons (Brown & Hestrin 2009, Morishima et al. 2011, Kiritani et al. 2012, Shepherd 2013).

It has long been known that specific cortical projection types carry distinct information (Movshon & Newsome 1996, Hahnloser et al. 2002, Sato & Svoboda 2010). In the context of motor planning, ALM PT neurons, but not IT neurons, develop preparatory activity with a contraversive bias late in the memory epoch (Li et al. 2015, Duan et al. 2021). ALM PT neurons can be subdivided further into one class that projects to the thalamus but not to premotor centers in the medulla and another class that projects to the medulla but not to the thalamus (Economo et al. 2018) (both classes share projections to the SCm, pons, and striatum). The thalamus-projecting PT neurons maintain planning-related activity during the memory epoch. In contrast, the medulla-projecting neurons develop selectivity late and also carry a large proportion of the execution mode after the Go cue (**Figure 5***b*). These measurements provide a circuit-based explanation of the geometrical picture for why movements may not be triggered during planning (Kaufman et al. 2014) (see the section titled From Planning to Execution). More generally, these studies illustrate how specific types of information are transmitted across brain regions via structurally and molecularly defined projection neuron types.

Despite their obvious importance for understanding the principles underlying multiregional communication, recordings from defined cell types are rarely done. A deeper understanding of information flow in the brain will require the development of methods to routinely link recorded neurons to specific cell types, including projection types, that correspond to nodes of neural circuits.

CONCLUSIONS AND OUTLOOK

In this review we discussed the neural algorithms and circuits underlying motor planning and transitions to movement initiation. Converging evidence from primates and rodents implicates dynamic attractors in creating preparatory activity in the motor cortex. Slow changes in preparatory activity are caused by the movement of attractors in activity space. The attractor landscape is controlled by subcortical signals from the basal ganglia, midbrain, cerebellum, and medulla, which ascend into the frontal cortex via the thalamus. Subcortical signals also terminate preparatory activity and initiate motor commands that trigger execution of movement.

The principles revealed here may apply to computations beyond motor control (Mante et al. 2013, Hunt & Hayden 2017, Stavisky et al. 2017, Wu et al. 2020, Yoo & Hayden 2020, Libby & Buschman 2021). Animal behavior often consists of multiple distinct phases, each corresponding to different computations. STM, mediated by attractor dynamics, is required to link these computations. Control signals could reshape such attractor landscapes to gradually or abruptly switch between computations.

Similar circuit motifs could also be shared across cognitive functions. For example, preparatory activity is maintained in cortico-thalamocortical circuits involving motor cortex and motor thalamus (Guo et al. 2017). Similar cortico-thalamocortical loops, involving different cortical and thalamic areas, could underlie working memory, integration of sensory evidence, and other cognitive functions (Ito et al. 2015, Schmitt et al. 2017). Recent computational models have explored the notion that thalamus routes simple signals that control flexible and complex dynamical systems implemented by cortical connectivity (Heeger & Mackey 2019). This division of labor between cortex and inputs to thalamus maps onto powerful machine learning algorithms such as long short-term memory networks. Cortico-thalamocortical loops correspond to the recurrent neural network, whereas inputs to thalamus provide the update and reset signals that select the information to process and to erase. These networks are computationally powerful because they allow representing and manipulating long-term dependencies, as required for most behaviors. Concurrent optogenetic perturbations and physiological recordings guided by dynamical system models, as described here, will pave the way to test specific hypotheses.

The investigations of neural network mechanisms are only in their initial stages. Linear decompositions of population activity in ALM in the context of a simple directional licking task have already revealed constraints on network models and required modification to standard attractor models. Additional structure of the population activity likely plays key roles in behavior. Recently developed methods to analyze activity manifolds, cell type–specific and multiregional recording methods, and cellular-resolution perturbations are promising to reveal finer features of behavior-related neural dynamics.

So far, the study of cognitive processes in mammals has focused on representations and dynamics produced by networks of anonymous neurons. The last decade has seen an explosion of studies mapping the brain's cell types and connections, especially in fruit flies and mice (Tasic et al. 2018, Bates et al. 2019, Winnubst et al. 2019, Scheffer et al. 2020). Evolution acts on the genome, which in turn tunes the properties of cell types and their synapses, which in turn constrain computation. Neural computations therefore have to be understood in the context of biophysics and structured neural circuits. Cell type–specific analysis of neural dynamics will reveal how neural circuits implement computations to drive behavior and will reveal novel principles of computation.

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