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Neuromodulation and Neurophysiology on the Timescale of Learning and Decision-Making

Cooper D. Grossman and Jeremiah Y. Cohen

The Solomon H. Snyder Department of Neuroscience, Brain Science Institute, and Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; email: jeremiah.cohen@jhmi.edu

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Abstract

Nervous systems evolved to effectively navigate the dynamics of the environment to achieve their goals. One framework used to study this fundamental problem arose in the study of learning and decision-making. In this framework, the demands of effective behavior require slow dynamics—on the scale of seconds to minutes—of networks of neurons. Here, we review the phenomena and mechanisms involved. Using vignettes from a few species and areas of the nervous system, we view neuromodulators as key substrates for temporal scaling of neuronal dynamics.

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INTRODUCTION

We are dynamic organisms living in a dynamic world. Our nervous systems must flexibly adapt to changes in the environment and our internal state that occur at varying temporal scales and levels of abstraction, while nonetheless maintaining robustness. The brain is constantly exposed to new information, but cognition and behavior often show remarkable continuity while still being sensitive to relevant changes. How do cognitive processes, and the neural activity that supports them, continuously integrate information about the world and self to balance stable behavior with flexibility? How are these ongoing processes shaped by changes on various temporal scales?

Much of the knowledge within systems neuroscience lies in the fast time domain. We are especially good at correlating neuronal activity with events in the outside world—such as a sensory stimulus or a movement of the body—that occur on short timescales. For example, neurons in neocortical areas that receive input from primary sensory thalamic nuclei respond within tens of milliseconds to stimuli in their receptive fields (Armstrong-James et al. 1992, Maunsell & Gibson 1992, Raggio & Schreiner 1994). Neurons in neocortical areas that are presynaptic to premotor or motor neurons in the brainstem and spinal cord respond in the tens of milliseconds preceding muscle activation (Evarts & Tanji 1976). More abstract quantities such as errors of predicted reward appear in dopamine neuron firing rate changes over tens to hundreds of milliseconds (Schultz et al. 1997, Bayer & Glimcher 2005). Errors of predicted movements appear in cerebellar Purkinje neurons over similar timescales (Medina & Lisberger 2008, Kimpo et al. 2014). At the other extreme, we know a lot about long-term structural changes in the nervous system from molecular, cellular, and developmental neuroscience. For example, many forms of synaptic plasticity involve the insertion of new proteins in neuronal membranes (Diering & Huganir 2018), and development involves gross changes in neuronal morphology.

While learning and decision-making certainly rely on the faster and slower neural activities described above, they largely occur at the timescales in between (Soltani et al. 2021). We argue that it is precisely this medium range—seconds to minutes—that must occupy more of our attention as a field (Kiebel et al. 2008). How does neural activity support cognition and behavior on this timescale? Sensory or reward feedback is often quick, while changes in the environment and internal state occur on multiple timescales. But decision-making and receptivity to learning are often continuous processes that occur on this middle timescale. How are the temporally and spatially extended neural substrates modified to meet the changing demands of environments and goals?

Neuromodulators occupy a unique anatomical niche in the brain that may allow them to support and modify activity in this time domain: Each system comprises small numbers of cells that project axons very broadly. For example, there are approximately 9,000 serotonin neurons in the mouse dorsal raphe that supply this transmitter to most of the forebrain (Ishimura et al. 1988). This is a remarkable degree of divergence, suggestive of an important neuromodulatory "broadcast" signal (Jacobs & Azmitia 1992, Dayan & Huys 2009). Although these neurons are heterogeneous and often innervate specific regions, their axons make dense, broad arborizations and release neurotransmitter synaptically and extrasynaptically, allowing for both synaptic and volume transmission (Azmitia & Segal 1978, Moore et al. 1978, Jacobs & Azmitia 1992, Descarries & Mechawar 2000). Possibly related to these two signaling modes, these neurons also exhibit dynamics on multiple, behaviorally relevant timescales (Fornal et al. 1996, Nakamura et al. 2008, Ranade & Mainen 2009, Miyazaki et al. 2011, Li et al. 2013, Cohen et al. 2015, Hayashi et al. 2015, Y. Li et al. 2016). This activity is interpreted by a large number of ionotropic and metabotropic receptors with regional, cell type, and morphological specificity. Such a widespread signal and diversity of receptors could modulate how information is represented at the level of neurons, circuits, and networks on varying timescales. The overarching claim of this review is that neuromodulators adjust how neuronal networks encode, update, and transmit task-specific variables over varying timescales in order to initiate, stabilize, and modulate ongoing learning and decision-making.

NEURAL ACTIVITY AND BEHAVIOR ON THE TIMESCALE OF COGNITION

In the reductionist framework of science, even material interactions on the smallest, subatomic levels that occur in the shortest amount of time can be defined as neural activity. Given the complexities of hierarchical structures and properties that emerge at different levels of organization, it is often not useful nor feasible to think about neurobiological function with such a fine spatiotemporal grain. Rather, the relevant spatial and temporal scales should be those with the maximal causality on the function of interest (Tononi 2004). In models of single neuron activity, for example, the opening of ion channels in a certain dendritic branch or release of neurotransmitter from a specific axon bouton can be understood as a discrete event—these events may constitute fundamental units of computation when considering action potential function.

Perception, cognition, and behavior are obviously supported by such transient neuronal activities but occur over substantially longer epochs. Ignoring unconscious or reflexive processes, only the most specialized instantiations of these processes occur on short timescales. Olympic sprinters can, on rare occasions, achieve reaction times close to 100 ms in response to the starting tone (Lipps et al. 2011). Primates can execute express saccades in less than 100 ms (Fischer & Boch 1983, Munoz & Wurtz 1992). But such response times depend on a singular, known, and expected stimulus and a highly trained, stereotyped motor response (Luce 1986).

When considering perception, cognition, and behavior in more typical settings, the relevant timescales become substantially longer. Decision-making, for example, often involves computations and choices over seconds and minutes. Behavioral tasks that focus on this timescale typically require an animal to hold information online between successive events in the world. Examples include making a sensory discrimination for later retrieval (Brody et al. 2003), preparation of an upcoming movement (Schall & Hanes 1993), or prediction of an upcoming reward (Hull 1943, Watanabe 1996, Leon & Shadlen 1999).

In the case of decision-making, the time it takes to make and execute a decision varies broadly, scaling with the level of abstraction of the goal or plan (Gallistel & Gibbon 2002). Abstract goals can be broken down into subgoals that can be further divided in a hierarchical fashion until they

consist of actionable behavior (Sutton et al. 1999). For example, the decision to apply to graduate school, among other subgoals, requires seeking letters of recommendation. This goal, in turn, requires a complex and temporally diffuse set of behaviors that results in building a relationship with a mentor and eventually asking them for a letter. Ultimately, such long-term behavior can be conceived of as being maximally reliant on ongoing, conscious decision-making. Although the spatiotemporal grain of activity that is most relevant for a given conscious process may vary, it should match the subjective experience of that process (Tononi 2004). Subjectively, conscious decision-making typically occurs on the scale of seconds to minutes.

The relevant neural representations then must be maintained in activity over similar periods of time. The dynamics of persistent activity in neurons and populations is thought to explain such cognitive and behavioral functions. In vivo, individual neurons show persistent changes of activity on timescales of hundreds of milliseconds to tens of seconds during tasks that require the animal to maintain information over similar timescales. This type of persistent activity was first observed in the monkey prefrontal cortex during working-memory tasks in which the maintenance of information about reward location in working memory relied on the continued firing of neurons in that region (Kubota & Niki 1971, Fuster 1973, Funahashi et al. 1989). Persistent activity was subsequently observed in premotor and prefrontal areas during decision-making, movement preparation, and reward anticipation in monkeys and rodents (e.g., Kim & Shadlen 1999, Curtis & Lee 2010, Kopec et al. 2015, N. Li et al. 2016).

Below, we discuss a theoretical framework for cognition and behavior that further illustrates the computational need for this scale of activity and how such systems could be made more flexible. We then discuss potential neural mechanisms to support these processes, highlighting the proposed roles for neuromodulators throughout.

Reinforcement Learning Implemented in the Nervous System

Making decisions in nonstationary, stochastic environments is a major challenge. The nervous system must develop a robust policy (probability distribution of actions) that achieves its goals (e.g., maximizing reward for a foraging mammal) while also continuing to learn. If a policy is too stable, it suffers from becoming suboptimal as soon as the external world changes drastically. On the other end of the spectrum, if a policy is too labile, it may perform suboptimally at all times and can approximate random behavior. One theoretical framework used to approach this type of cognition comes from control theory and reinforcement learning (Bertsekas & Tsitsiklis 1996, Sutton & Barto 1998). Here, behavioral policies arise by learning from errors: We make a decision, receive feedback from the world (for example, a reward), compare it to the expected outcome of the decision, and calculate the discrepancy between expected and received rewards (reward prediction error). This prediction error, in turn, is used to update behavioral policies.

Within this framework, work over the past 25 years has studied the relationship between model variables and activity of neurons in several key brain structures. There are two types of model variables: hidden (or latent) and observable. Latent variables are key to understanding the internal computations that the nervous system performs to produce outwardly observable decisions. During experiments, the variables observed from outside the nervous system are typically low-dimensional choices, indicated by the movement of the eyes, tongue, or forelimbs to one of a few target locations. The hypothetical hidden variables are estimated from observed behavior and give the experimenter a guess about the underlying processes the nervous system used to select an action at a particular time. Many of these variables would need to be represented over long timescales in order to support behavior on those timescales, only changing or updating as a result of new information or changing behavior demands.

Among the infinite set of possible latent variables used to solve these tasks, a few have received special attention. The first breakthrough was the insight that brief changes in activity of midbrain dopamine neurons signal reward prediction errors, first discovered in monkeys (Schultz et al. 1997) and subsequently found in rats (Roesch et al. 2007), humans (Zaghloul et al. 2009), and mice (Cohen et al. 2012). Recent work has built on these early observations by testing specific hypotheses emerging from early work as well as adding important detail to—and identifying shortcomings of—the original framework.

The key decision variables used to make choices in one class of reinforcement learning models (but see Dayan & Abbott 2001, Li & Daw 2011) are action values. These variables estimate the expected value of reward given an action in a particular state. The space of admissible actions is assigned a set of action values, an abstract representation of the worth of each possible choice in the task. Action values are expressed in changes in firing rates in the striatum (Samejima et al. 2005, Lau & Glimcher 2008, Kim et al. 2009, Cai et al. 2011, Wang et al. 2013, Shin et al. 2021) and prefrontal cortex (Tsutsui et al. 2016, Bari et al. 2019).

Natural behavior, as well as many laboratory tasks, requires animals to make decisions at unknown times in the future. For example, in many free-choice tasks, intertrial intervals are distributed randomly. Thus, the nervous system must be capable of holding the value of a decision variable online for arbitrary durations. Indeed, in a dynamic foraging task, the firing rates of single neurons in mouse medial frontal cortex were found to track the difference between action values (relative value) estimated from a reinforcement learning model (Bari et al. 2019) (**Figure 1*a***). Relative value is the hypothetical variable used in the softmax decision function—one of the most commonly used decision functions in reinforcement learning models (Daw et al. 2006). The estimated relative value variable predicted choice behavior probabilistically, consistent with the proposed decision computation. Further, the variable was reliably represented in firing rates over the longest intertrial intervals, matching the independence of choice behavior from length of time between trials (Bari et al. 2019) (**Figure 1*c*,*e***). Pharmacological inactivation of this activity almost completely abolished the flexible decision-making for which these online, persistent representations were shown to be responsible.

In addition to learning how to maximize reward in stochastic environments, the nervous system also learns how to move effectively as the body experiences dynamic forces on it. Control theory has been used extensively to model this problem (Wolpert & Ghahramani 2000, Shadmehr et al. 2010, Haith & Krakauer 2013, Roemmich & Bastian 2018). Like reinforcement learning, motor learning requires neural dynamics on multiple timescales (Smith et al. 2006). One example within middle timescales lies at the intersection of reinforcement learning and motor learning.

When humans and other animals expect a large reward, the velocity of movements increases and response times to initiate movements decrease, which is collectively defined as vigor (Dudman & Krakauer 2016, Shadmehr et al. 2019, Shadmehr & Ahmed 2020). On longer timescales, it is not only the expected magnitude of reward that varies with vigor but also the reward rate of the environment (Niv et al. 2007, Guitart-Masip et al. 2011, Yoon et al. 2018, Shadmehr et al. 2019). When the reward rate increases, vigor increases. These observations imply the existence of a representation of reward rate in the nervous system over slow timescales (tens of seconds to minutes). Many of these tasks were inspired by classic literature in ecology on animals foraging in the wild (Stephens & Krebs 1987, Houston & MacNamara 1999). Consider an animal foraging for food. While harvesting at a particular location (a patch), the rate of reward decays as the food supply diminishes. At a certain point, it becomes beneficial to leave the current patch, even when there is food remaining, and forage at a new location. The marginal value theorem states that a forager should leave a depleting patch as soon as its rate of reward falls below the average reward rate of the environment (Charnov 1976). Under certain circumstances, animals forage optimally,

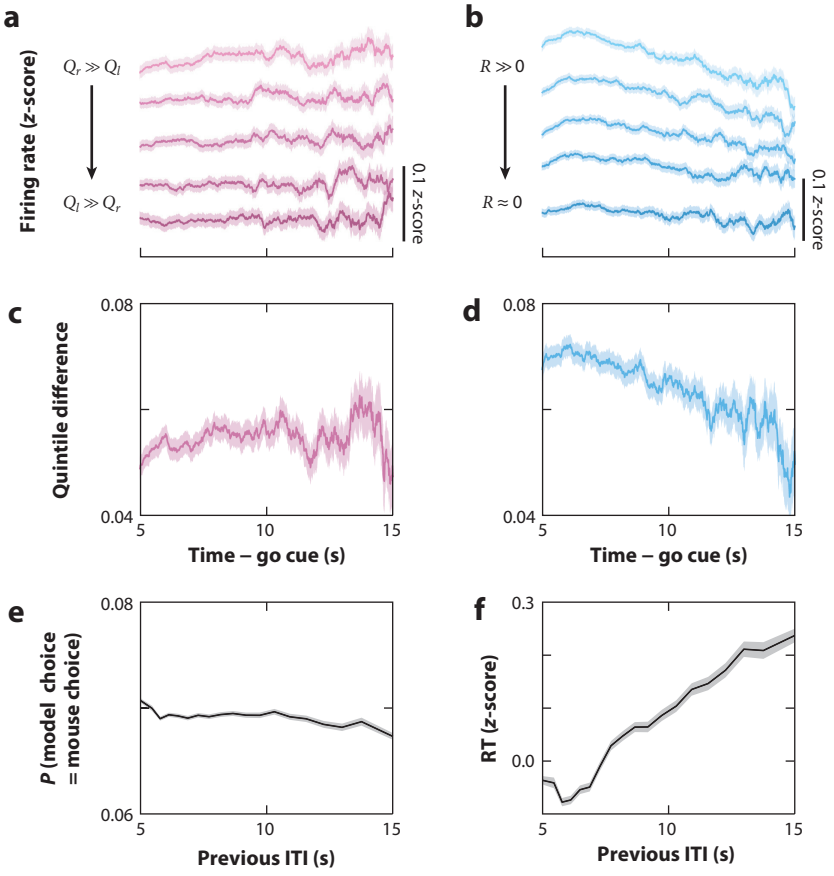

Figure 1

Relative-value signals are persistent and stable in time, while total-value signals are persistent but decay over time. (*a*) Firing rates of relative-value neurons in mouse medial frontal cortex during intertrial intervals (ITIs) of a dynamic choice task, split by quintiles of relative value. (*b*) Firing rates of total-value neurons during ITIs, split by quintiles of total value. The difference across quintiles (averaged across adjacent quintiles) remained stable over time for relative-value (*c*) but not total-value (*d*) neurons. (*e*) The probability that the reinforcement learning model choice matches the mouse's choice remains stable as a function of previous intertrial interval. (*f*) Response time (RT) increases following longer ITIs. Figure adapted with permission from Bari et al. (2019).

implying the existence of slowly varying activity in the brain that estimates overall reward rate (Stephens & Krebs 1987, Houston & MacNamara 1999).

Several studies have found neuronal correlates of such a variable and have demonstrated how it may be used to generate behavior. Neurons in the frontal cortex show firing rates that covary with vigor (often operationally defined as inverse response time) (Shima & Tanji 1998, Iwata et al. 2013, Reppert et al. 2018, Bari et al. 2019). Cortical input to basal ganglia (Stalnaker et al. 2010, Hayden et al. 2011, Opris et al. 2011, Wang et al. 2013, Thura & Cisek 2017), together with input from dopamine neurons (Salamone & Correa 2002, Satoh et al. 2003, Niv et al. 2007, Guitart-Masip et al. 2011, Panigrahi et al. 2015), likely generates the observed covariation of vigor and reward rate, although the exact mechanisms are still rather mysterious (Pasquereau & Turner 2013, Varazzani et al. 2015).

One clue about how the nervous system tracks reward rate comes from the aforementioned study of mouse dynamic foraging (Bari et al. 2019). In addition to relative value, the firing rates of single neurons in medial frontal cortex tracked the sum of the action values (Bari et al. 2019) (total value; see **Figure 1*b***). This variable is not used to make decisions in this context but tracks reward rate. Unlike the relative-value representations, encoding of total value decayed over long intertrial intervals (Bari et al. 2019) (**Figure 1*d***). This decay matched the increase in reaction times observed over longer periods between trials (Bari et al. 2019) (**Figure 1*f***).

Metalearning and Neuromodulation

Reinforcement-learning models, as with all models, fail to describe certain features of observed behavior. One limitation of the basic form of these models is that they lack the flexibility to adapt to different outcome statistics as a consequence of a new or changing environment—or a different behavioral task altogether. For example, the parameter that controls learning rate is often treated as a fixed value. However, learning rates should change to complement the statistics of the environment. Indeed, in decision-making tasks primates modulate their learning rates in response to the rate of change in contingencies between actions and outcomes (Behrens et al. 2007, Krugel et al. 2009, Nassar et al. 2012, Massi et al. 2018). These findings accord with normative ideas about volatility and learning; when the environment changes frequently, it is better to learn quickly because only the most recent information is likely to be relevant. Humans, monkeys, and mice do indeed learn more quickly when a sudden change is perceived in the environment, when outcomes diverge from recent variability (Nassar et al. 2012, McGuire et al. 2014, Bartolo & Averbeck 2020, Grossman et al. 2022).

Learning higher-order statistics of the environment in order to fine-tune learning from outcomes to make decisions is referred to as meta-learning, and it has been proposed that neuromodulatory systems are responsible. Neuromodulators have been mapped onto parameters or variables in reinforcement learning models (Daw et al. 2002, Doya et al. 2002), functions within Bayesian frameworks (Yu & Dayan 2005, Dayan & Yu 2006), and conceptual theories (Jacobs & Fornal 1991; Azmitia 2001, 2007; Aston-Jones & Cohen 2005a,b; Bouret & Sara 2005) that are all related to meta-learning. Also related, flexibility in learning and decision-making may be the output of a mixture of experts in the brain (Dickinson 1985, Daw et al. 2005, O'Doherty et al. 2021), and the mediation between systems may be supported by neuromodulators (Iigaya et al. 2018). These theories were largely developed on appeals to anatomy as well as evidence from manipulations of neuromodulatory systems during behavior. These theories have been further refined with observations of the activity of neuromodulatory neurons themselves, providing clues as to which computations are performed to enable meta-learning.

Acetylcholine has been implicated in the working memory of a sensory stimulus (Fransén et al. 2002, Hasselmo 2006, Decker & Duncan 2020), pattern completion and retrieval (Hasselmo et al. 1996, Haam & Yakel 2017, Záborszky et al. 2018), enhancing attention (Gil et al. 1997, Kimura et al. 1999, Hsieh et al. 2000, Klinkenberg et al. 2011, Decker & Duncan 2020), and promoting switching between behavioral modes that enables flexibility (Honey et al. 2017). The activity of some optogenetically identified acetylcholine neurons in the basal forebrain shows interesting dynamics over multiple timescales, responding to rewards and punishments, even more so after surprising ones (Hangya et al. 2015, Laszlovszky et al. 2020). A separate population of cholinergic neurons in this region predicted behavioral performance (Laszlovszky et al. 2020). Theoretical work proposes that basal forebrain acetylcholine neurons may track the expected uncertainty of correlative relationships in the environment in order to guide attention, learning, and inference (Yu & Dayan 2005). For instance, expected uncertainty can be used to slow learning when the

variability of an outcome is well known; one should not update their well-established belief about the probability of a fair coin flip if the coin happens to land heads up several times in a row.

Manipulations of the noradrenergic system result in alterations of sensory processing, memory formation, attention, working memory, and other cognitive functions (Moore & Bloom 1979, Aston-Jones & Cohen 2005a, Sara 2009). Neurons in the locus coeruleus, the region that provides most of the noradrenergic input to the forebrain, respond to rewarding and punishing outcomes, the cues that predict them, and goal-directed behavior (Sara & Segal 1991, Aston-Jones et al. 1997, Bouret & Sara 2004, Kalwani et al. 2014) as well as the first few presentations of salient sensory stimuli (Hervé-Minvielle & Sara 1995). In reversal tasks, contingencies between stimuli or actions and rewards are reversed, and the cue- or action-related activity adapts rapidly during behavioral adaptation. Optogenetically identified norepinephrine neurons in locus coeruleus increase firing rates preceding an expected predictive cue and are inhibited during consumption of an expected reward (Xiang et al. 2019, Yang et al. 2021). The first time that the rule for whether a cue or behavior predicted reward was switched, firing rates increased, but not for subsequent switches. These and other findings have led to theories that norepinephrine tracks unexpected changes in the environment or task state that fall outside of the typical, expected uncertainty (Yu & Dayan 2005, Dayan & Yu 2006). This unexpected uncertainty signal can detect change and is used to interrupt ongoing functions in downstream regions (Tervo et al. 2014), potentially enhancing learning. This hypothesis encompasses both the adaptive gain theory, which suggests a role for norepinephrine in switching between exploration and exploitation (Aston-Jones & Cohen 2005a,b), and the network reset theory, which proposes that behavioral flexibility is driven by norepinephrine-mediated functional reorganization in cortex (Bouret & Sara 2005).

Serotonin neurons have also been shown to modulate flexible behavior in response to changes in correlative relationships in the environment, like those between actions or stimuli and the outcomes they tend to predict (Clarke et al. 2004, 2007; Boulougouris & Robbins 2010; Bari et al. 2010; Brigman et al. 2010; Matias et al. 2017; Iigaya et al. 2018; Grossman et al. 2022). The activity of serotonin neurons in dorsal raphe tracks reward statistics across cues and actions (Liu et al. 2014, Cohen et al. 2015, Y. Li et al. 2016, Matias et al. 2017), consistent with a role in tracking the uncertainty of a behavioral policy (not just a specific action) to guide how quickly new information should be incorporated into behavior (Grossman et al. 2022).

Meta-learning computations introduce more decision variables that would require persistent representation between choices that are updated when new information is observed. For example, serotonin neurons represent the expected uncertainty of a behavioral policy over many seconds and track unexpected uncertainty—which is hypothetically used to update expected uncertainty—at the time of the outcome (Grossman et al. 2022). The theories outlined above would then predict that these meta-learning variables would modulate other persistent decision variables and how they are updated by new information. How are decision variables (not just those proposed by the reinforcement learning framework) maintained in the nervous system in the times between choices? How are these persistent representations stabilized and modulated to drive flexible behavior? These are fundamental, unanswered questions about timescales.

HOW CAN NEURONS PRODUCE LONG-LASTING DYNAMICS TO GENERATE BEHAVIOR?

In maintaining activity on the timescale relevant to cognition and behavior, some neurons have certain intrinsic mechanisms that allow them to fire action potentials persistently (Major et al. 2004). Spinal motor neurons maintain persistent firing through plateau potentials (Kiehn & Eken 1998). Once a plateau potential has begun, a neuron can fire action potentials persistently without any synaptic drive. Pyramidal cell dendrites in cortex and hippocampus are also able to produce

local plateau potentials in the dendrite and cell body that are mediated by NMDA receptor activation (Milojkovic et al. 2004). These potentials may enable persistent or burst firing modes.

Even these intrinsic mechanisms for persistent activity require synaptic activity to initiate; without synaptic connectivity, most neurons are restricted in their ability to produce and maintain activity over longer intervals. Synapses and recurrent connectivity allow single neurons and populations to fire persistently and thus are able to represent task-relevant variables on the timescales of hundreds of milliseconds to minutes. Modeling and in vitro studies have shown that single neuron properties, along with plasticity mechanisms, can work together with circuit structure to allow for different, stable modes of firing in those single neurons (Major et al. 2004).

The oculomotor integrator is a canonical circuit that produces long-lasting activity changes across vertebrates (Cannon et al. 1983, Arnold & Robinson 1997). Located in the brainstem, these neurons serve to integrate eye velocity into position to stabilize gaze. Classic work in monkeys led to the hypothesis that oculomotor integrator neurons make excitatory synapses with each other to maintain persistent activity as long as the eye is held in position (Aksay et al. 2003). A recent study used electron microscopy to reconstruct the synaptic connections among oculomotor integrator neurons in the larval zebrafish (Vishwanathan et al. 2017). They found evidence of synaptic connections among integrator neurons, indicating that recurrent connectivity serves to maintain persistent activity in this circuit. Is recurrent connectivity a more general circuit motif for maintaining persistent activity changes?

Models of persistent activity have relied on recurrent connectivity among excitatory neurons, a feature of frontal cortex pyramidal neurons that has been studied extensively in slice preparations (Wang et al. 2006). Early theories proposed that fluctuations in synaptic inputs produce higher probabilities that the membrane potential will cross a threshold, resulting in increased spiking rates (Wang 1999, Brunel & Wang 2001). Indeed, pyramidal neurons in neocortex operate in a high-conductance state, thought to arise from their large number of synaptic inputs (Steriade et al. 2001, Destexhe et al. 2003, Zagha & McCormick 2014). Certain motifs in circuit structure that include inhibition, such as feedforward inhibition and disinhibition, likely also aid in persistent activity (Pressler & Strowbridge 2006, Lim & Goldman 2013). These patterns of connectivity also coordinate persistent activity, leading to rhythmic oscillations at the level of field potentials. This rhythmicity may also contribute to the endurance of persistent activity.

Neurons in premotor (Inagaki et al. 2019) and medial frontal cortex (Kim et al. 2021) of mice show persistent increases in membrane potential during motor preparation or reward anticipation. Expectation-related signals such as these may contain information about timing and may aid in gating relevant behavior and sensory information. They also likely contribute to learning, providing a potential mechanism for the comparison of expectations to actual outcomes or the maintenance of other decision variables. Recent work indicates that persistent spiking rate changes in these cells arise from increased mean and variance of membrane potential changes (Kim et al. 2021) that can be explained by attractor dynamics of recurrent connections within cortex, as well as via long-range connections with thalamus (Guo et al. 2017, Wang et al. 2021). Consequently, the relevant spatial scale of persistent activity varies from subcellular up to network mechanisms. While many studies, like those described above, have focused on the relationship between persistent activity of single neurons in relation to task and cognitive variables, information may be represented on all of these spatial scales (Barack & Krakauer 2021).

HOW CAN LONG-LASTING DYNAMICS BE MODULATED TO ACCOMMODATE FLEXIBILITY?

Change in the environment and in motivation is inevitable, so behavior and the activity responsible for it must be flexible. In addition to neural activity (Bernacchia et al. 2011), these external and

internal changes occur at different timescales themselves (Soltani et al. 2021). A sudden loud noise is temporally distinct from day turning into night, just as the pain of an acute injury is much faster than the gradual creeping in of hunger. When observed over sleep/wake cycles, most neurons exhibit substantial state-dependent changes in baseline firing rates (for review, see Navarro-Lobato & Genzel 2019). In a related way, many neurons also show differences over light and dark cycles. During the day, neurons in the suprachiasmatic nucleus are highly depolarized by various calcium, sodium, and hyperpolarization-activated, cyclic nucleotide–gated currents. Inputs from the retina, among other feedback, contribute to persistent activity patterns of these neurons in their sensitized state (Colwell 2011). Local circuitry also allows these neurons to maintain rhythms in activity without input from other regions. At night, changes in transcription and translation as well as differences in synaptic input result in decreased membrane potentials and substantial inhibition. Rhythms over such long timescales allow for the enhanced contribution of slower, protein expression–dependent mechanisms for regulating activity on more immediate timescales. Unsurprisingly, changes in long-lasting dynamics are driven by changes in the world and rely on multiple mechanisms across temporal and spatial scales.

Long and short timescale information about internal state also drives changes in ongoing activity. Agouti-related peptide (AgRP) neurons in the hypothalamus are modulated by ghrelin (released by the stomach) and leptin (released by fat stores), hormones that indicate hunger and satiety, respectively. Artificial stimulation of these neurons incites feeding, even in satiated mice (Aponte et al. 2011, Krashes et al. 2011). Recordings from optogenetically identified AgRP neurons in behaving mice showed relatively steady firing rates over the course of minutes (Mandelblat-Cerf et al. 2015). These recordings revealed changes in those rates between morning and night, mapping onto differences in typical mouse feeding patterns. Changes in intrinsic excitability across these longer timescales are mediated by transcriptional changes in these neurons (Cedernaes et al. 2019). These changes correlate with sleep/wake cycles and satiety levels, potentially aligning the latter with the former. On this timescale, structural changes also play a role. During fasting, spinogenesis occurs on AgRP dendrites (Liu et al. 2012). On timescales of learning and decision-making, firing rates of these neurons were elevated in food-deprived mice but dropped abruptly when food was expected, before consumption (Mandelblat-Cerf et al. 2015). Firing rates of AgRP neurons also demonstrated phasic dynamics locked to bouts of licking. There is evidence that local connectivity and long-range inputs contribute to both of these phasic and persistent activities (Cowley et al. 2001, Krashes et al. 2014, Branco et al. 2016). For example, AgRP neurons inhibit local proopiomelanocortin neurons, which have opposing effects on feeding downstream (Cowley et al. 2001). AgRP neurons are also reciprocally connected with paraventricular hypothalamus, whose inputs excite AgRP neurons (Krashes et al. 2014).

In these two examples, specific circuits receive direct, multitimescale information about internal and external state that mediates changes in ongoing activity in order to drive changes in behavioral state. These behavioral changes seem to be mediated by distinct, opposing pathways, like the antagonism between AgRP and proopiomelanocortin neurons. How are less drastic forms of flexibility, like modulating an ongoing cognitive process (e.g., meta-learning), implemented in neural structures? And how does the brain drive flexibility across larger spatial scales, like the distributed networks implicated in learning and decision-making? While the answers to these questions are still largely unknown, decades of research point to a role for neuromodulators in mediating this type of flexibility.

NEUROMODULATORS AND NEURAL FLEXIBILITY

When considering decision-making, even for the slower internal and external changes, evidence is often observed and integrated on shorter timescales—a person may note changes in light at

discrete times during the day or the increase in hunger at different time points before seeking sustenance. Other sensory feedback, like the receipt of valued outcomes, also often happens quickly, even if this feedback indicates environmental change on longer timescales. So despite variability in the impact new information has on beliefs and behavior, the updating and representation are still often happening on the same neural timescale. In a volatile environment, for example, the expected value of an action may be influenced more by a single outcome, but that decision variable is still being represented in neural activity for the same duration between choices. If the decision variable is being represented by the magnitude of firing rates (Samejima et al. 2005, Cai et al. 2011, Wang et al. 2013, Tsutsui et al. 2016, Bari et al. 2019), that activity needs to be more sensitive to outcomes, but just as persistent. If that information is being represented in populations, the same logic still applies. In the case of multiple experts, the contributions of separate learning systems (e.g., fast and slow) may be mediated to suit the environment. This organization would still require persistent representations of decision variables but also some mechanisms for modulating how they drive behavior. How is activity on these various spatial scales—in firing rates and across regions—modulated to meet changing internal and external states? How are multiple, stable modes of persistent activity achieved within circuits and networks?

Pervasive neuromodulatory neurons and their distributions of assorted receptors regulate cell, circuit, and network function to tune ongoing activity and enable flexibility (Marder & Thirumalai 2002). Neuromodulators have multiple mechanisms for modifying ongoing neural activity. They have been shown to modulate the excitability of single neurons through an assortment of ionotropic and metabotropic receptors that can excite or inhibit cells for milliseconds to seconds. The differential effects of neuromodulators on neuron subtypes, like inhibitory and excitatory cells, can shape circuit dynamics. Long-range inputs and outputs can also be differentially modulated, resulting in changes in network activity. These capacities to simultaneously enact opposing effects across spatial scales put neuromodulatory systems in a unique position to enable flexibility in neural activity and behavior. Machine learning research has even taken inspiration from these systems, employing principles of neuromodulation to enable flexibility in artificial systems that learn multiple tasks or behaviors (Miconi et al. 2020, Vecoven et al. 2020). Here, we briefly discuss some of the cell, circuit, and network effects of serotonin. We also mention other neuromodulators that have received attention in this domain: dopamine, norepinephrine, and acetylcholine, although they have been reviewed extensively elsewhere. We also note the almost-entirely unknown combinatorial functions of these neuromodulators.

Serotonin neuron axons pervade the central nervous system, and its signals are interpreted by at least 14 subtypes of receptors (Vilaró et al. 2020), not including gene and splice variants. In slice preparations of mouse medial prefrontal cortex, brief pulses of serotonin drive excitatory, inhibitory, and biphasic responses in separate groups of layer 5 pyramidal neurons (Stephens et al. 2014). Serotonin application also produced these effects when current was injected into the recorded neurons, revealing persistent modulation of activity that lasted tens of seconds (Stephens et al. 2014). It was also found that the direction of the modulation mapped onto the projection pathway of the neurons, demonstrating the ability of serotonin to modulate persistent activity in single neurons as well as mediate the relative strengths of a region's outputs. Another study found that serotonin enhanced the excitability of inhibitory interneurons in the same region, enhancing responsivity to gamma-frequency inputs (Athilingam et al. 2017), a frequency associated with tasks that require working memory (Howard et al. 2003). Serotonin also modulates gamma-band activity in cortex in vivo (Puig et al. 2010), providing further evidence for its ability to modulate coordinated persistent activity.

The effects of inputs to a target region may also be gated by serotonin neurons. Presynaptic serotonin receptors gate callosal and hippocampal inputs to prefrontal cortex (Kjaerby et al.

2016). In visual cortex, despite expression of excitatory and inhibitory serotonin receptors, iontophoretic application of serotonin in awake, behaving monkeys almost uniformly decreases firing rates (Seillier et al. 2017). Given the local precision of neuromodulator delivery, the unidirectional effects are likely mediated by local circuit interactions. Functionally, this manipulation resulted in a decrease in the gain of responses to visual stimuli, tempering bottom-up signals, without affecting the selectivity. Serotonin neurons' effects on persistent activity during behavior are likely specific to each region and are still largely unexplored. While similar patterns of activity have been observed in individual neurons, there is considerable heterogeneity, and it is not yet clear that response profiles predict anatomy. Regardless, these findings and others demonstrate the existence of multiple mechanisms for modifying ongoing activity on behaviorally relevant timescales and across spatial scales.

Related roles in the flexibility of neural processes have been ascribed to other neuromodulators as well. Acetylcholine can enable persistent firing through plateau potentials (Andrade 1991, Fraser & MacVicar 1996, Haj-Dahmane & Andrade 1998, Egorov et al. 2002) and modify network interactions, like biasing cortex to input from thalamus as opposed to cortex (Hasselmo et al. 1996, Gil et al. 1997, Kimura et al. 1999, Hsieh et al. 2000). Norepinephrine can also enable persistent firing in prefrontal cortex neurons (Kovács & Hernádi 2003, Dembrow et al. 2010, Zhang et al. 2013) while suppressing it in hippocampus through cellular mechanisms (Valero-Aracama et al. 2021). Dopamine modulates excitatory inputs to prefrontal cortex (Seamans et al. 2001) as well as the excitability of its output neurons (Yang & Seamans 1996, Chen et al. 2004), potentially increasing the robustness of the persistent activity (Durstewitz et al. 2000, Furman et al. 2021). These mechanisms for stabilizing persistent representations, biasing information streams, and mediating network interactions, among others, demonstrate the capacity of neuromodulatory systems to modulate ongoing activity across spatial and temporal scales. These mechanisms were investigated on shorter timescales relevant to the experimental design but are likely sustained by the persistent activity of neuromodulators observed in vivo. The persistence of the effects of neuromodulators is also a consequence of subcellular and plasticity mechanisms (Lee et al. 2021, Zhang et al. 2021).

Studies of neuromodulatory systems individually have brought considerable understanding of their functions, but much less is known about their interactions (Briand et al. 2007, Avery & Krichmar 2017). Neuromodulatory systems target overlapping areas (Foote & Morrison 1987), and their receptors are often expressed in the same neurons, even colocalizing in the same dendrites (Mitrano et al. 2014). Neuromodulators interact with each other in downstream targets through presynaptic receptors (Beani et al. 1978). The regions composed of neuromodulatory neurons that target the forebrain (i.e., dorsal raphe, basal forebrain, locus coeruleus, and ventral tegmental area) are also all connected, either in one direction or reciprocally (Briand et al. 2007).

These systems even have some similar functional effects, like those of serotonin and norepinephrine on the receptive field properties of sensory neurons (Hurley et al. 2004). Long-term, drastic manipulation of one system, like cellular ablation, often has very minor effects on observable behavior. Mice that cannot make dopamine, for example, are still capable of reward learning (Cannon & Palmiter 2003). These subtle effects might be the result of compensatory mechanisms between the systems or overlapping functions—a type of degeneracy that may be indicative of their fundamental importance to healthy brain function (Edelman & Gally 2001, Goaillard & Marder 2021).

There are some findings about the functional consequences of these interactions, in circuits and behavior, but most rely on pharmacological manipulation of individual receptor subtypes. In this way, acetylcholine has been shown to modulate the release of norepinephrine, dopamine, serotonin, and acetylcholine itself via presynaptic nicotinic receptors, for example

(Briand et al. 2007). There is, of course, insight to be gained from such experiments, especially considering that certain receptor subtypes may be selectively activated by different concentrations of neuromodulator (Briand et al. 2007), which may be a consequence of different modes of neuromodulatory neuron firing. However, little is known about the interactions that occur consequent to endogenous neuromodulator release, especially during awake behavior.

Theories of neuromodulatory neuron function, like those discussed above, have largely focused on individual systems. Some have tried to unite these separate functions into a single framework (Doya 2008). The aforementioned ideas about acetylcholine tracking expected uncertainty and norepinephrine tracking unexpected uncertainty come from the same theoretical framework, proposing both conflicting and cooperative interactions (Yu & Dayan 2005). Another theory posited opponent interactions between dopamine and serotonin in reporting rewards and punishments (Daw et al. 2002). In every case, interactions occur through converging effects on other variables or processes that do not necessitate (but could entail) direct interactions between neuromodulatory systems. While it is still useful to investigate these systems in isolation, a comprehensive understanding of neuromodulator function must include their interactions and combinatorial functions.

The omnipresent anatomy and diverse receptors of neuromodulatory systems have, for some time, led to speculation about these systems' role in regulating neural and behavioral state. Such a general function has been largely substantiated by the mechanisms and behavioral effects summarized here, among many others, but more specific descriptions are necessary. There remains a substantial gap between the cellular and circuit effects found in vitro and the behavioral consequences of manipulation in vivo. Research has clearly demonstrated the capacities of neuromodulators to effect change in neural activity from subcellular signaling cascades to network-level synchrony and from immediate changes in membrane potential to long-term plasticity. But many questions remain about how these spatially and temporally diverse mechanisms converge to modulate information processing on the timescale of cognition and behavior. Observing the dynamics of neuromodulatory neuron activity, neurotransmitter release, and the corresponding postsynaptic effects on ongoing activity during awake behavior will be crucial for a more comprehensive understanding of these systems. The cognitive variables of internal and external state that the brain employs to generate behavior are often hidden from the outside observer. Consequently, careful behavioral design and computational models will continue to be necessary to describe the representational nature of ongoing activity and how it is modulated to meet the ever-changing demands of self and environment.

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