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Neuromodulation of Brain State and Behavior

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Abstract

Neural activity and behavior are both notoriously variable, with responses differing widely between repeated presentation of identical stimuli or trials. Recent results in humans and animals reveal that these variations are not random in their nature, but may in fact be due in large part to rapid shifts in neural, cognitive, and behavioral states. Here we review recent advances in the understanding of rapid variations in the waking state, how variations are generated, and how they modulate neural and behavioral responses in both mice and humans. We propose that the brain has an identifiable set of states through which it wanders continuously in a nonrandom fashion, owing to the activity of both ascending modulatory and fast-acting corticocortical and subcortical-cortical neural pathways. These state variations provide the backdrop upon which the brain operates, and understanding them is critical to making progress in revealing the neural mechanisms underlying cognition and behavior.

Contents

INTRODUCTION

The activity of the brain is constantly varying, wandering between states, and profoundly affecting not only our neural responses to sensory inputs but also our ability to process this influx of information, make decisions, and take appropriate action. Indeed, our entire inner world, both cognitively and emotionally, is in a constant state of flux, flittering from state to state, thought to thought. Ever since Richard Caton (1887) performed the first recordings from the mammalian brain in the late 1800s, it has been known that the patterns of activity generated depend on the behavioral state of the animal.

Today, with advances in imaging technology, it is possible to monitor network activity throughout large parts of the brain at a wide variety of spatial and temporal scales. These technological advances have led to a new level of observation of rapid variations in the waking brain and how these influence sensory processing, cognition, and motor responses. This topic is extensive and beyond the limitations of the present format. For this reason, we focus here on new findings that help us bridge between mouse and human, bringing together information from neurons, synapses, and neuromodulators to the large-scale network activity [e.g., as revealed by functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG)] associated with perception and cognition. We first discuss a tentative framework for classifying variations of spontaneous brain activity into states and how these impact neural circuit function and behavior. We then provide a review of recent literature on the modulatory and network mechanisms that may underlie these state changes.

What is a brain/behavioral state, and why is it important? To adequately meet their demands, animals must stitch together sensation, memories, expectations, and motor commands. All of these tasks run on a highly variable background of ongoing neuronal activity in the brain. Rather than reflecting random electric noise generated by ensembles of neurons, these variations represent a multiplexing of the various needs of the nervous system and are tightly linked to the behavioral context of the animal. This behavioral context relates in part to changes in the level of arousal, motor activity, and attention. Apart from behavioral context, variations in ongoing activity are also impacted by a wide variety of housekeeping tasks, and some patterns of activity may even simply arise as a byproduct of the brain's anatomical and physiological architecture (McCormick & Bal 1997, McCormick et al. 2015, Steriade et al. 1993, Tononi & Cirellu 2014, Xie et al. 2013).

The state of the brain at any given time can be thought of as a point in an extremely high-dimensional space, where its position along each dimension corresponds to the activity of a relevant neural unit, such as a neuron, neuronal group, or brain region. Over time, constantly varying activity manifests as a trajectory in this state space (**Figure 1*a***). Not all locations in the state space

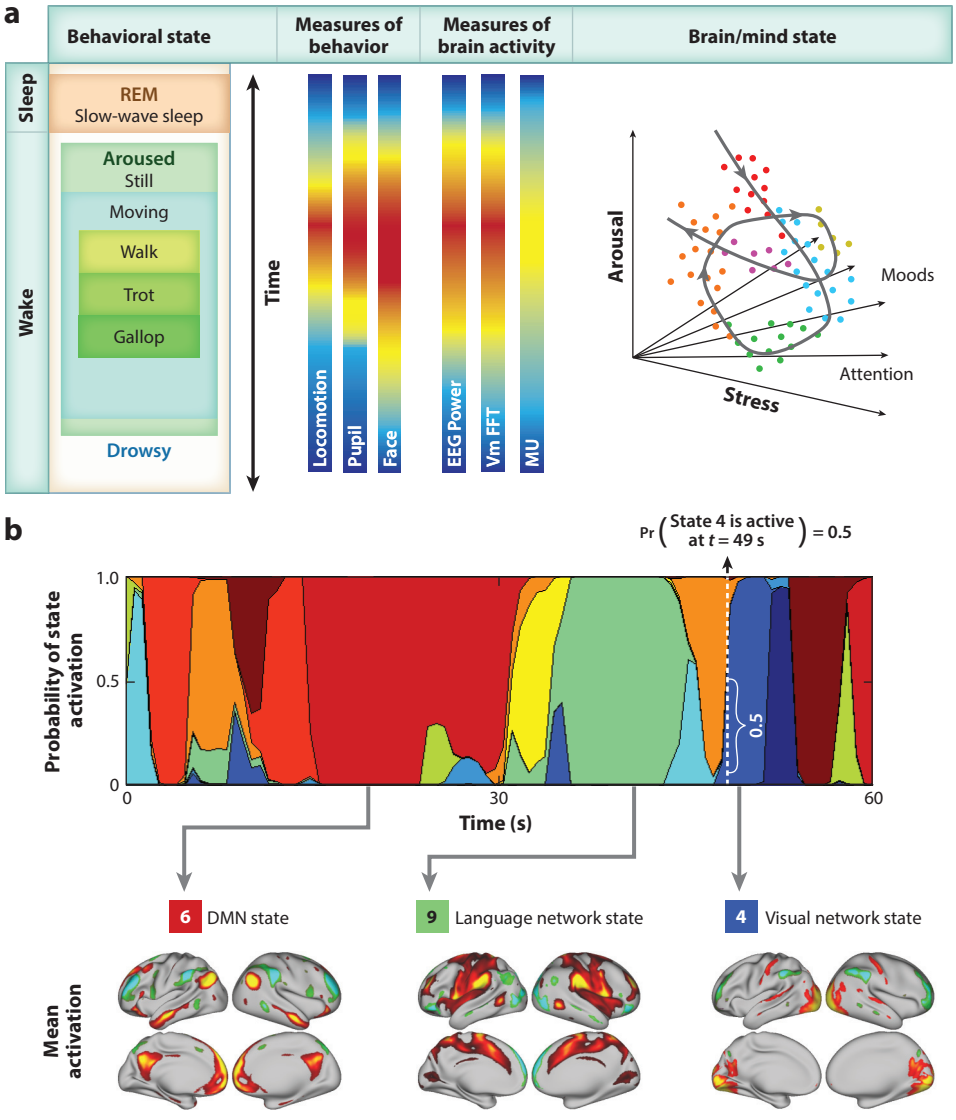


Figure 1

Behavior and brain activity move through preferred states. (*a*) Characterization of behavioral and brain states. Behavioral state typically consists of nested states. Sleep contains substates such as REM and slow-wave sleep. Waking can be characterized along multiple behavioral or neural dimensions, which vary rapidly or slowly over time. We hypothesize that plotting these variables in high-dimensional space would result in clouds of preferred states (*colored dots*) and preferred trajectories through these states. Not all states would be discrete—some states would be connected together as a continuum. (*b*) Brain state continuously varies in human fMRI activity. A hidden Markov model estimates a number of brain networks (or states) that are common to all subjects, together with a specific state time course for each subject indicating when each state is active. The states are characterized by their mean activation and functional connectivity matrix. (*Top*) Sixty-second section of the state time course for one example subject. (*Bottom*) Mean activation maps (projected from 50-dimensional independent component analysis space to brain space) for 3 of the 12 inferred states. Panel *b* adapted with permission from Vidaurre et al. (2017). Abbreviations: DMN, default mode network; fMRI, functional MRI; Pr, probability; REM, rapid eye movement.

are equally probable. In fact, given anatomical and functional constraints, large regions of state space are prohibited or never visited (Luczak et al. 2009). Among the permitted regions, there are certain locations that are visited much more often than others, forming discrete states such as awake, attentive, moving, etc. Within each discrete state, spontaneous activity may vary across different substates (such as quiescence versus locomotion) and sub-substates (such as walking versus running), which may be discrete but connected (e.g., walk, trot, gallop) or vary along a continuum (e.g., walking slowly to walking quickly). While externally observed variables such as movements and pupil size explain a significant fraction of the variance in ongoing brain activity (**Figure 2*a***), the inner lives of our thoughts and emotions are richer and more varied than our externally observable behavior may suggest. We take it as a given that the measure of a sufficient, but not exhaustive, number of behavioral and brain variables can well define the varied states of this behavioral/neural life (**Figure 1*a***).

We propose several basic features of brain states. First, variation in brain states is a high-dimensional property. The dimensions may be independent, interdependent, or simply correlated. Measuring the dimensions that have the most explanatory power would be desirable. Second, spontaneous variation in brain states is a nested property. Each state will exhibit substates of neuronal dynamics among a variety of interacting subsets of neurons and networks. Third, brain states can change discretely or continuously. Above we have emphasized discrete examples, yet continuous changes are possible, such as a continuum of pupil size or movement speed, or continuous variation in the activity of a network. Fourth, changes in externally observable states (such as pupil diameter or movements) are rooted in changes in brain state, yet brain states can vary without clear external markers. Even so, these internal variations in brain state may have powerful effects on perception, cognition, and behavior. While brain and behavioral states inhabit a high-dimensional space (e.g., there are a significant number of cognitive, affective, and other states), current research into circuit mechanisms has been largely limited to a much smaller state space, such as variations in arousal, attention, engagement, and movement. For the remainder of this review, we focus on current research on this more limited set of brain/behavioral states.

STATE INFLUENCES CORTICAL ACTIVITY AND DETECTION/DISCRIMINATION PERFORMANCE

Mouse Studies

The mouse is an ideal system to investigate the cellular and network mechanisms of state-dependent variations and their relevance for behavior owing to the multiple genetic-based tools available. Recent studies in mice have examined the effects of variations within the waking state on go/no go and 2-alternative forced/unforced choice signal-detection tasks (Bennett et al. 2013; Jacobs et al. 2018; Lee et al. 2016; Lovett-Barron et al. 2017; McGinley et al. 2015a; Neske et al. 2019; Sachidhanandam et al. 2013; Salkoff et al. 2020; Speed et al. 2019, 2020; Vyazovskiy et al. 2011; Zatka-Haas et al. 2018). In general, these studies find a significantly reduced ability of mice to accurately and quickly respond to threshold sensory stimuli if those stimuli are presented when slow oscillatory activity is prominent in the cortex, particularly if the animal exhibits overt signs of drowsiness such as immobility, small pupil diameter, or prominent down states in cortical activity (Lovett-Barron et al. 2017; McGinley et al. 2015a; Speed et al. 2019, 2020; Vyazovskiy et al. 2011). If, however, the sensory stimuli are well above threshold, animals appear able to respond even in this state (Einstein et al. 2017, Fanselow & Nicolelis 1999).

Examining the effects of cortical state on performance in mice has revealed multiple components that vary in both spatial (e.g., global versus local) and temporal (e.g., fractions of a second

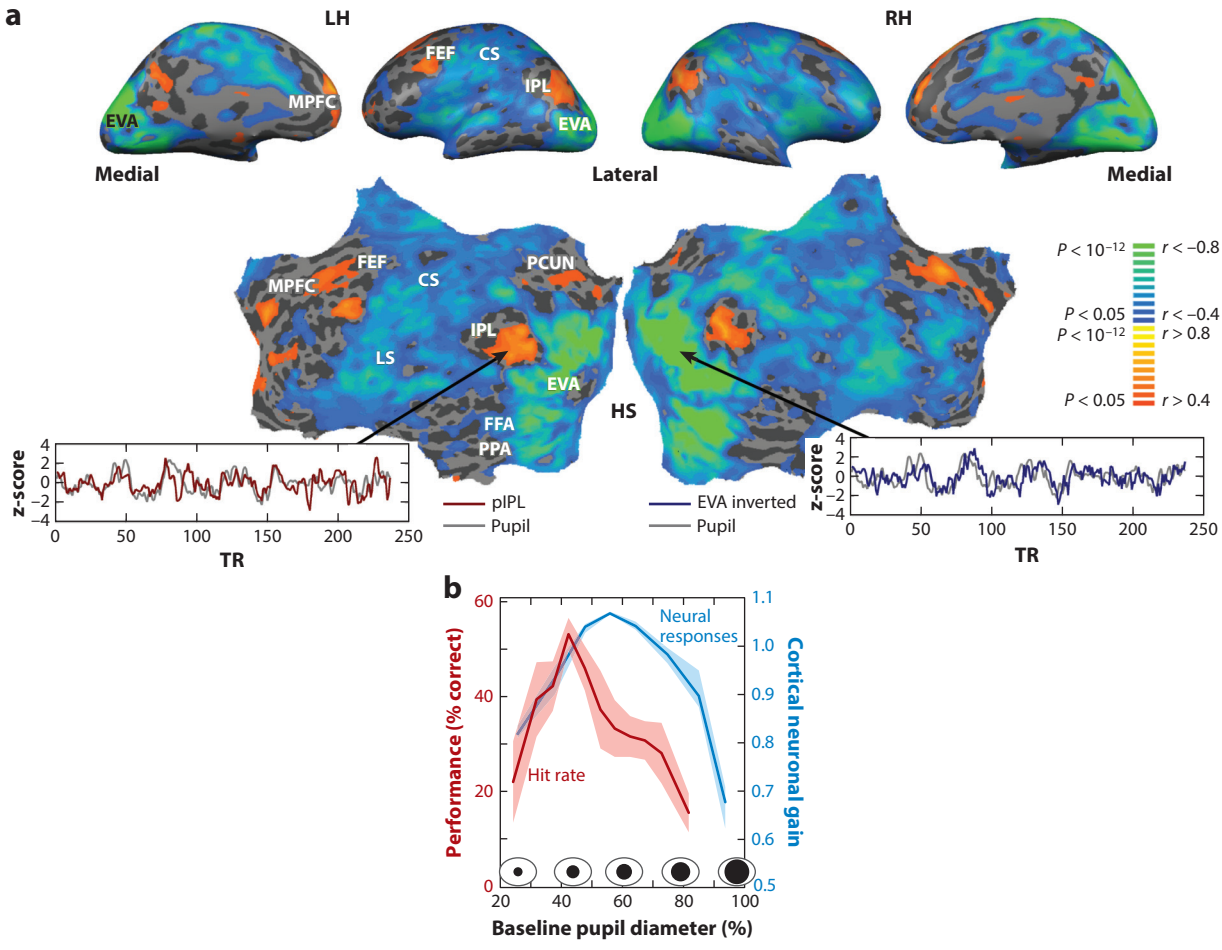


Figure 2

Pupil diameter can be measured in both animals and humans and reveals variations in brain state. (*a*) Spatial topography of pupil-BOLD signal correlations in rest-fixation experiment. Single-subject correlation map, projected on an inflated (*top*) and unfolded cortex (*bottom*). Note that in both maps, sensorimotor areas are negatively correlated and default mode areas are positively correlated to the pupil diameter predictor. Color scale indicates statistical significance. Yellow/orange regions represent areas for which the BOLD signal was positively correlated to the pupil predictor, whereas blue/green regions indicate negative correlations. Panel *a* adapted with permission from Yellin et al. (2015). (*b*) Optimal performance on an auditory detection task occurs at intermediate levels of arousal in mice, as revealed by pupil diameter. Performance on the detection task varies with pupil diameter. Hit rate (*red*) peaked at intermediate pupil diameters, similar to the Yerkes-Dodson curve (Yerkes & Dodson 1908). Similarly, responses to sound in the auditory cortex also exhibited an inverted-U relationship with arousal. Small or large pupil diameters, indicating low or high arousal levels, were associated with nonoptimal task performance and auditory cortical responses. Panel *b* adapted with permission from McGinley et al. (2015a). Abbreviations: CS, central sulcus; EVA, early visual cortex; IPL, inferior parietal lobule; IPS, intraparietal sulcus; LH, left hemisphere; LS, lateral sulcus; MPFC, medial prefrontal cortex; PCUN, precuneus; RH, right hemisphere.

to hours) extent. For example, cortical activation (i.e., slow oscillations are suppressed) is typically broad and does not vary with sensory modality being tested when mice perform sensory discrimination tasks that do not require spatial or selective attention (Jacobs et al. 2018). In these tasks, cortical activation was found to relate to task engagement rather than to an increase in performance accuracy (Jacobs et al. 2018). However, mice are able to attend to specific sensory

(e.g., visual) locations, and this attention is associated with an enhanced sensory-evoked response in the corresponding cortical region, in comparison to cortical responses to stimuli in unattended locations (Speed et al. 2020). Within the temporal domain, tracking the arousal state of a head-fixed mouse through pupillometry reveals rapid (seconds) and continual changes that are highly correlated with the patterns of activity generated in the neocortex and hippocampus and the behavioral performance of the animal. Sorting the task performance of the mouse by the pupil diameter at the onset of the trial revealed an inverted-U relationship between arousal and task performance (e.g., hit rate), which is remarkably similar to the amplitude (relative to pretrial spontaneous activity) of the neuronal response initiated by complex sounds in the auditory cortex (McGinley et al. 2015a) (**Figure 2*b***). Optimal performance was achieved in a state of quiet engagement or readiness, in which sound-evoked activity in the auditory cortex was robust and occurred on a background of relative quiescence. Reduced accuracy on the behavioral task was associated with the appearance of slow oscillatory activity in cortical networks or with high arousal and/or locomotion (McGinley et al. 2015a).

Why might these two states (low arousal with slow oscillations or high arousal with or without locomotion) alter the ability of an animal to detect a near-threshold stimulus? To perform a stimulus-detection/discrimination task, the nervous system must detect the stimulus and propagate an accurate representation through the decision and motor response networks, with the activity neither growing disproportionately nor weakening to ineffectiveness. We hypothesize that the presence of large, spontaneous, slow oscillations disrupts the accurate propagation of sensory-decision-response activity. At the neural level, the delivery of sensory stimuli during periods of prominent slow oscillatory activity, such as drowsiness, inattentiveness, and sleep (or anesthesia), often results in highly variable responses that can initiate either a weak response or a disproportionately large propagating wave of cortical activity, owing in part to the cyclical variations in network properties (Haider et al. 2007, Hasenstaub et al. 2007, Shu et al. 2003, Stroh et al. 2013, Zagha et al. 2013). Interestingly, induction of synchronized low-frequency (but not higher frequency) oscillations in area V4 of the primate visual cortex can significantly impair the ability of the animal to make fine sensory discriminations, confirming a disruptive influence of slow oscillatory activity on cortical sensory processing (Nandy et al. 2019).

Suppression of slow rhythms and the initiation of the activated or depolarized cortical state may tune sensory systems from one of detection to fine discrimination. In this theoretical framework, behavioral and cortical stillness (e.g., reduced activity), while also attentive and engaged, may be optimal for detection of sensory stimuli (McGinley et al. 2015b). The depolarization of cortical neurons associated with movement or arousal may enhance sensory discrimination, in part through multiplicative gain control, which is likely an important mechanism by which cortical neuronal networks control neuronal responsiveness and therefore the flow of information through the highly interconnected cortical network (Ferguson & Cardin 2020, Haider & McCormick 2009, Murphy & Miller 2003). Rapid multiplicative gain control can be generated through the activation of barrages of excitatory, balanced with inhibitory, synaptic potentials coming from other cortical or subcortical neurons (Haider & McCormick 2009, Haider et al. 2007, Murphy & Miller 2003), such as feedback from frontal motor control regions involved in movement or orientation (Bouvier et al. 2020, Guitchounts et al. 2020, Hill et al. 2011, Leinweber et al. 2017, Nelson & Mooney 2016, Schneider & Mooney 2018, Zagha et al. 2013).

Movement and/or arousal is strongly associated with the suppression of lower-frequency oscillatory activity in both cortical and subcortical structures (McCormick et al. 2015, Musall et al. 2019, Petersen 2019, Poulet & Crochet 2018, Reimer et al. 2014, Stringer et al. 2019, Vinck et al. 2015). At present, it is unknown if this is the result of the central neural mechanisms of movement generation, per se, or because movement is associated with increases in arousal

(McGinley et al. 2015b). Indeed, recent theories of the neural control of state propose that movement and arousal control systems are intimately interlinked (Liu & Dan 2019). In mice, movement has varied effects on cortical activity, depending on cortical region (McGinley et al. 2015b, Niell & Stryker 2010, Petersen 2019, Schneider & Mooney 2018, Shimaoka et al. 2018). Locomotion and facial movements (e.g., whisking) are typically associated with strong depolarizations in visual, auditory, and somatosensory cortical areas. Voltage-sensitive protein imaging, however, suggests that movement, and the associated change in state, may result in complex depolarization and hyperpolarization sequences of different cortical regions, particularly outside primary sensory cortex (Shimaoka et al. 2018). Interestingly, even though purposeful movement (e.g., locomotion or whisking) results in depolarization of pyramidal neurons in somatosensory, visual, and auditory cortical areas, the effects on responses to sensory stimuli are mixed, with a facilitation in visual neurons and a suppression in auditory and motor-cortical-projecting somatosensory cortical neurons (McGinley et al. 2015b, Petersen 2019, Poulet & Crochet 2018, Schneider & Mooney 2018, Yamashita & Petersen 2016). Whisking and/or walking not only decreases sensory-evoked responses in auditory and some somatosensory cortical neurons but also decreases the ability of animals to accurately detect weak stimuli (Kyriakatos et al. 2017, McGinley et al. 2015a). This is not to say, however, that movement suppresses all types of sensory encoding in these pathways. Movement, especially in the whisker system, is critical to detecting fine features of explored objects; active whisking appears to enhance, or at least not degrade, sensory coding in pathways hypothesized to be critical for object discrimination (Yamashita et al. 2013); and object detection can cause a prolonged depolarization in these neurons, even during whisking (Yamashita & Petersen 2016). In the mouse visual system, locomotion has a strong facilitatory effect on visual responses (Ayaz et al. 2013, Bennett et al. 2013, Niell & Stryker 2010, Polack et al. 2013) and, together with head movement–related effects, provides information that may be useful in distinguishing between self- and world-generated movements of visual scenes (Leinweber et al. 2017, Bouvier et al. 2020, Guitchounts et al. 2020). It is not yet clear how locomotion affects performance on visual tasks. In one study, locomotion had a mild enhancing effect on visual detection (Bennett et al. 2013), while in another, locomotion with high arousal was associated with decreased performance (Neske et al. 2019).

Not all of these state-dependent effects originate in the neocortex. In fact, state shifts affect nearly all, or all, parts of the nervous system (and body). Recordings from thalamic and prethalamic structures, and perhaps even the retina, exhibit changes with locomotion in their responsiveness to sensory stimuli (Erisken et al. 2014, McGinley et al. 2015a, Schröder et al. 2019, Steinmetz et al. 2019, Williamson et al. 2015). Any comprehensive theory of state-dependent behavior will need to take these broad effects into account.

Human and Nonhuman Primate Studies

Studies of state effects on performance and cortical neural activity in nonhuman primates have often focused on attentional effects in the visual system. Selective attention enhances behavioral performance (Anton-Erxleben & Carrasco 2013, Cohen & Maunsell 2011, Desimone & Duncan 1995, Maunsell 2015, Spitzer et al. 1988), increases the amplitude and reliability of evoked neuronal responses (Mitchell et al. 2009, Nandy et al. 2017, Reynolds & Chelazzi 2004), and decreases correlations between nearby neurons (Cohen & Maunsell 2009, Mitchell et al. 2009, Ni et al. 2018), especially at lower frequencies (<10 Hz) (Mitchell et al. 2009, Nandy et al. 2017). These effects vary with cortical layer and cell type (Nandy et al. 2017) and are similar to those occurring with arousal (Ruff et al. 2018). Although attention may induce neuronal effects that are similar in some regards to arousal, attention can exhibit much higher precision in both feature space and

time (e.g., shifting attention within fractions of a second to search for precise combinations of features such as a particular face or object) (Maunsell & Treue 2006, Nobre & van Ede 2018). The cellular, synaptic, and network mechanisms underlying changes in neuronal activity associated with changes in attention in nonhuman primates remain to be determined, but some progress has been made in recent years (e.g., Buschman & Kastner 2015). Interestingly, it was recently shown that spatial attention in mice similarly enhances neural responses and behavioral performance, as is found in primates (Speed et al. 2020). Mice may therefore serve as a model system in the future to dissect the precise neural mechanisms of some attention-related state changes.

Fewer studies in nonhuman primates have focused on state changes that are unrelated to attention. In one such study, the baseline activity of a higher visual area during a visual search task was found to correlate with the success rate of the monkey and to not be directly related to spatial attention (M. Zhang et al. 2014). The fluctuations of this baseline activity may have reflected changes in arousal, motivation, or intrinsic state and may therefore resemble arousal-related state changes reported in mice. Another nonhuman primate study in a different higher visual area found that desynchronization in the local population in the awake, activated state enhances information processing and behavior (Beaman et al. 2017). Interestingly, the local fluctuations in population synchrony observed in that study were found to be related to neither attention nor general arousal, suggesting that other mechanisms possibly related to emergent properties of the local circuit may contribute to spontaneous state fluctuations.

Important mechanistic insights into state changes in monkeys that further bridge the gap to the mouse literature were recently obtained in a patch-clamp study. Whole-cell recordings in the primary visual cortex of monkeys trained to maintain eye fixation revealed barrages of synaptic inputs that correlated with prominent, but isolated, low-frequency events in the local field potential (LFP) that were in some regards similar to those of mice in the quiet resting (non-movement) state (Tan et al. 2014). Visual stimulation during fixation resulted in prolonged depolarization and synaptic activity, similar to the activated cortical state associated with movement in mice (see above). This result suggests that the quiet resting state in both mice and primates is associated with the generation of intermittent action potentials resulting from synchronized (e.g., correlated) activity within a subpopulation of cortical (and subcortical) neurons, initiating barrages of synaptic potentials that summate and cause action potentials in other postsynaptic neurons. The activated state (e.g., active sensation, movement) may then be related to a cessation of these correlated clusters of action potentials and the generation of a more sustained depolarized state in which neurons are interacting at a faster time scale, as was previously demonstrated in waking cats (Steriade et al. 2001).

Studies in humans have examined neural state through fMRI, EEG, and MEG. As with animal studies, these investigations reveal the brain to be continuously active, varying according to cognitive, emotional, arousal, attentional, and other states. Rather than random, the resting-state activity of the human brain, as observed through fMRI and MEG, exhibits strong correlational relationships, such that subnetworks of cortical regions are activated with repeating spatiotemporal structure (reviewed in Petersen & Sporns 2015, Raichle 2015) (**Figure 1*b***).

As in animals, fMRI investigations in humans reveal that spontaneous activity can predict behavioral performance. Using threshold-level auditory/somatosensory detection tasks, it was found that prestimulus baseline activity in large-scale brain networks, including the thalamus, the salience network (including insular and anterior cingulate cortex), the frontoparietal network (FPN), and the default-mode network (DMN), influences detection behavior. Interestingly, higher prestimulus activity in the FPN and lower prestimulus activity in the DMN were found to bias subjects toward more hits in the somatosensory task (Boly et al. 2007) but more misses in the auditory task (Sadaghiani et al. 2009). Whether this reflects a genuine difference between

modalities remains to be tested. Using bistable visual stimuli, Hesselmann et al. (2008) revealed that prestimulus activity in visual regions selective for particular object categories (houses versus faces) influenced the subject's perception of an ambiguous image.

At the level of the EEG (or electrocorticogram), prolonged wakefulness and increased sleep need are associated with prolonged reaction times and increased power in regional slow and theta activity in humans (Bernardi et al. 2015, Nir et al. 2017). Unit recordings from the medial temporal lobe of patients following prolonged waking revealed increased reaction times in a visual categorization task that correlated with decreased neuronal response amplitude, longer latency in action potential responses, and reduced desynchronization in slower/theta frequencies (Nir et al. 2017). These results are reminiscent of the increased prevalence of slow oscillations, including down states (brief cessations of activity), associated with decreased task performance following sleep deprivation in rodents (Vyazovskiy et al. 2011).

The prominent spontaneous alpha (~10 Hz) oscillation is strongly correlated with changes in human perceptual behavior. Moreover, in line with the idea of nested brain states, both the power and phase fluctuations of alpha oscillation influence detection performance. Convergent results across visual and somatosensory domains suggest that reduced alpha oscillation power in sensory cortex is correlated with increased cortical excitability and biases the subject toward a higher hit rate in detection tasks (van Dijk et al. 2008, Weisz et al. 2014), perhaps through a change in detection criterion, without influencing sensitivity (Iemi et al. 2017). Interestingly, the phase of the alpha oscillation may modulate perception such that stimuli presented during the peak of an alpha wave recorded by EEG are more likely to be detected (Mathewson et al. 2009), and two consecutive stimuli presented within the same alpha cycle are more likely to be perceived as a single stimulus (Baumgarten et al. 2015, Chakravarthi & Vanrullen 2012).

Lower-frequency changes in cortical activity also have prominent effects on cognition and performance. One of the main forms of low-frequency variation in cortical activity and excitability is expressed in the EEG as a slow cortical potential (SCP), with the negative components of the SCP corresponding to cortical activation across a wide variety of tasks (Khader et al. 2008, Rockstroh et al. 1989). Spontaneous fluctuations in the SCP have the same organization as resting-state networks observed in fMRI (He et al. 2008), and negative SCP correlates with fMRI activation in simultaneous recordings (Kahn et al. 2013, Pan et al. 2013).

Recent evidence suggests that within the SCP frequency range (<5 Hz), infraslow activity (ISA) (<0.1 Hz) and delta-band activity (0.5–4 Hz) might reflect distinct physiological phenomena. The delta-band activity easily entrains to periodic external stimuli and can act as an instrument for attentional selection (Schroeder & Lakatos 2009). The ISA exhibits state-dependent (waking versus anesthesia) trajectories across cortical layers (Mitra et al. 2018) distinct from the delta activity, and its phase modulates power fluctuations of higher-frequency activity as well as human subjects' hit rates in a threshold-level detection task (Monto et al. 2008) (**Figure 3*c***). Therefore, contrary to a recent suggestion (Drew 2019), although vascular phenomena can contribute to ISA activity, the ISA band contains genuine neurophysiological phenomena of functional significance.

Recent work has further underscored the influence that prestimulus delta-range SCP activity wields on perceptual behavior. A study using LFP recording in the primary somatosensory cortex of awake mice found that the highly variable single-trial sensory-evoked responses could be significantly predicted by the power and phase of LFP in a 2-s prestimulus window (Sederberg et al. 2019). Using large-scale brain activity patterns from a 2-s prestimulus window, a recent MEG study in humans found that there are two separate spontaneous brain processes that influence object recognition behavior in distinct manners (Podvalny et al. 2019) (**Figure 3*a***). A non-content-specific general process (which is linked to moment-to-moment arousal fluctuations indexed by pupil size) influences recognition by shifting the detection criterion without

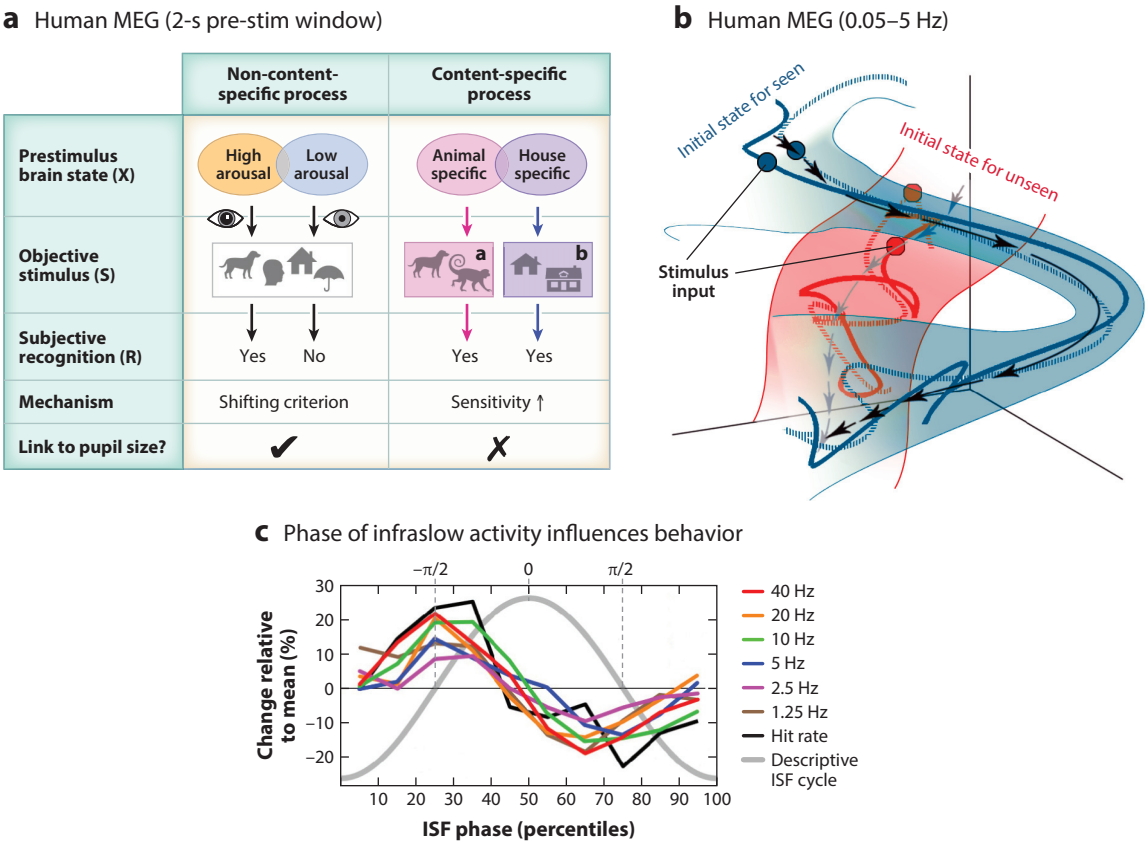


Figure 3

Variations in human state and effects on behavior. (*a*) Using whole-head magnetoencephalography (MEG), two separate spontaneous processes were discovered in the 2-s time window before the onset of a brief visual stimulus: A non-content-specific (NCS) general process indiscriminately influences visual object recognition by shifting the decision criterion regardless of the content of the stimulus. By contrast, a content-specific (CS) process influences visual object recognition of specific object categories by enhancing the recognition sensitivity (i.e., enlarging the distance between real and scrambled objects) for stimuli from a specific category. The NCS, but not CS, spontaneous process is correlated with spontaneous fluctuations in pupil size and hence is arousal linked. Panel *a* adapted with permission from Podvalny et al. (2019). (*b*) Trajectories of MEG activity on seen trials (*blue lines*) begin in a location distinct from those of unseen trials (*red lines*) for people performing a threshold-level visual perception task. The time of stimulus onset is indicated by circles, and different stimulus orientations are indicated by solid or dashed lines. For seen trials, the voyage of the trajectory through state space is characterized by a marked increase in velocity following stimulus onset, indicated by the length of black arrows. Unseen trials, on the other hand, only accelerate minimally following stimulus onset, indicated by the length of gray arrows. Seen and unseen trajectories remain well separated throughout the trial. For seen trials, across-trial variability decreases substantially following stimulus onset (*green shading*). Panel *b* adapted with permission from Baria et al. (2017). (*c*) The phase of infraslow activity [infraslow electroencephalography fluctuations (ISF); *gray line*] recorded by electroencephalography modulates higher-frequency activity power (*colored lines*) and hit rate (*black line*) in a threshold-level somatosensory detection task in humans. Panel *c* adapted with permission from Monto et al. (2008).

influencing sensitivity. This non-content-specific process operates such that, during heightened arousal, subjects are more likely to see an object regardless of whether it is present in the sensory input and what category it may be. By contrast, a content-specific spontaneous process influences object recognition in a category-specific manner. For example, within this process, a particular activity pattern may facilitate the recognition of animals, while a different pattern may facilitate

the recognition of houses. The content-specific process influences recognition by enhancing recognition sensitivity with no impact on criterion and is not correlated with pupil-linked arousal fluctuation (Podvalny et al. 2019).

What is the mechanism of the initial brain state's influence on perceptual behavior? Human and animal studies suggest that ongoing activity and evoked responses can negatively interact (Arazi et al. 2017, Baria et al. 2017, Churchland et al. 2010, He 2013, He & Zempel 2013, Sederberg et al. 2019, Steinmetz & Moore 2010). Under a negative interaction, higher prestimulus ongoing activity, particularly at lower frequencies (<10 Hz), results in a smaller stimulus-evoked activation or even a deactivation. This negative interaction leads to the often-observed stimulus-triggered, across-trial variability quenching. Building upon this observation, a recent MEG study showed that, depending on the initial state of the large-scale activity pattern in the SCP range, an identical threshold-level visual stimulus may trigger the brain to follow distinct trajectories in the state space that result in seen versus unseen perceptual outcomes, respectively (**Figure 3*b***); in addition, across-trial variability in seen trials was substantially reduced, suggesting that ongoing activity negatively interacted with evoked responses (Baria et al. 2017, He 2018).

Relatively few studies have examined the effects of movement and arousal on cortical responses in humans, in part owing to the requirements of the lack of overt movements for fMRI and MEG (and to some extent EEG) investigations. In two studies, human subjects sat on stationary bikes while solving visual discrimination tasks at rest or during physical exercise (e.g., Bullock et al. 2017). The amplitude of visually evoked neural responses was found to follow an inverted-U-shaped relationship, with largest responses at modest levels of exercise. Interestingly, an inverted-U-shaped relationship was also recently identified between the level of global arousal (e.g., pupil diameter) and response sensitivity, and between auditory cortical desynchronization and response bias/latency, during a demanding auditory discrimination task in humans (Waschke et al. 2019).

CELLULAR AND NETWORK MECHANISMS OF STATE-DEPENDENT ACTIVITY

To delve deeper into the cellular and local network mechanisms of spontaneous activity and its state dependence requires investigations in animals. While this field has a long and fruitful history (reviewed in Buzsaki 2006, Haider & McCormick 2009, Harris & Thiele 2011, McCormick & Bal 1997, Steriade 2003, Steriade et al. 1993), more recent studies have turned to the mouse as a model system, where tens of thousands of neurons, or their synaptic inputs, can be monitored through imaging or extracellular/intracellular recording (Musall et al. 2019, Salkoff et al. 2020, Steinmetz et al. 2019, Stringer et al. 2019).

Intracellular recordings from waking rodents that are voluntarily immobile frequently reveal cyclical bursts of synaptic potential that initiate action potentials (**Figure 4**), in a manner that is reminiscent of the slow oscillation prevalent during drowsiness and sleep (Bennett et al. 2013, Crochet & Petersen 2006, Gentet et al. 2010, McGinley et al. 2015a, Nelson & Mooney 2016, Petersen 2019, Polack et al. 2013, Poulet & Crochet 2018, Reimer et al. 2014). The cortical slow oscillation is generated in local regions of the cerebral cortex as a recurrent excitation between pyramidal cells that is balanced by local inhibition (Haider & McCormick 2009, Haider et al. 2006, Sanchez-Vives & McCormick 2000, Shu et al. 2003, Steriade et al. 2001) (**Figure 4*c***). These slow (<4 Hz) rhythms are strongly suppressed by movement (e.g., whisking, walking) or arousal (increases in pupil diameter) and can occur locally during drowsiness or in response to sleep deprivation, prior to the onset of sleep (Huber et al. 2004, Nir et al. 2011, Vyazovskiy et al. 2011).

One of the most prominent indicators of the state of synaptic and membrane potential in the cortical neurons of waking animals is movement, which has typically been measured as periods of

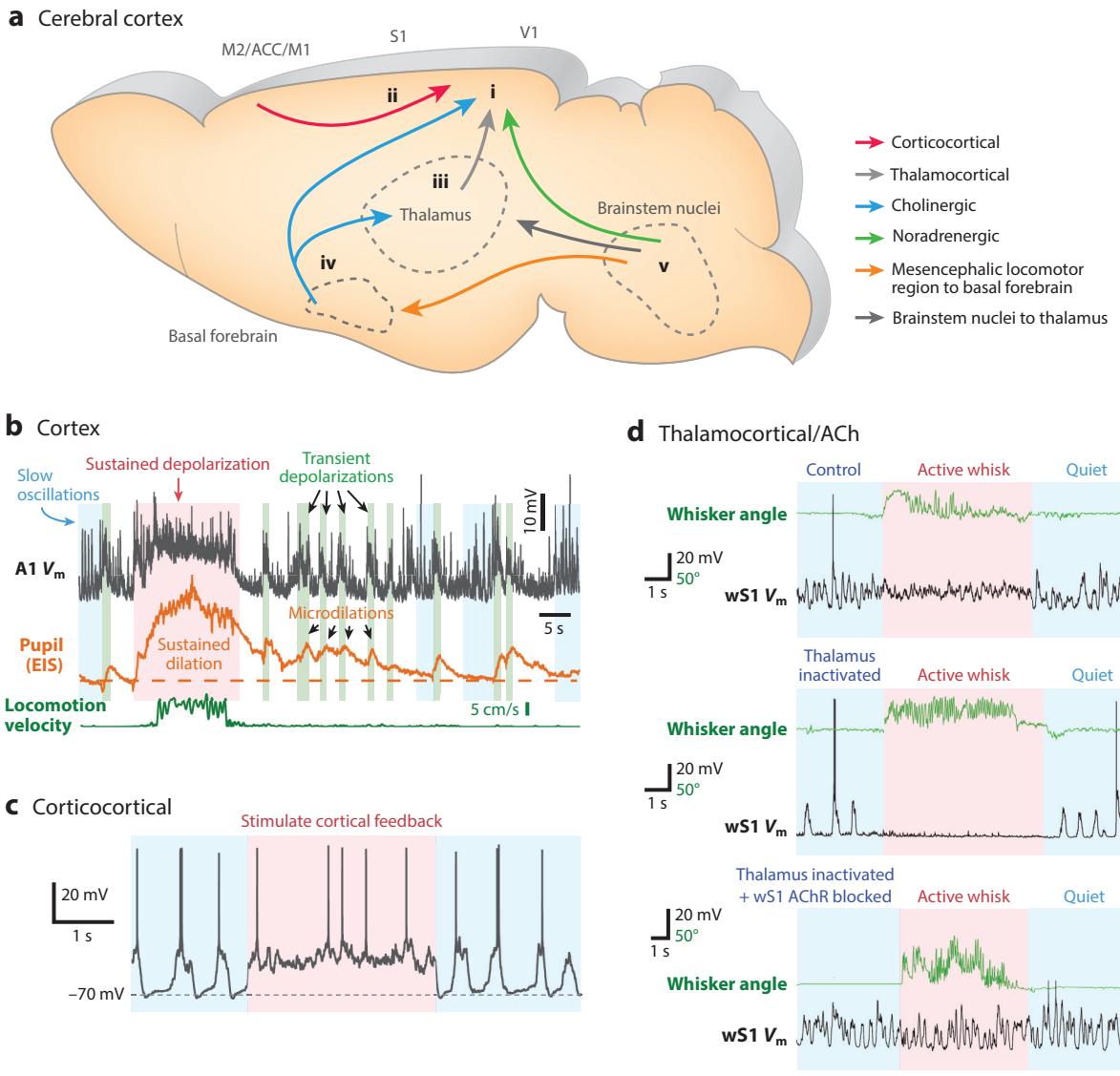


Figure 4

Pathways and mechanisms involved in rapid modulation of waking cortical state. (*a*) Graphic illustrating that the rapid modulation of the state of a region of cortex (*i*) may be influenced by other cortical areas (e.g., feedback; *ii*); subcortical inputs (e.g., thalamus; *iii*); and modulatory transmitter systems from the basal forebrain (*iv*), hypothalamus, or brainstem (*v*). (*b*) Whole-cell recording of a deep-lying pyramidal cell in auditory cortex during spontaneous variations in behavioral state. During periods of small pupil diameter, the cortical network may generate slow oscillatory rhythms, presumably through intracortical mechanisms (McCormick et al. 2015). Periodically, this activity is interrupted by microarousals associated with pupil dilations and membrane potential depolarization, owing to a barrage of synaptic potentials. During a period of walking, the membrane potential depolarizes strongly, slow oscillatory activity is suppressed, and the pupil dilates, indicating increased arousal. (*c*) The state of cortical activity can be altered through the stimulation of corticocortical feedback pathways. In this whole-cell recording of a pyramidal cell in the primary somatosensory cortex, activation of the feedback pathway from the motor cortex results in a rapid depolarization and cessation of slow rhythmic activity of anesthesia. (*d*) Blocking thalamic inputs results in a suppression of the whisker movement–associated depolarization of somatosensory cortical pyramidal cells, although the slow oscillatory activity is still suppressed. However, if both the thalamic and cholinergic pathways are blocked, then movement no longer has these effects on rhythmic synaptic activity. Panel *b* adapted with permission from McGinley et al. (2015a), panel *c* adapted with permission from Zagha et al. (2013), and panel *d* adapted with permission from Poulet & Crochet (2018).

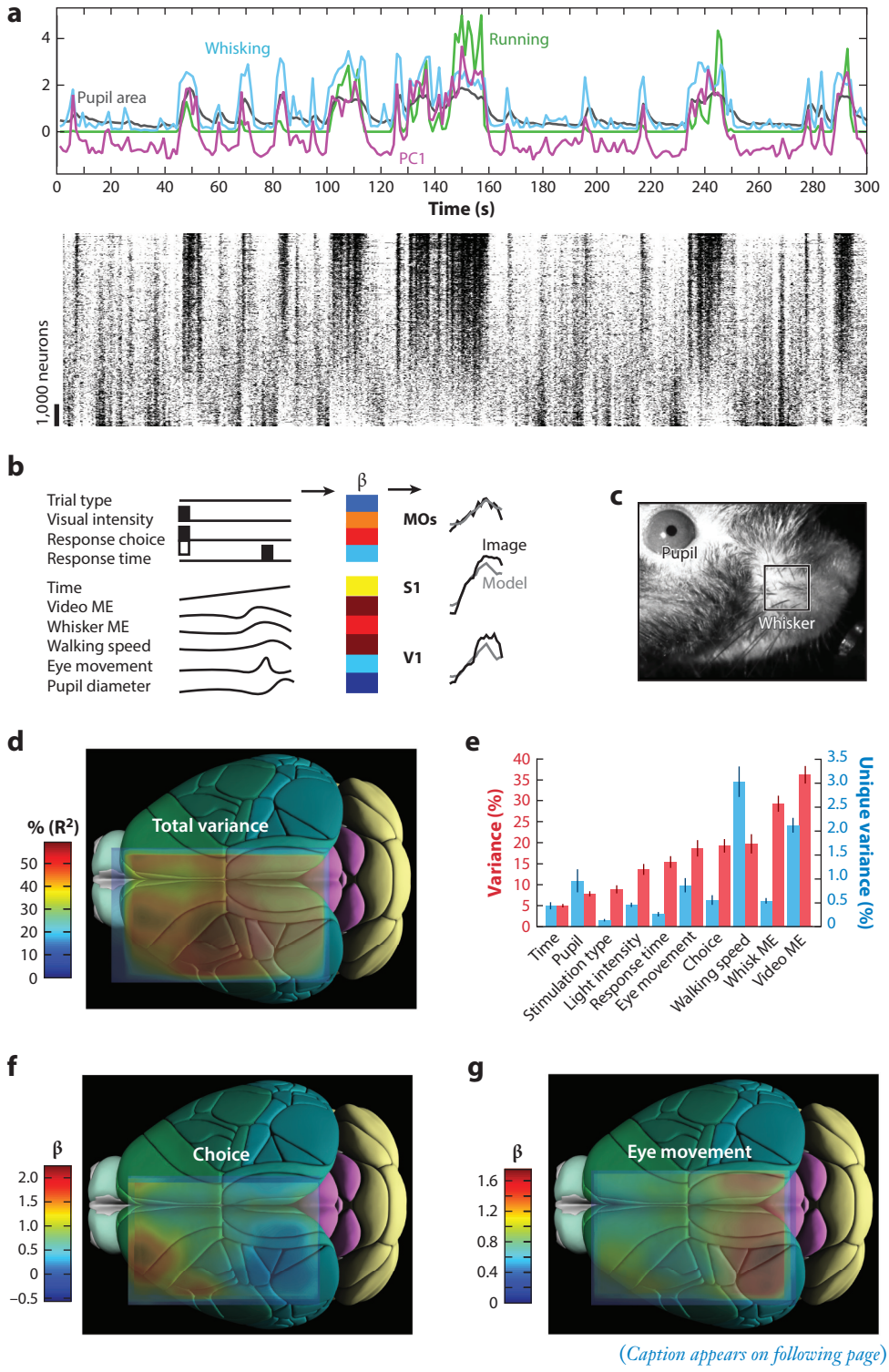
walking on a cylinder or whisking (although movements in behaving animals occur as coordinated interactions of many body parts). During periods of walking or whisking, the membrane potential of layer 2/3 or 5 pyramidal neurons in primary visual, auditory, and somatosensory cortex maintain a steady depolarization along with a suppression of slow rhythmic synaptic barrages (McGinley et al. 2015a, Petersen 2019, Poulet & Crochet 2018) (**Figure 4**). Outside these periods of walking with whisking, there are also periodic bouts of depolarization associated with arousal, as measured by increases in pupil diameter (McGinley et al. 2015a,b) (**Figure 4*b***). In our own recordings, we have found that these bouts of arousal are associated with movements of the whiskers or face (e.g., twitches) without overt walking (D.B. Nestvogel & D.A. McCormick, unpublished observations). The presence of strong depolarizations of the membrane potential of cortical pyramidal cells during brief or prolonged movements of the body and face suggest that the activity of a large number of cortical neurons is affected by these behaviors.

In confirmation of this suggestion from intracellular studies, recordings in mice, by either electrophysiology or 2-photon imaging, have revealed that the activity of large numbers of neurons throughout the dorsal cerebral cortex, and within select subcortical structures (McGinley et al. 2015a, Schröder et al. 2019, Stringer et al. 2019), is highly state dependent, with the largest component corresponding to movements of the face and body (**Figure 5**). Similarly, optical examination of cortical activity on the widefield level in behaving mice revealed complex patterns, the largest component of which is related to movements of the face (e.g., whiskers, mouth, tongue, eyes) and body (e.g., locomotion) (Musall et al. 2019, Salkoff et al. 2020) (**Figure 5**). Linear models of these broad patterns of brain activity, on either the widefield or neuronal level, have been able to explain a large fraction (e.g., 25–55%) of the variance of neural activity through examining varying components of facial/body movements, arousal (pupil diameter), and task performance (Musall et al. 2019, Salkoff et al. 2020, Stringer et al. 2019) (**Figure 5**). The ability of external observations of behavioral state to explain a significant component of neural activity in the dorsal cortex of mice indicates that this activity is not random and independent of behavior—it reflects variations in the behavioral state of the animal along multiple dimensions (e.g., **Figure 5*e***) that are highly interrelated and correlated. For example, movements are associated with arousal, and increases in arousal (as measured by pupil diameter) often precede movements. Additionally, in mice, locomotion is always associated with whisking (although whisking can occur without locomotion). These overt and coordinated body movements are also related to large changes in the state of other parts of the body, for example, changes in heart rate, respiration, gut motility, and such.

Although a significant fraction of dorsal cortical activity in mice may be related to behavioral state, there is still a majority of activity that cannot yet be explained by these measures, particularly when large numbers of single neurons are monitored (Musall et al. 2019, Salkoff et al. 2020, Stringer et al. 2019). Even so, the degree to which the general activity of the cortex of the mouse is related to behavioral state and movement is impressive (see **Figure 5**).

NEUROMODULATORY/NEURAL CONTROL OF STATE

Brain state is controlled through slow-acting neuromodulators, which typically are localized in brainstem/hypothalamic nuclei that have broad projections, as well as local and long-range rapidly acting excitatory and inhibitory neurotransmitter pathways (Boucetta et al. 2014, Brown et al. 2012, Dasgupta et al. 2018, Goard & Dan 2009, Jones 2019, Lee & Dan 2012, Liu & Dan 2019, McCormick & Bal 1997, Muñoz & Rudy 2014, Pinto et al. 2013, Saper & Fuller 2017, Sara 2009, Sara & Bouret 2012, Scammell et al. 2017, Thiele & Bellgrove 2018, van den Brink et al. 2019, Zagha & McCormick 2014). These two broad categories of control systems are not mutually exclusive. For example, acetylcholine, serotonin, and glutamate can activate both rapid



(Caption appears on following page)

Figure 5 (*Figure appears on preceding page*)

Movements of the face and body and behavioral state explain a significant portion of ongoing and trial-related activity in the mouse dorsal cortex. (*a*) Example time course of running speed (*green line*), pupil area (*gray line*), whisking (*light blue line*), and first principle component (PC1) of spontaneous population neuronal activity (*magenta dashed line*) in an untrained mouse alternating between behavioral quiescence and movement. Neuronal activity is shown in the raster plots (*bottom*), with neurons sorted vertically by PC1 weighting. (*b*) A ridge regression linear model was used to fit the pixel-by-pixel amplitude-time course of wide-field brain activity (e.g., panel *b*) in a mouse performing a visual detection task. Regressors used in the model include unitary variables such as trial type (visual, auditory, catch), intensity of visual stimulus (low or high), response choice (hit/no response/false alarm), and response time and continuous variables such as time, motion energy in the entire video, motion energy in the whisker pad only (see panel *c*), walking speed, eye movement amplitude, and pupil diameter. The linear model generated spatiotemporal maps of β weights for each variable (see panels *f*,*g*) and was used to predict the amplitude-time course of each pixel of the widefield movie of cortical activity. Examples of the activity (*black lines*) and model fit (*gray lines*) for averaged regions of pixels in secondary motor cortex (MOs), primary somatosensory cortex (S1), and primary visual cortex (V1) are shown. (*c*) Example frame from a video of the mouse face and eye during the performance of the task. The video was used to examine movements of the face [video motion energy (ME)], whisker pad (whisk ME), eye, and pupil diameter. (*d*) The model is able to explain a significant fraction (approximately 35–55%) of neural activity variance during performance of the task. (*e*) Total and unique explained variance for each parameter. Movement (video, whisk, walk, eye movement) explains a high degree of neural activity, while other variables such as arousal (pupil diameter), response choice, and timing also make significant contributions. Bars are mean +/− standard error of the mean. (*f*,*g*) Spatial maps of the β weights of the model for choice and eye movement. Note that behavioral choice peaks in MOs. The activity maps are roughly aligned to the Allen Institute Common Coordinate Framework (Oh et al. 2014) for illustrative purposes. Panel *a* adapted with permission from Stringer et al. (2019), and panels *b*–*g* adapted with permission from Salkoff et al. (2020).

ionotropic receptors and slower-acting metabotropic pathways. In the realm of broadly projecting neuromodulatory pathways, traditional anatomical, recording, stimulation, and lesion studies have revealed several important groups, including cholinergic brainstem and basal forebrain nuclei, noradrenergic brainstem nuclei (e.g., locus coeruleus), serotonergic brainstem neurons, histaminergic hypothalamic cells, and other less-well-investigated pathways (Jones 2019, Lee & Dan 2012, Muñoz & Rudy 2014, Saper & Fuller 2017, Sara & Bouret 2012) (**Figure 4**). Investigations into the actions of these modulatory pathways have revealed their ability to influence nearly every aspect of brain function. A major difficulty in the field of neuromodulation is knowing which of these diverse mechanisms are activated when and how they contribute to rapid changes in the waking behavioral/cognitive state.

The application of modulatory transmitters, such as acetylcholine, norepinephrine, or serotonin, to forebrain neurons can profoundly influence their state of activity and excitability. For example, the propensity of thalamocortical networks to generate sleep rhythms can be strongly suppressed through the depolarization of neuronal membrane potential by the reduction of a resting K^+ current or enhancement of the h current. In cortical pyramidal cells, activation of metabotropic receptors, for example, by acetylcholine or norepinephrine, often changes neuronal excitability through the activation or reduction of resting or activity-dependent K^+ currents (Zagha & McCormick 2014). While reduction of K^+ currents typically occurs over the time course of seconds, the activation of K^+ currents is faster, occurring over a period of hundreds of milliseconds. These changes in neuronal excitability are likely to be relevant to the changes in brain state in this temporal scale (hundreds of milliseconds to seconds).

Intracellular recordings (**Figure 4**), or simultaneous multiple neuronal extracellular recordings (**Figure 5**), reveal that the transitions from stillness to movement (and importantly vice versa) are associated with rapid (<100 ms) transitions in the state of neuronal activity within cortical networks. Could these rapid transitions be mediated by the activity of cholinergic or

noradrenergic transmitter pathways? Monitoring the activity of cholinergic and noradrenergic axons in the neocortex of waking mice reveals that they are strongly activated by facial movements, locomotion, and arousal (Eggermann et al. 2014, Lee et al. 2014, Reimer et al. 2016), suggesting that these transmitter pathways may participate in the network dynamics associated with the sustained membrane-potential depolarization in pyramidal cells that is associated with these states (Goard & Dan 2009, Meir et al. 2018, Metherate et al. 1992, Nelson & Mooney 2016, Pinto et al. 2013, Polack et al. 2013, Sara & Bouret 2012) (**Figure 4**). While noradrenergic fibers do not activate fast ionotropic responses, acetylcholine can activate nicotinic and muscarinic receptors, resulting in both rapid and potentially longer-lasting responses. The rapid transition of cortical activity from activated to inactivated in mice with the cessation of movement (e.g., the rapid hyperpolarization of the membrane potential upon cessation of movement) suggests that long-lasting metabotropic receptor–mediated neuromodulatory actions are not the main driver of the movement-associated activated state in mice (**Figures 4** and **5**), since these would be expected to persist even after the cessation of neurotransmitter release.

Optical imaging of different subtypes of neurons in the mouse visual cortex during locomotion revealed that VIP interneurons in the superficial layers are strongly activated by locomotion. This activity dependence appears to be largely driven by the activation of nicotinic receptors (Fu et al. 2014). The activation of nicotinic receptors can also activate other types of GABAergic interneurons in the superficial cortex and deep-lying pyramidal cells in some cortical regions (Hedrick & Waters 2015). The activation of these interneurons can result in either the direct inhibition or disinhibition of excitatory neurons in the cortex (Dasgupta et al. 2018; Lee et al. 2013; Letzkus et al. 2011, 2015; Pfeffer et al. 2013; Pi et al. 2013). As stated above, cholinergic (and noradrenergic) fibers are strongly activated by movement such as whisking, walking, and arousal (Reimer et al. 2016). Although the pathway for this rapid activation of modulatory pathways by movement is not yet decisively known, one possibility is that large integrator neurons of the mesencephalic brainstem form a general arousal system that is sensitive to sensory and motor conditions (Pfaff et al. 2012). In one study, stimulation of the mesencephalic locomotor region (MLR) above or below the threshold of movements induced cortical changes in V1 that were reminiscent of those observed during locomotion (Lee et al. 2014). Similar changes were observed when MLR axon terminals were optogenetically activated in the basal forebrain, which in turn provides cholinergic input to various brain regions such as V1. Together, these results suggest the existence of a regulatory brainstem circuit that links movement, cholinergic activity, and cortical state (**Figure 4**).

The activation of VIP, and other types of superficial, interneurons by acetylcholine could rapidly activate cortical areas through disinhibition. For example, VIP interneurons can inhibit other interneuron cell types, including somatostatin (SOM)-containing interneurons and parvalbumin, presumably fast-spiking, interneurons. Since SOM interneurons target the apical dendrites of pyramidal cells, the hypothesis is that movement may modulate cortical activity through rapid disinhibition of pyramidal cells, particularly through their apical dendrites (Dasgupta et al. 2018; Lee et al. 2013; Letzkus et al. 2011, 2015; Pfeffer et al. 2013; Pi et al. 2013). This model suggests that the depolarization of pyramidal cells associated with locomotion or facial movements (e.g., whisking; **Figure 4**) is mediated at least in part by an initial decrease in inhibitory postsynaptic potentials and a subsequent increase in excitatory postsynaptic potentials (EPSPs) arriving in the neurons. These barrages of EPSPs may result in a transition of the cortical network from one of slow oscillatory activity (such as during drowsiness) to a more sustained pattern of activity, e.g., one rich in gamma-band oscillations.

In addition to this disinhibition pathway, thalamic inputs can also rapidly and strongly modulate activities within the cerebral cortex. This has been particularly well investigated in the

rodent somatosensory system, where inactivation of the thalamic input prevents depolarization of somatosensory cortical neurons with movements of the whiskers but does not prevent the suppression of ongoing, slow, oscillatory-like activity with movement (Poulet et al. 2012) (**Figure 4*d***). This remaining movement-related suppression of ongoing activity may be mediated by the activation of cholinergic pathways, since suppression of both thalamic and nicotinic pathways (pharmacologically) results in a near complete loss of movement-modulated changes in activity in the somatosensory cortex (Eggermann et al. 2014) (**Figure 4**). How might cholinergic pathway activation suppress network activity without prolonged depolarization of the recorded neurons? The endogenous release of acetylcholine can potently inhibit layer 4 excitatory neurons through activation of a muscarinic receptor–mediated increase in K^+ conductance (Dasgupta et al. 2018) as well as inhibit activity through the nicotinic activation of local inhibitory cells (see above). The multiple pathways by which cholinergic pathways may modulate cortical activity (e.g., nicotinic activation of inhibitory neurons, disinhibition of excitatory neurons, muscarinic inhibition of layer 4 spiny stellate neurons, muscarinic depolarization of pyramidal cells) give this system considerable flexibility.

Noradrenergic inputs from the locus coeruleus project broadly throughout the cerebral cortex, and increases in locus coeruleus activity can result in activation of the forebrain (e.g., suppression of slow oscillatory activity similar to arousal or movement) (Carter et al. 2010, Sara & Bouret 2012). Whole-cell recordings coupled together with pharmacology in mice have implicated the ascending noradrenergic pathway in the reduction of slow oscillatory activity and promotion of depolarized (activated) cortical networks with locomotion and/or arousal (Constantinople & Bruno 2011, Polack et al. 2013). In addition, there is strong evidence that modulation of noradrenergic pathways can alter cognitive function through modulation of cortical activities (Arnsten et al. 2012, Aston-Jones & Cohen 2005, Sara 2009). In the mouse, the discharge of cortical noradrenergic fibers is strongly correlated with changes in pupil diameter (Reimer et al. 2016), suggesting an important role in general arousal and engagement with the external world (Aston-Jones & Cohen 2005, Sara & Bouret 2012). The close relationship between arousal and noradrenergic activity is relatively undifferentiated across the cortex, a hypothesis that is in keeping with the mostly uniform, concerted activity of noradrenergic neurons and their axons in awake behaving animals (Reimer et al. 2016, Usher et al. 1999; L. Collins & D.A. McCormick, unpublished observations). It is possible that, although not yet well investigated, superimposed upon this general activation mode of locus coeruleus activity, a more regionally specific control of cortical areas may occur (Chandler et al. 2014, Totah et al. 2018). Interestingly, performance and neural response during an auditory detection task exhibit an inverted-U relationship with pupil diameter (arousal) (**Figure 2*b***), which may be related to an inverted-U relationship between cognitive performance and locus coeruleus activity on more complex tasks involving working memory and decision-making (Arnsten et al. 2012, Aston-Jones & Cohen 2005).

Since movement has a strong influence on the state of activity in the mouse cortex, the possibility that this effect is mediated by direct or indirect feedback from the primary or secondary motor cortex has been examined (Dipoppa et al. 2018, Hill et al. 2011, Khan & Hofer 2018, Leinweber et al. 2017, Nelson & Mooney 2016, Schneider & Mooney 2018, Schneider et al. 2014, Sommer & Wurtz 2008, Zagha et al. 2013, S. Zhang et al. 2014). Inactivation of frontal cortical regions, including secondary motor and anterolateral motor cortical areas, is associated with decreased ability to perform appropriate learned lick responses. These areas exhibit activity during delay periods between stimulus and motor response that is consistent with attractor network dynamics that may prepare the animal for the response (Guo et al. 2014; Inagaki et al. 2018, 2019; Li et al. 2015, 2016; Salkoff et al. 2020; Zagha et al. 2015). Optogenetic stimulation of feedback projections from motor cortex to somatosensory cortex can strongly activate the later, resulting in a

response that is similar to movement-induced changes in somatosensory cortical activity (Zagha et al. 2013) (**Figure 4**). Movement has a strong effect on activity not only in somatosensory cortex but also in visual and auditory cortical areas (reviewed in McGinley et al. 2015b), although these effects are not homogenous and may vary even within subdivisions of a sensory cortical region (Shimaoka et al. 2018). There is growing evidence that movement-related modulation of sensory cortical areas tunes the sensory cortical region for movement-compensated sensory processing (Bouvier et al. 2020, Guitchounts et al. 2020, Leinweber et al. 2017, Schneider & Mooney 2018, Schneider et al. 2014).

In addition to these four pathways (cholinergic, noradrenergic, thalamic, and cortical feedback), other modulatory pathways, both rapid and slow in action, have been identified (Brown et al. 2012, Jones 2019, Lee & Dan 2012, Liu & Dan 2019, Saper & Fuller 2017, Scammell et al. 2017). These include histamine-, orexin- and melanin-concentrating hormone–containing inputs from the hypothalamus and GABAergic and glutamatergic inputs from the basal forebrain and brainstem. The role of these modulatory pathways in the control of brain state is largely unexplored. One important outstanding question is the spatial specificity of each of the modulatory transmitter pathways. There is generally thought to be a gradient of spatial and temporal specificity in neuromodulatory actions, with broadly projecting systems, such as the locus coeruleus, regulating large regions of the cerebral cortex and related structures together, and more localized systems, such as basal forebrain cholinergic pathways, providing for a more spatially selective modulation of neuronal activity (Aston-Jones & Cohen 2005, Kim et al. 2016, Muñoz & Rudy 2014, Saper & Fuller 2017, Záborszky et al. 2018). Finally, fast-acting glutamatergic corticocortical and subcortical-cortical pathways can control selected and interrelated subgroups of neurons at a fine temporal resolution (e.g., milliseconds).

SUMMARY AND FUTURE DIRECTIONS

The brain exhibits repeating nonrandom patterns of activities that correlate with, and strongly influence, behavior. Understanding the states of the brain, their mechanisms of generation, and how they interact with sensorimotor and cognitive processing is essential to achieving a thorough understanding of neural mechanisms of natural behavior. While progress is being made on both the human and animal fronts, large gaps remain. Neuroscience investigations into the mouse brain tend to treat all cortical areas as operating on a common theme, yet regional variations in cortical function are an important aspect of the human brain. Likewise, while the cellular and network mechanisms of a few different basic patterns of neuronal activity (e.g., spindle waves, slow waves) are now roughly known, there are many patterns of activity in the human brain (e.g., SCPs, infraslow oscillations) for which cellular- and circuit-level understanding are still in their infancy. The same is true for neurotransmitter systems that control brain state. While some of the major players have been identified, we are still far from understanding what drives the activity within these modulatory systems and precisely how they interact to control the state of the brain in a behaviorally appropriate manner. Perhaps one of the most intriguing areas for study in the near future is the possibility that corticocortical or corticosubcortical glutamatergic/GABAergic systems rapidly and precisely (in both space and time) control the state of brain activity, bringing out the rapid transitions that are critical to behavior and cognition in real-life scenarios. Even though the gaps of knowledge are large, they are narrowing. We now know a great deal more about neural circuits of state-dependent processing than we did just a decade or two ago. The continued rapid advances of recording, imaging, and manipulation tools will only speed our progress toward filling these gaps in knowledge, ultimately resulting in a functional schematic of brain-state control and its influence on behavior.

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