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Review

Why is everyone talking about brain state?

Abigail S. Greene,[1,2,9,*] Corey Horien,[1,2,9,*] Daniel Barson,[1,2,3,9,*] Dustin Scheinost,[1,4,5,6,7] and R. Todd Constable[1,4,5,8]

The rapid and coordinated propagation of neural activity across the brain provides the foundation for complex behavior and cognition. Technical advances across neuroscience subfields have advanced understanding of these dynamics, but points of convergence are often obscured by semantic differences, creating silos of subfield-specific findings. In this review we describe how a parsimonious conceptualization of brain state as the fundamental building block of whole-brain activity offers a common framework to relate findings across scales and species. We present examples of the diverse techniques commonly used to study brain states associated with physiology and higher-order cognitive processes, and discuss how integration across them will enable a more comprehensive and mechanistic characterization of the neural dynamics that are crucial to survival but are disrupted in disease.

Highlights

Recent advances in neuroscientific data acquisition and analysis have permitted novel insights into neural dynamics.

These advances have motivated substantial interest in the concept of 'brain state', but approaches differ in spatial and temporal scale, yielding siloed lines of inquiry and subfield-specific definitions of a brain state.

We describe how a unified concept of brain state as a whole-brain activity pattern that emerges from, and has consequences for, physiology and/or behavior holds the promise of integrating these levels of analysis, organizing fast-growing literatures, and permitting a more comprehensive characterization of neural dynamics.

We explore how this conceptualization of brain state can guide future integrative work to reveal the biology underlying brain dynamics in health and disease.

Brain state as a framework to advance understanding of neural dynamics

The brain is a dynamic organ that continuously adapts in response to a changing world. Recent technical advances in recording methods and computational analysis have created an opportunity to better describe brain dynamics and their relation to brain function, but these approaches differ widely in temporal and spatial resolution, as well as in the nature of the signal measured (Figure 1). These technical differences have driven subfield-specific definitions of **brain state** (see Glossary), yielding siloed, parallel lines of inquiry into how brain-wide activity changes subserve behavior. Individually, these definitions and related constructs have enabled researchers to describe phenomena ranging from membrane potential fluctuations of single neurons [1] to the evolution – over seconds to minutes – of behaviorally relevant, whole-brain functional connectivity patterns in humans (e.g., [2]). However, the picture offered by such work is incomplete. To further current understanding of the dynamic brain we must integrate across these levels of analysis to capitalize on the complementary insights they offer.

We do not argue for a single spatiotemporal definition of a brain state, but instead for a shared, conceptual framework of a brain state as a pattern of brain activity or functional coupling that emerges from, and has consequences for, physiology and/or behavior. This definition transcends spatiotemporal scales and can be used to organize this vast and expanding literature, thus revealing points of convergence that are often obscured by semantics. It yields three criteria that must be met by all brain state research: (i) a brain state is the product of a specified cognitive or **physiological state**, (ii) a brain state is characterized by a widely distributed pattern of activity or coupling, and (iii) a brain state affects the future physiology and/or behavior of the organism. Implicit in this framework is the possibility that, at any point in time, multiple brain states may be expressed, such that each snapshot of brain activity can be decomposed into these constituent parts. Further, a brain state is a neurobiological phenomenon that likely results from neuronal activity that propagates across the structural scaffold of the brain and is modified by neuromodulatory tone. This definition is consistent with, but not limited to, varied conceptualizations of brain state that have been recently reviewed: brain state as 'a background of spontaneous, ongoing activity' ([3]; *cf* [4]), as internal **behavioral states** (e.g., arousal) with neuronal correlates [5], and as 'the amount of common fluctuation in population

[1]Interdepartmental Neuroscience Program, Yale School of Medicine, New Haven, CT 06520, USA
[2]MD/PhD program, Yale School of Medicine, New Haven, CT 06520, USA
[3]Department of Neuroscience, Yale School of Medicine, New Haven, CT 06520, USA
[4]Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT 06520, USA
[5]Department of Biomedical Engineering, Yale School of Engineering and Applied Science, New Haven, CT 06520, USA
[6]Department of Statistics and Data Science, Yale University, New Haven, CT 06511, USA
[7]Child Study Center, Yale School of Medicine, New Haven, CT 06520, USA
[8]Department of Neurosurgery, Yale School of Medicine, New Haven, CT 06520, USA
[9]Equal contributions

*Correspondence:
abigail.greene@yale.edu (A.S. Greene),
corey.horien@yale.edu (C. Horien), and
daniel.barson@yale.edu (D. Barson).

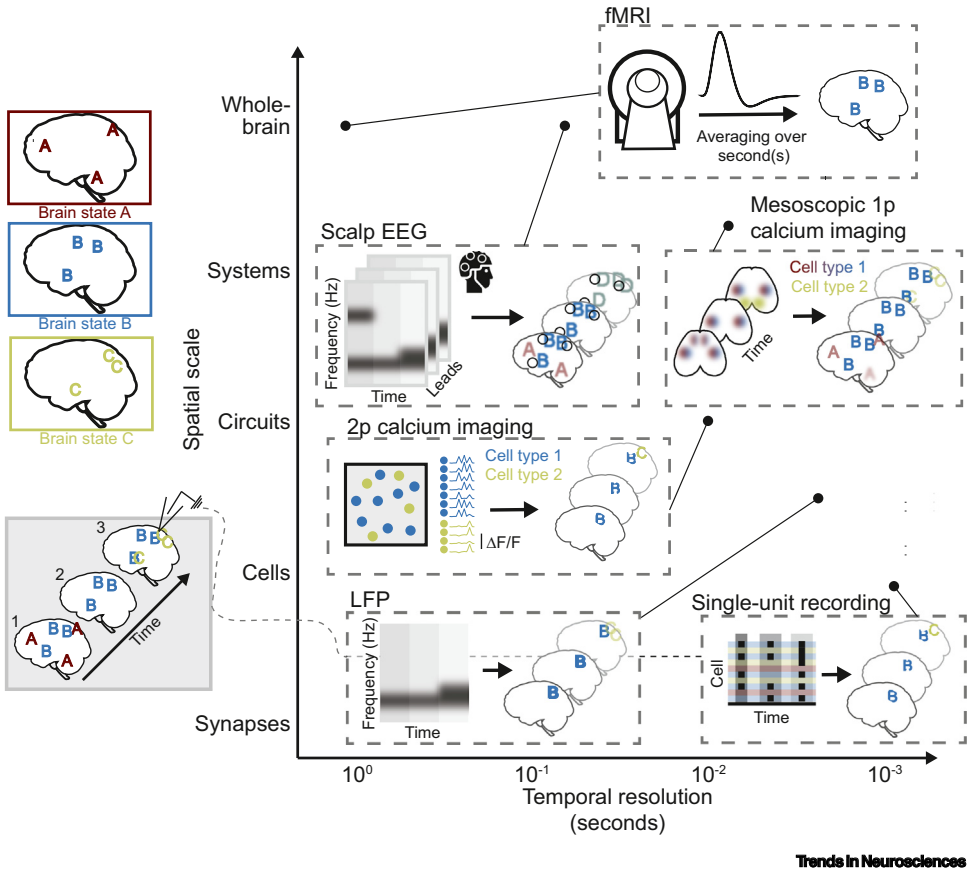


Figure 1. Systems and cognitive neuroscience techniques each offer partial, but complementary, insights into brain states. In this example, three schematic brain states, A, B, and C, are depicted (upper left). Each brain state is defined by a stereotyped pattern of whole-brain activity, and brain states can occur in isolation (timepoint 2; bottom left) or in combination (timepoints 1 and 3). Commonly used techniques are schematized and placed (see corresponding point) according to their approximate relative temporal resolution and spatial scale (i.e., field of view size), as typically implemented. Single-unit recording: schematized raster plot represents cell spiking at three timepoints. The limited field of view is represented by focal patterns, and cell response heterogeneity that may obscure patterns is represented by incomplete 'B' and 'C'. The identity of the cells is typically unknown. Two-photon (2p) calcium imaging (where ΔF/F indicates the change in fluorescence divided by the baseline fluorescence) suffers from many of the same limitations (represented by focal, partial brain state patterns and heterogeneous calcium signal at the individual cell level), but can offer insights into the cell type specificity of brain state expression (represented by colored cells, each of which preferentially responds during the brain state of that color). Local field potentials (LFPs) capture regional fluctuations in activity with high temporal resolution, and can be used, for instance, to assess changes in frequency of extracellular oscillations across brain states. Mesoscopic single-photon (1p) calcium imaging has slightly lower temporal resolution, but captures cell type specific patterns of brain activity across the cortical mantle, yielding more complete representations of brain states (although with limited resolution of activity in deep structures, represented by blurred pattern elements). Scalp electroencephalography (EEG), like LFPs, captures brain state-associated differences in power across frequency bands, but suffers from imprecise source localization (represented by enlarged, blurred, and conflated pattern elements – i.e., pattern D that merges brain states B and C). Functional magnetic resonance imaging (fMRI), like EEG, offers whole-brain coverage in humans, but has low temporal resolution, such that brain state patterns will be effectively averaged over seconds. In this example, the only resolved brain state will thus be brain state B, which persists across all timepoints.

spiking activity' [6]. Finally, every technique for recording neural activity offers different – and, we argue, complementary – insights into these whole-brain patterns (Box 1). In fact, we suggest that a comprehensive characterization of a given brain state, as well as the disentangling of multiplexed brain states, can only be achieved by integrating across these levels of analysis.

Box 1. Data acquisition techniques

Acquisition techniques at all levels of analysis offer insights into brain states, but when used in isolation each offers only a partial view of brain dynamics (Figure 1 in the main text). In parallel, there are a range of analytical approaches to make sense of these data, and in many cases these approaches offer a means to bridge levels of analysis (e.g., [125]).

Single-unit electrophysiological recordings offer high temporal and spatial resolution, permitting high-fidelity observation of the movement of a given cell through brain states. Insights gained from these recordings are limited, however, by cell response heterogeneity: a state-selective cell likely does not respond with perfect consistency – in firing rate or inter-spike interval – when that state is visited [131,132], and neighboring cells may be recruited by different brain states [28,30,31], an issue compounded by the lack of cell type specificity of the technique. Further, measured signals lack regional, inter-regional, and whole-brain context. The technique thus offers a focal, partial view of relevant activity.

In vivo two-photon calcium imaging, although an abstraction from spiking activity, offers the crucial benefit of cell type specificity that can aid exploration of cell response heterogeneity. Like single-unit recordings, two-photon imaging offers a highly focal window into neural activity, but is devoid of broader context, although recent work has demonstrated the feasibility of significantly expanded spatial scale [133,134].

Local field potentials (LFPs) offer some context, and can capture regional and local inter-regional motifs with moderately high temporal resolution [135,136]. Single-photon mesoscopic calcium imaging, often likened to whole-brain LFPs, offers more complete insight into inter-regional interactions as well as cell type specificity. It is, however, a further abstraction from spiking activity, and is largely limited to the cortical mantle (*cf* [137]).

Two commonly used human neuroscience techniques are scalp electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Their non-invasive nature makes them crucial for the study of brain state dynamics in humans, but they offer limited insight into mechanism. EEG has moderate temporal resolution and whole-cortex coverage, but poor spatial resolution that may obscure or conflate brain state patterns. fMRI has better spatial resolution than EEG but poor temporal resolution, likely 'blurring' fast neural dynamics and only resolving pattern combinations with long dwell times and/or high recurrence (although 'fast fMRI' can be used to resolve distinct arousal states [138]). Further, the blood oxygen level-dependent (BOLD) signal on which it is based is an indirect measure of neural activity that is confounded by many variables (e.g., heart and respiratory rate, neurovascular coupling, and neuroenergetics [139–142]), which may interact with behavioral states – and thus distort the brain states resolved. Nevertheless, the ease of fMRI data acquisition during a variety of behavioral states makes it a crucial tool to acquire large quantities of data suitable for studying dynamics at both short (e.g., [143]) and long (minutes to years) timescales in healthy and clinical populations.

Glossary

Behavioral state: any state involving a discrete physiological (bottom-up and low-level) or cognitive (higher-order; e.g., as induced by a cognitive paradigm) process.
Brain state: recurring activity patterns distributed across the brain that emerge from physiological or cognitive processes. These patterns are neurobiological phenomena with functional (e.g., behavioral) relevance.
Cognitive paradigm: any experimental manipulation, ranging from traditional controlled to naturalistic experiments, that provides a more specific means to study brain states associated with higher-order processes. Cognitive paradigms can be used as brain state manipulations and also offer an environmental context that can be used to interpret the behavioral consequences of brain state changes.
Physiological state: the bottom-up manifestation of homeostatic processes with effects throughout the body of the organism, including metabolic (hunger, satiety), arousal-related, and immunological states.

The promise of multiscale, multimodal neuroscience has been recognized before – this philosophy has, for example, motivated the US National Institutes of Health (NIH) BRAIN Initiative – but divergent conceptualization and operationalization of brain state has often proved limiting. In what follows we propose that a shared concept of brain state can facilitate this work. Specifically, we describe in general terms the principles of organization and biological underpinnings of brain states across levels of analysis. We then apply the three proposed criteria to past studies grouped based on commonly employed measures of physiological state (discussed in the section on Physiological changes are reflected in reproducible brain states) or **cognitive paradigms** (section on The brain on task, and Figure 2). We show how these studies collectively contribute to the characterization of a common brain state across spatial and temporal scales (criterion 2; Figure 3). Finally, when possible, we demonstrate how each of these brain states influences subsequent behavior and physiology (criterion 3). We do not seek to exhaustively review a specific set of brain states (as has been done previously, e.g., [6]), but instead aim to develop a conceptual framework, supported by these examples, to reveal opportunities for an interdisciplinary study of brain dynamics. Although the application of this framework to previous work demonstrates its validity and generalizability, its greatest utility lies in its guidance for future studies of brain state, as exemplified by several recent papers (discussed in the section on Using brain state to unify the study of neural dynamics). We provide an example case to illustrate how, in the absence of multimodal data from a single study, focusing on brain state may still facilitate integration of results from independent studies using distinct modalities to characterize brain dynamics (Figure 4). Crucially, this approach is prospective rather than retrospective: we provide recommendations to

first identify a brain state of interest and consider its manifestation across scales and modalities, and then, within a single project, pursue these predictions by directly mapping results across levels of analysis. Such work promises to yield a more complete description of functionally relevant, stereotyped brain states, with the ultimate goal of revealing the biology underlying brain function in health and disease (Box 2).

The organization, biology, and measurement of brain states

There is growing evidence for stereotyped, transient, and meaningful whole-brain activity patterns at all levels of analysis. In humans, combined neuroimaging and electrophysiological methods have shown converging patterns of activity and dynamic functional connectivity, regardless of the source of the signal (i.e., blood flow or electrical currents) or the precision of spatial localization [7,8]. Paired measurements in animal models have further validated the robust relationship between neural activity, local field potential, and hemodynamics ([9–11]; *cf* [12]), as well as the consistency of inter-region functional connectivity across modalities [13–15]. Work in rodents links these patterns to variation in fast and transient neuronal coactivation patterns [16,17]. Thus, brain states can be resolved by using many measurement and analytical techniques, each of which offers limited, but complementary, insights into their cause, representation, and consequences (Box 1 and Figure 1).

Although largely inaccessible in humans, the neuronal underpinnings of brain states can be readily studied in animal models, reflecting the importance of merging findings across species and techniques. In rodents, for example, the biological bases of these spontaneously evolving whole-cortex brain states are increasingly well described. First, studies relating spontaneous activity patterns to detailed anatomical atlases [18] have demonstrated that recurring mesoscale activity motifs [19,20] are well, but not entirely, predicted by patterns of axonal projections. These results are consistent with the finding in humans that functional connectivity is constrained by structural connectivity [21,22]. Second, transitions between whole-brain activity patterns can be triggered by activation of neuromodulatory centers, such as the ventral tegmental area [23] and locus coeruleus [24], and the expression of specific patterns of activity may be a function of both the heterogeneous innervation of brain regions by neuromodulatory axons [25,26] and the divergent responses of those regions to neuromodulator release [24,27]. Third, although entire brain regions are recruited by these activity patterns, within local cortical (and subcortical [28,29]) circuits, neighboring neurons are often recruited by different patterns of cortical activity [30,31], suggesting that the distinct computations performed by individual neurons may be, at least in part, a function of the brain-wide functional networks to which they belong. Together, this work suggests a model of brain states as transient, anatomically constrained patterns of activity that are influenced by neuromodulatory tone, and that differentially recruit individual neurons while overall synchronizing distributed brain regions. This model helps to rectify seemingly discrepant findings across modalities and species (Box 1). We turn next to recent and ongoing work to characterize the brain states that correspond to physiological and cognitive processes.

Physiological changes are reflected in reproducible brain states

We first discuss brain dynamics associated with fluctuating physiology – the bottom-up manifestation of homeostatic processes with effects throughout the body. Consistent with our proposed criteria, a growing literature (in humans [32] and animals [33]) suggests that there are recurring patterns of brain activity that emerge from physiological state, have a stereotyped representation in the brain, and have consequences for future behavior.

Physiological changes induce distinct brain states

Although numerous physiological changes have been related to brain dynamics [5], the physiological state measure most commonly related to large-scale patterns of brain activity is arousal, which

is typically quantified using markers such as heart and respiratory rates, skin conductance, and pupil diameter. Changes in pupil diameter occur on the order of seconds and are associated with alterations in brain activity measured at levels ranging from cellular membrane potential [1,34] to circuit-level synaptic and firing rate synchronization [35] and to brain-wide network coupling [36,37], all of which comprise or reflect brain state dynamics. Pupillometry has similarly been used to track arousal in human functional magnetic resonance imaging (fMRI) studies [38,39], and recurring patterns of brain-wide activity have been associated with epochs of changing pupil diameter, but not the absolute size of the pupil [38], suggesting that, as in the mouse [35], spontaneous, whole-brain activity is highly sensitive to abrupt transitions in physiological state. Further, direct manipulation of pupil-indexed arousal through stimulation of neuromodulatory nuclei [40,41] or the vagus nerve [42–44] is sufficient to induce brain-wide changes in neural activity.

Neural representation of physiology-related brain states

Such physiology-induced brain state changes have a stereotyped representation in the brain at multiple levels of analysis. Using human neuroscience techniques such as fMRI and electroencephalography (EEG), arousal-related changes in distributed activity patterns can be resolved [45–47] and demonstrate convergent patterns across studies. Key emergent trends include a negative coupling between pupil diameter and brain activity in sensorimotor regions [48], and a positive coupling between pupil diameter and brain activity in higher-order areas such as the frontoparietal network [38,48]. Further, increased network integration is a hallmark of increased arousal, as indexed by pupil size [39], consistent with the idea that increased arousal and related brain activity track increased attention and task performance [48], although only to a point [4] (next section).

The animal literature offers complementary insights into arousal-related brain state expression, although integration across studies is limited by the variable use of movement and pupil diameter as state measures. Large-scale recordings of activity using high-density extracellular electrophysiology or cortex-wide optical imaging of fluorescent reporters have shown that patterns of spontaneous activity are high-dimensional (with dimensionality scaling with the resolution of the recording method [49]). Although these patterns of activity are not specific to arousal states, they are preferentially expressed, such that arousal measures can be predicted from moment-to-moment fluctuations in activity [50,51] (and vice versa [36,37]) as well as from rapid changes in functional coupling between areas at the transitions between quiet wakefulness and elevated arousal [51,52]. Further, studies have demonstrated a posteromedial to anterolateral gradient of arousal modulation in mouse cortex, where sensory and association areas in the posterior and medial cortex exhibit greater modulation by arousal [30,31,37,50,51,53], consistent with previous studies in rodents performed within single brain regions, but in opposition to what has in many cases been described in humans. Recent theory-driven work has begun to address this apparent contradiction by demonstrating that arousal-locked traveling waves are present in humans (using fMRI) and non-human primates (using electrocorticography) similar to those observed in rodents [13,17,54–56], and suggests a model for future multimodal investigation.

Behavioral consequences of physiologically induced brain states

Physiology-related brain states profoundly affect the subsequent behavior of the organism. For example, optimal task performance occurs at intermediate levels of arousal in both animals and humans [4]. This is likely attributable to the permissive effect of arousal on task engagement and other ongoing cognitive processes, which elicit stereotyped brain states [57,58] that predict task performance and may be abolished at high arousal [1]. In humans, moderate arousal increases brain integration, thus facilitating task performance, an effect that is apparently driven by the catecholaminergic system [59]. Interestingly, in rodents, increasing arousal coincides with global cortical desynchronization (as in humans [60]), population-level suppression of

spontaneous activity [61] (although notably some cell types exhibit higher levels of activity [62]), and increased task engagement [57,58]; an inverse relationship between arousal and BOLD and global signal amplitude has similarly been noted in humans [63,64]. Further, these physiologically induced brain states can be directly modulated or reproduced – titrated vagus nerve stimulation improves motor learning through activation of the ascending cholinergic system [65], the influence of which is likely mediated by cortex-wide and subtype-specific effects of acetylcholine on different interneuron populations [66]. Arousal-related behavior changes have also been shown with activation of noradrenergic and other neuromodulatory deep brain nuclei [41]. Similar changes in brain-wide spontaneous neural activity and behavior have been shown for satiety signals across species [67–70], demonstrating that other homeostatic processes can drive behavior. Lastly, work probing individual differences [71] and circadian patterns [72] reinforces that spatially distributed, complex activity patterns reflect physiology-related brain states and hold potential for clinical translation (Box 2).

Limitations and outstanding questions

In the absence of experimental manipulation, it is difficult to demonstrate that brain states both facilitate behavior and reflect changes in physiological states. For example, physiological recordings rely on measures that may index numerous processes with distinct relations to brain activity [73]. Other means to manipulate arousal, such as through pharmacology [74] and sleep deprivation (recently reviewed in [75]), can be used to study physiological brain states, but have limitations, including the imprecise mechanisms of action of pharmacologic agents and the non-physiologic nature of sleep deprivation. Similarly, the observed dynamics in resting-state data, comprising much of the human work cited above, may be confounded by uncontrolled and unmeasured processes [37,76,77]. Although direct manipulation to address related questions is increasingly feasible in model organisms, this is not often the case for human neuroscience (discussed further in the section on Establishment of causal links), thus limiting cross-species translation. These limitations highlight the opportunity that external manipulations present: inducing distinct patterns of brain activity using constrained tasks can offer additional insights into brain state across species.

The brain on task: brain states induced by cognitive processes

Given the challenges of studying physiology-associated brain states, externally modulated, controlled changes to the environment of an individual present an appealing framework for the study of brain states (Figure 2). Such manipulations come in many forms; we focus on use of task paradigms to study cognitive processes of interest in both the human and animal literatures. Carefully designed tasks – traditional controlled experiments and, increasingly, naturalistic paradigms [78,79] – provide a more specific means to study brain state because they can be used both as brain state manipulations and as an environmental context to interpret the behavioral consequences of brain state changes [2]. Tasks as manipulations provide a window into the neural representation of brain states, whereas tasks as environmental context provide a means to validate and interpret them.

Task-induced brain state changes are substantial and reliable

Although the overall functional architecture of the brain has been found to be relatively stable across various task and resting states [80], task-induced changes in functional brain organization – at the whole-task, block, or even trial levels – are nevertheless substantial [2,81,82], consistent [83], and relevant to the task at hand [84–88]. For example, long-range functional connectivity strength ('integration' in graph theoretic terms) increases during cognitively demanding tasks ([39,89–91]; *cf* [88]), tracking increases in arousal [92], particularly within and between cognitive control and task-relevant macroscale networks [93,94]. A growing body of interdisciplinary work suggests that this load-dependent change in integration may result from bottom-up catecholaminergic activity [39,40,59,95,96] as well as top-down corticocortical feedback [85,97–99].

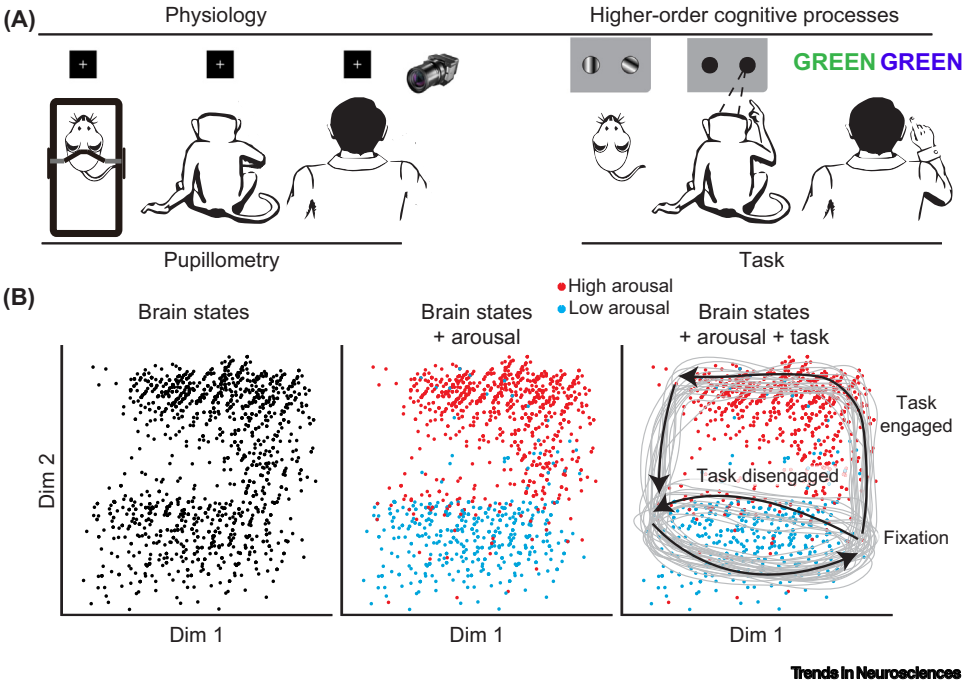


Figure 2. Using physiological states and cognitive paradigms to characterize corresponding brain states. (A) In this article we discuss brain states that correspond to physiological states and cognitive paradigms. The former offers an opportunity to study spontaneous fluctuations in brain activity, but the lack of clearly defined behavioral state boundaries complicates interpretation of these changes (although studies have demonstrated the potential to segment behavioral sequences from spontaneous activity; e.g., [156]). Cognitive paradigms can offer clearer behavioral state boundaries. (B) As represented in simulated neural data embedded via dimensionality reduction in a 2D state space, clusters of similar timepoints are clearly visible, but cannot be labeled (left panel). With a distinct and supporting modality, such as pupillometry to index arousal (middle panel), one can observe the influence of physiology on whole-brain activity, and identify timepoints at which patterns correspond to high and low arousal. Further interpretation of these brain states is made possible by knowledge about the structure of the cognitive paradigm during which data were collected (right panel), and can reveal stereotyped trajectories through state space on high- and low-engagement trials, with low-arousal activity patterns being more common on low-engagement trials, perhaps tracking decreased task performance. These boundaries likely do not fully explain the traversal of the brain through state space (task-defined states can also be affected by other factors), underscoring the need to study brain states at multiple temporal scales (Figure 3). Nevertheless, each approach offers distinct but complementary insights into the nature and functional implications of neural dynamics. Abbreviation: Dim, dimension.

Neural representation of task-induced brain states

More generally, cognitive tasks limit the number of accessible brain states [2,100] (Figure 2), as demonstrated, for example, by decreased functional connectivity variability during tasks relative to rest [94,101]. This constrained repertoire may explain the recent finding that, across a wide range of tasks, task-based functional connectivity better reveals brain-phenotype relationships than resting-state functional connectivity [86,102,103]. Recent work in rodents has shed further light on this. Although trial-to-trial and interindividual variability in cortical activity is best explained by putatively task-irrelevant behaviors, tasks both reveal and constrain such variability [37,97], and demonstrate how behavior may interact with cognitive demands to limit the accessible brain states [37,104,105].

Although tasks have been shown to elicit (and require) specific whole-brain activity patterns, they also reliably induce cell- and circuit-level changes that have been extensively characterized in animal models. We propose that the concept of brain state links these fields, and suggests ways in which local changes scale to yield whole-brain patterns. For example, task-induced brain state

changes manifest at the circuit level through oscillatory synchronization, as has been shown for high-level cognitive processes such as working memory and attention (in both humans [106] and animal models [107,108]). Neurons representing an attended stimulus are transiently and locally synchronized [109–111], and in turn entrain downstream neuronal populations [112,113], thus amplifying representation of task-relevant information. Further, consistent with the observation that tasks constrain accessible brain states in humans, tasks induce patterns of brain activity that are important for sensory gating by spontaneous activity [114,115]. This suggests a potential mechanism by which tasks constrain brain states in a highly specific manner that modifies interareal effective connectivity [107,116].

Behavioral consequences of task-induced brain states

In addition to affecting brain states, tasks provide a key, of sorts, to decode them. That is, relating recurrent brain states to task events offers a means to interpret those activity patterns by tracking their relevance to ongoing cognitive processes and subsequent behaviors. This approach has been leveraged by human neuroscience, given its access to complex cognitive processes, with the consistent finding that distributed brain activity patterns, as captured by functional connectivity, stably and distinctly represent different cognitive tasks [83,117]. The cognitive processes invoked by each task can in turn be used to interpret such patterns; for example, changes in functional connectivity patterns reflect real-time task demands, with task-relevant brain areas transiently drawn into brain-wide networks related to task performance [84,85]. That task performance improves with greater expression of such task-relevant activity patterns validates their functional relevance, a finding that has been replicated in various domains and species [87,89,91,99,104,118].

These examples underscore the cognitive specificity of brain state changes; together, this work illustrates both the utility of brain states to characterize task-related brain activity and the utility of task paradigms to validate the behavioral consequences of resolved brain states.

Limitations and outstanding questions

Although tasks can help to resolve the nuanced interactions among physiological and cognitive states (hereafter **behavioral states**), the beginning and end of a task manipulation are unlikely to clearly demarcate the beginning and end of discrete behavioral states, which are difficult to disentangle not least because they evolve on varying timescales (e.g., task demands superimposed on background physiological and cognitive states; Figure 3). To date, the neural influence of each such behavioral state has largely been studied in isolation, but this approach fails to acknowledge the simultaneous expression of many behavioral states and corresponding brain states (Figure 3).

We propose that this presents an opportunity for interdisciplinary approaches to integrate across spatial scales and modalities to provide a more complete picture of these complex dynamics and to disentangle multiplexed brain states. By linking seemingly disparate approaches, a shared concept of a brain state offers an organizing framework for this work, to which we turn next.

Using brain state to unify the study of neural dynamics

In the preceding sections we highlighted the diverse ways in which physiological and cognitive processes can be studied across species using brain states. The highlighted field-specific techniques differ in temporal and spatial scale, in their capacity to offer mechanistic or whole-brain insights, and in practical application (Box 1). Nevertheless, a shared concept of brain state can relate seemingly disparate findings across these scales and disciplines. That is, brain states, as the fundamental unit of whole-brain neural dynamics, evolve and combine to yield observations at every temporal and spatial scale. Combining these methods of observation will thus permit a more comprehensive understanding of how and why the brain moves through stereotyped

states. This will, in turn, shed light on the neurobiological underpinnings of the dynamic brain, of the behavioral states that these brain states subserve, and of disease-specific alterations in these dynamics (Box 2). In what follows we highlight how such interdisciplinary work can use the concept of brain state to map and integrate results across levels of analysis, with a look to the future (see Outstanding questions).

Theoretical considerations

Each neuroscience technique, when used in isolation, offers a partial view of brain dynamics, from high-fidelity observation of the cycling of a single neuron through brain states to the characterization of brain-wide activity patterns related to high-level cognitive processes over long timescales (Box 1). In combination, however, they hold the promise of more completely characterizing and interpreting brain states.

Such interdisciplinary work will require a willingness to think outside the box about how brain states manifest across modalities [119] and species [120]. One could ask, for example, how local changes in single-unit activity and population synchrony scale up to yield corresponding whole-brain activity patterns for a given behavioral state. The experimental steps may also be reversed by using the advantages of human neuroscience techniques to identify regions or patterns of interest for more focal study of mechanism in animal models. Finally, one may explore analogous properties of the dynamic brain across modalities, such as network small-worldness [121].

Two crucial challenges in these lines of work are to identify recurring brain states over time, during apparently distinct behavioral states, and to disentangle jointly expressed brain states. To date, the greatest progress has been made on the former by treating any given moment as representative of a single behavioral state, identifying corresponding brain states, and searching for the expression of those brain states in distinct behavioral states. In actuality, however, many behavioral (and corresponding brain) states are entangled at any given moment, and their separation is necessary for a complete and precise characterization of brain dynamics. This will require bridging levels of analysis, either at the data acquisition or analysis stage. We turn next to selected works that exemplify this, and use them to clarify key, practical recommendations for the approach we propose.

Identification of recurrent brain states: applied examples

Several recent studies, leveraging techniques at varying levels of spatial and temporal analysis within a single project, have demonstrated that brain states recur over time during distinct behavioral states. Using human fMRI-based functional connectivity, it was recently demonstrated that a brain state that predicts attention across individuals also predicts attention fluctuations within individuals across time and physiological states (e.g., light anesthesia and sedation) [74]. Others similarly demonstrated the recurrence of two distinct brain states in a highly sampled individual across time and physiological states (e.g., hunger and satiety) [122]. A strength of these human studies is the complexity of behavior that can be related to brain states, but insights into mechanism are limited. Conversely, a recent study used two model organisms – larval zebrafish and mice – to mechanistically characterize conserved neuromodulatory cell types that shape brain states corresponding to arousal, a relatively low-level physiological state [41].

Leveraging the strengths of both of these approaches by studying humans and model organisms together, a recent study first used human fMRI to identify a brain state induced by reward anticipation in an inferential reasoning task, and then employed invasive methods to both record and manipulate its expression in mice [123]. By using a common task and method of analysis to link

data across modalities and species, the authors were thus able to comprehensively characterize a conserved brain state underlying complex behavior.

We propose that the unifying concept of a brain state has the potential to make such interdisciplinary work widely accessible. No single study or research group must perform every stage of this process, but individual studies should be designed to identify common brain states. Examples include the collection of physiological data (e.g., pupillometry, facial movement) and implementation of tasks that are readily adaptable across species, as well as the development of analytical frameworks that are applicable across modalities. Such work will permit interspecies comparison of brain states to identify useful points of convergence. We leverage example data from unrelated papers to illustrate this point (Figure 4). The use of a common physiological construct – arousal – permits changes in whole-brain activity in humans to be directly linked to fast, cell type-specific activity in comparable physiological states in the mouse (Figure 4A). Alternatively, a common analytical approach, such as whole-brain functional connectivity calculation, similarly offers a bridge across levels of analysis. For example, functional connectivity patterns can be compared across species during matched arousal states; human study offers the opportunity to use complex arousal manipulations (e.g., vigilance task in sleep-deprived participants) with implications for cognition, and animal models again offer a route to mechanistic explanation (Figure 4B). The examples illustrated in Figure 4 are not intended to make specific scientific claims but instead aim to illustrate the notion of synthesizing data across modalities and species, even in unrelated experiments, using common measures and analytical tools.

Separation of jointly expressed brain states: applied examples

All of these examples treat each moment in time as a single behavioral state, with a single corresponding brain state. As described above, however, a second key challenge for the study of brain dynamics is to disentangle the many brain – and behavioral – states that may be jointly expressed at any given time, but that have traditionally been studied in isolation (e.g., Figure 3), particularly at rest [124]. Temporal decomposition techniques (e.g., [13,17,36]) are widely used to explore recurring, overlapping spatiotemporal activity patterns – blind source separation frees such analyses from theory-driven assumptions about the temporal evolution of brain states [125], but correspondingly poses challenges for neurobiological interpretations that link the patterns resolved to physiological and cognitive processes. Efforts to decompose each timepoint into such interpretable brain states are crucial to accurately attribute brain activity patterns to a given behavioral state. This was recently achieved by performing near-whole-brain, chronic extracellular electrophysiological recordings in rodents and applying machine-learning methods to separate neurobiologically distinct, but jointly expressed, activity patterns ('electomes') underlying stress vulnerability and stress-related dysfunction [126]. This study disentangles fast time-varying signals that contain information about slowly unfolding mood phenomena, and raises the question of what other unmodeled but co-occurring behavioral states could be identified using similar techniques.

Such work separates multiplexed brain states, which can then be identified and studied in other modalities. This does not need to be accomplished in a single experiment; our proposed brain state-based approach provides a roadmap to combine observations across modalities and levels of analysis. This yields a common space to isolate distinct brain states by identifying and removing the neural manifestations of other co-occurring behavioral states (Figure 3).

Establishment of causal links between brain and behavioral states

Finally, establishing a causal relationship between brain and behavioral states requires direct manipulation of brain states. Such manipulation may be invasive (e.g., via optogenetics or direct

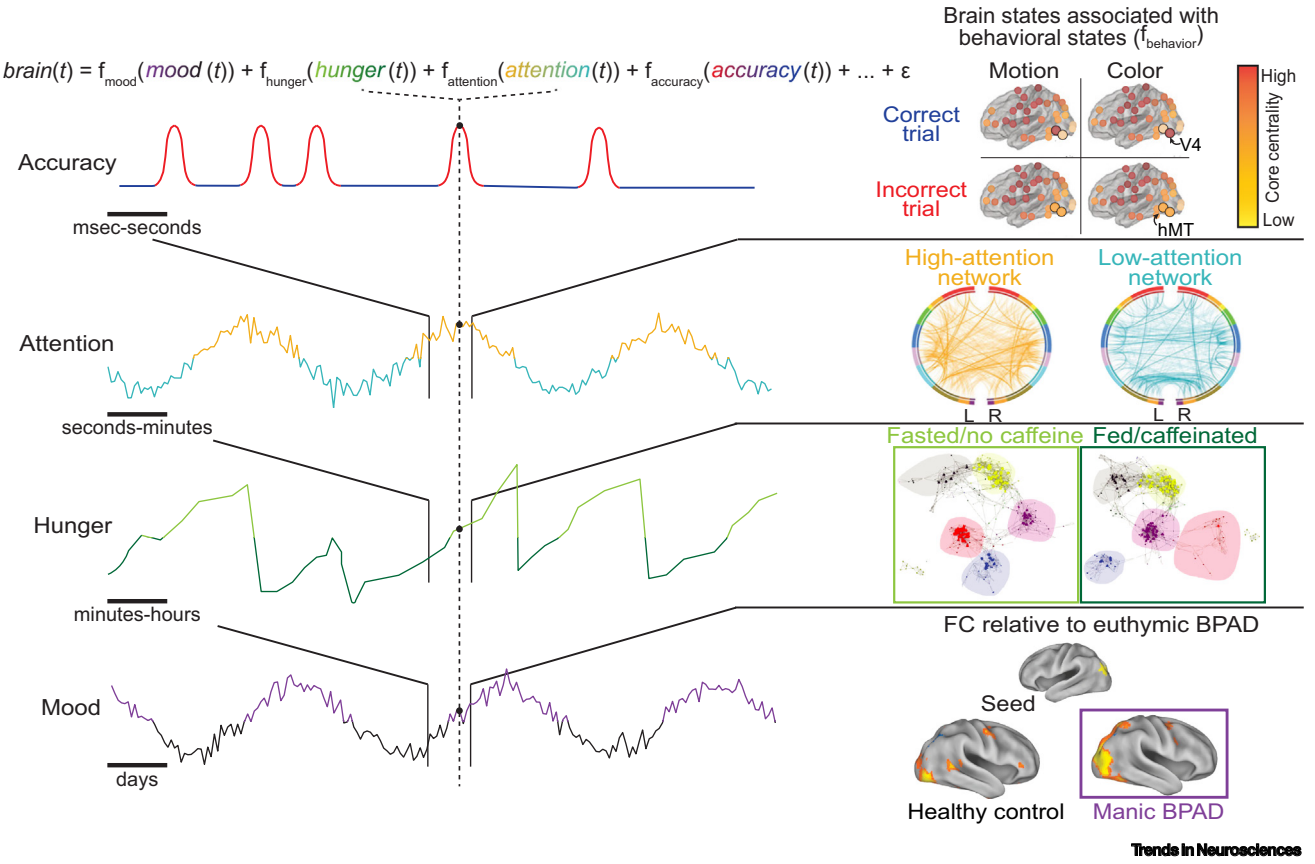
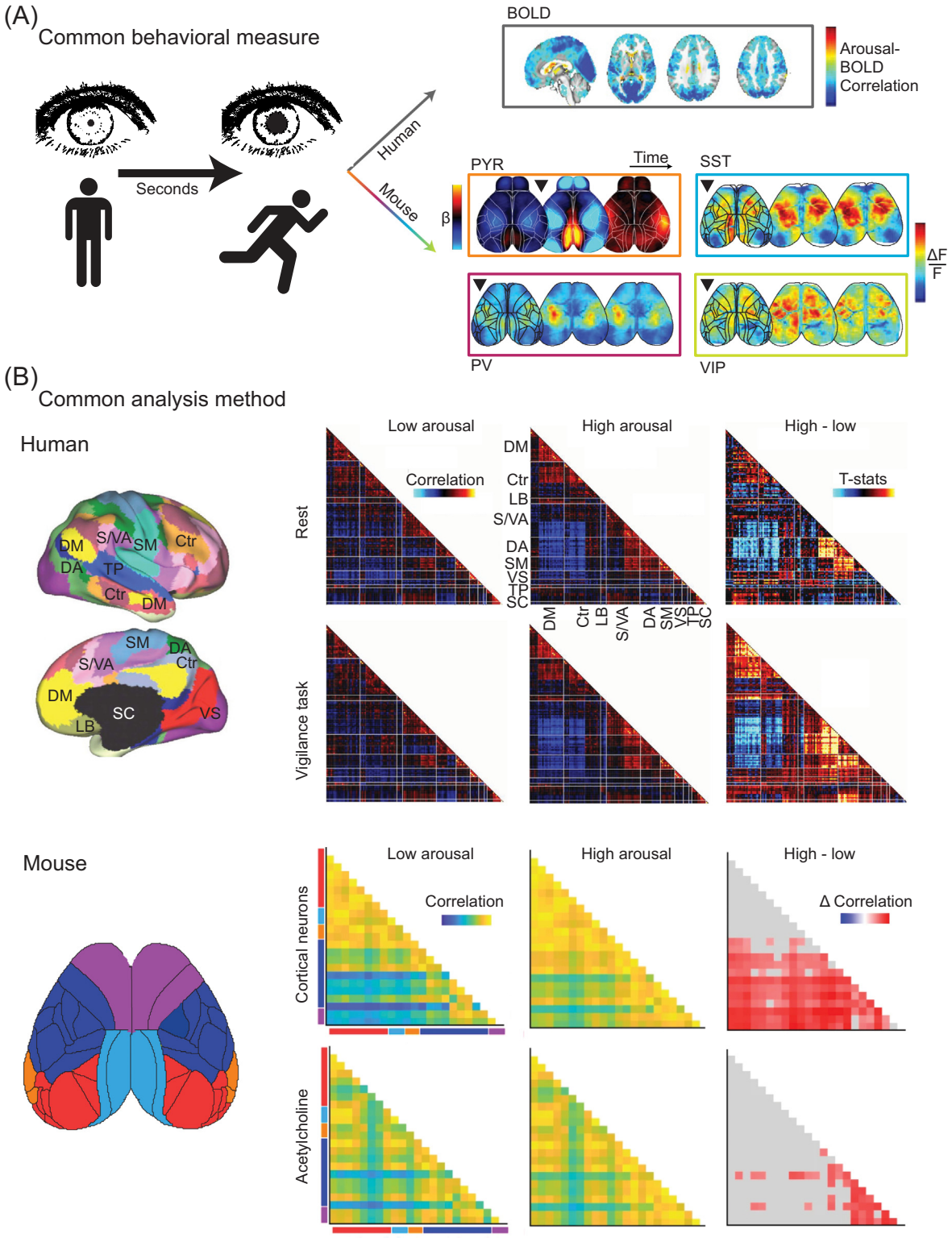


Figure 3. Behavioral states evolve at varied temporal scales and interact at each timepoint. (Left) Four examples of behavioral (i.e., physiological and cognitive) state domains – mood, hunger, attention, and task performance – are depicted by simulated timecourses. Each behavioral state unfolds on a different temporal scale, and brain activity at each moment in time reflects the combination of the behavioral states occurring and interacting at that time and the brain states underlying them. (Right) Examples of previous work studying patterns of brain activity (brain states) that correspond to each of these physiological and cognitive states in isolation. (Top) Network reconfiguration tracks task performance, such that core centrality of task-relevant regions [visual area V4 on color discrimination trials and middle occipitotemporal cortex (area hMT) on motion discrimination trials] increases during preparation for trials in which participants respond correctly. Schematized depiction of results from [85]. (Second from top) Functional connectivity patterns that predict low and high attention across two independent datasets. Colored bars represent 'lobes' (e.g., blue, temporal). Adapted, with permission, from [86]. (Second from bottom) Changes in whole-brain network organization, as measured using fMRI-based functional connectivity, in fed and fasted states. Each point represents a brain region, colored by network assignment (e.g., blue, visual network), with hub regions enlarged. Adapted, with permission, from [157]. (Bottom) Differences in seed-based functional connectivity (FC) between bipolar mania and bipolar euthymia, and between healthy control and bipolar euthymia. Adapted, with permission, from [158]. Abbreviations: BPAD, bipolar affective disorder; fMRI, functional magnetic resonance imaging; L, left; msec, milliseconds; R, right.

electrical stimulation in neurosurgical patients [127]) or noninvasive (e.g., via real-time, imaging-based neurofeedback [128,129], temporal interference [130], pharmacologic agents [74] or transcutaneous vagus nerve stimulation [44]). By manipulating circuits to achieve a given brain (and consequent behavioral) state, such work can both illuminate the neural dynamics underlying complex physiological and cognitive states and promote the use of inducible brain states for clinical intervention.

Concluding remarks

Each research community, from cellular to systems, cognitive, and clinical neuroscientists, motivated by the benefits and limitations of its available techniques, offers a different window into brain state. These perspectives are necessarily different – not because they are based on inherently different definitions of brain state, but because they often employ different techniques to study the



Trends in Neurosciences

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Box 2. Clinical applications

A growing body of evidence suggests that brain state patterns are altered in disease (e.g., [144]); a more complete understanding of brain state dynamics thus holds the promise of shedding light onto the neural bases and consequences of various neurological and neurodevelopmental conditions. Brain state dynamics in autism spectrum disorder (ASD) have been particularly well studied.

For example, there is growing evidence that spontaneous brain activity patterns differ in autistic people relative to typically developing (TD) individuals. In ASD-related mouse models, gamma band oscillatory EEG activity is increased [145] and decreased excitatory drive onto medial prefrontal cortex (mPFC) pyramidal cells results in reduced coordination of activity in delta and theta frequency bands [146]. Similar disruptions of oscillatory activity have been found in autistic people [147,148], although results are not always convergent (e.g., [149]). Recent work suggests a link between such disrupted oscillatory activity and connectivity alterations in ASD [150].

Although not always feasible in populations with neurological and neurodevelopmental conditions, the use of cognitive paradigms to manipulate brain state can also reveal clinically relevant alterations in brain states. Consistent with findings at rest, altered oscillatory and functional connectivity patterns have also been demonstrated in ASD during various tasks, and were found to track task performance [151]. Further, consistency of task-induced activity patterns may differ in ASD; lower consistency of task-induced brain states in ASD than TD participants was found to track the severity of restrictive behaviors [152].

More generally, cross-species approaches provide a means to recapitulate, mechanistically characterize, and test interventions for brain state alterations in human disease. For instance, a study on *Fmr1* knockout mice, which recapitulate aspects of fragile X syndrome (FXS), used a common visual discrimination paradigm to identify similar behavioral impairments in FXS individuals and the model mice, and then used the latter to show that these deficits are mediated by parvalbumin interneuron dysfunction [153]. Recent work using *15q dup* mice, a model of autism, revealed widespread hypoconnectivity compared to wild-type mice during wakeful rest. D-cycloserine rescued social behaviors and partially restored connectivity patterns in affected mice [154]. Although it is unlikely that D-cycloserine will be efficacious for all autistic individuals [155], integration of ongoing brain state research across species may help to define subgroups who are likely to benefit from it.

Such work demonstrates the promise of using interdisciplinary methods to characterize brain states and their causal mechanisms. Further, differences in the brain state repertoire across cognitive and disease processes may themselves be targets for intervention. Recent studies in mice [129] and humans [128] have used real-time feedback to train subjects to express large-scale patterns of brain activity, resulting in sustained changes in functional connectivity. Direct brain state manipulation has also been achieved (section on Establishment of causal links). These technological innovations offer the exciting possibility of better understanding and potentially intervening in a range of clinically relevant processes.

Outstanding questions

Is there a finite 'dictionary' of brain states that recur over time, and how should we interpret them in the context of continuously evolving and simultaneously expressed behavioral states?

Necessity: what features of a brain state are necessary to induce changes in behavior?

Sufficiency: can inducing a brain state associated with a given physiological state or cognitive paradigm – in the absence of that physiological process or paradigm – cause comparable changes in behavior?

How often and completely must a pattern of activity recur to be considered a brain state, both within and across individuals, and does this criterion depend on the data modality?

How do global brain states emerge from local phenomena?

To what extent do other species experience 'human-specific' brain states, and which cognitive and physiological states can be equated to study corresponding brain states across species?

How can we best disentangle co-occurring brain states by leveraging complementary hypothesis- and data-driven techniques?

How can we use direct manipulation of brain activity – in animal models and human patients – to study brain states and develop novel clinical interventions?

same construct. We have aimed to reframe these efforts as complementary work toward a common goal: a more comprehensive understanding of brain states – the structured, reproducible, and behaviorally relevant patterns of brain activity that allow an individual to successfully move through a changing world.

Figure 4. Using brain state to unify the study of neural dynamics. Common behavioral measures link the study of brain states across species: (A) Changes in arousal measures (i.e., pupil size, movement) occur on the order of seconds. (Top right) The slow dynamics of blood oxygen level-dependent (BOLD) signal fluctuations on this timescale yield persistent (but whole-brain) patterns related to changes in arousal. Adapted, with permission, from [159]. (Bottom right) Faster dynamics (each image represents changes over ~300 msec) can be captured with cell type specificity using mesoscopic calcium imaging in mice. Adapted, with permission, from [37] for PYR (pyramidal) and [66] for PV (parvalbumin), SST (somatostatin), and VIP (vasoactive intestinal polypeptide) neurons. Black triangles represent the onset of increased arousal. By matching behavioral states across species, more invasive and higher-resolution techniques in animal models can be leveraged to reveal mechanistic insights into the complex behavioral and cognitive processes that can uniquely be studied in humans. (B) Shared analytical methods also provide a tool to bridge disciplines: whole-brain activity patterns can be divided into parcels within functionally defined regions (left) and pairwise correlations of the timecourses of different parcels yield functional connectivity (FC) matrices, either from functional magnetic resonance imaging (fMRI) data in humans (left top) or from mesoscopic functional imaging data in mice (left bottom). FC can be calculated across physiological states (low versus high arousal) from data acquired during a given cognitive state (e.g., rest versus task) or from measures of neuronal activity or acetylcholine release. These FC matrices can be used to reveal common features of low- and high-arousal brain state patterns and yield mechanistic insights into how these states may be generated. For example, tasks amplify arousal-related FC increases in somatomotor networks in humans (right top and upper middle matrices). Adapted, with permission, from [160]. Increases in arousal also cause correlated acetylcholine release and synchronize neuronal activity in analogous networks in mice (right lower middle and bottom matrices). Adapted, with permission, from [27]. Human network labels: Ctr, control; DA, dorsal attention; DM, default mode; LB, limbic; SC, subcortical; SM, somatomotor; S/VA, salience/ventral attention; VS, visual; TP, temporoparietal. Mouse network labels: red, visual; orange, auditory; light blue, retrosplenial; dark blue, somatosensory; purple, motor.

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Declaration of interests

The authors declare no competing interests.

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