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On Arousal and the Internal Regulation of Brain Function: Theory and Evidence across Modalities and Species

Ryan Raut
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Division of Biology and Biomedical Sciences
Neurosciences

Dissertation Examination Committee:
Marcus Raichle, Chair
Adam Bauer
Jin-Moo Lee
Abraham Snyder
Lawrence Snyder

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by

Ryan Raut

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Acknowledgments

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I have done my best to limit myself to just one paragraph on Marc (after all, I am already dedicating the rest of this document to him!). Scientifically, the things I admire most about Marc are his unmatched enthusiasm, open-mindedness, broad curiosity, and unabashed conviction that the toughest questions in science not only have answers, but answers we should not be afraid to seek. All of these qualities have been essential to this dissertation. One quickly becomes acquainted with these qualities of Marc and, all of a sudden, his propensity for driving genuine paradigm shifts in neuroscience begins to make sense. All this said, Marc's best qualities are his character and mentorship. His support over the past five years has been so unwavering, and the way he treats others so inspiring, that it is difficult to imagine exactly *whom* I might have been now without it. From his endless empathy for my habitual procrastination (although I worry that

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Ryan Raut

Washington University in St. Louis

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Dedicated to Marc

ABSTRACT OF THE DISSERTATION

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Professor Marcus Raichle, Chair

The brain is an organ. It is subject to the same physiological regulatory processes that engage the rest of the body's organs, sculpted over hundreds of millions of years to sustain life so effectively. The central message of this thesis is that the holistic functioning of the brain, rather than operating at some level above or independent from these systemic regulatory processes, is deeply related to them. In short, as our limited attention spans might suggest: brain function is internally regulated. I propose that this internal regulation is a primary function of intrinsic brain activity. Chapter 2 provides a theoretical treatment of this issue, recasting intrinsic activity as an internal regulatory process operating on the brain's temporal "states" and spatial "networks". After establishing this framework, Chapters 3 and 4 provide tests of specific predictions. Thus, Chapter 3 confirms, in humans and macaque monkeys, the presence of topographically organized traveling waves occurring in synchrony with ongoing arousal fluctuations, with propagation occurring in parallel within the neocortex, striatum, thalamus, and cerebellum. This process is

argued to provide a heretofore lacking physiological account of “resting-state functional connectivity” and related phenomenology. Chapter 4 extends this observation by demonstrating a continuous and tightly coordinated temporal evolution of brain, body, and behavioral states along a latent arousal cycle. Across multiple recording techniques and species, this cyclic trajectory is shown to be coupled to the traveling wave process described in Chapter 3, thus providing a parsimonious and integrative account of intrinsic brain activity and its spatiotemporal dynamics. Taken together, this thesis argues for the existence of an intrinsic regulatory process for global brain function.

Chapter 1

Introduction

The scientific context for this thesis is provided in full in Chapter 2, which attempts to motivate a broader and more integrative perspective on intrinsic brain activity and its relation to body and behavior. As such, I will use this Introduction to briefly comment – in part, by recounting my own PhD trajectory – on why a systems neuroscience dissertation has been pursued on a topic as broad and seemingly mundane as arousal.

Traditionally, brain function has been probed by examining how neural activity responds or relates to experimentally controlled sensory stimuli or behavioral tasks. This approach has yielded considerable information on the specific functionalities of different regions and activity patterns in the brain. But the approach leaves unaddressed the continuous, ongoing nature of brain activity, whose considerable energetic demands change only subtly during the abovementioned "activation" studies. This motivates interest in what has come to be known as "spontaneous" or "intrinsic" brain activity (Buzsáki, 2019; Raichle, 2010). In other words – what is the brain doing all the time? That this intrinsic activity is in fact spatiotemporally organized is now widely recognized; however, the details of this spatiotemporal organization, as well as the physiological and functional significance of intrinsic brain activity, remain areas of active speculation and investigation (e.g., (Laumann & Snyder, 2021; Pezzulo et al., 2021; Stringer et al., 2019)).

Much of the attention to intrinsic brain activity over the past decade has come in the context of "resting-state functional connectivity" (RSFC). This term refers to the observation that, using non-invasive magnetic resonance imaging, blood oxygen levels in the brain are seen to spontaneously fluctuate over tens of seconds, and these fluctuations are synchronous among regions that are closely functionally related (Fox & Raichle, 2007). This property has made RSFC a widely used paradigm for mapping the functional organization of mammalian brains *in vivo,* based upon the correlation structure of spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal.

When I joined in 2017, the Raichle group had been pursuing an exciting hypothesis: that the spontaneous BOLD signal fluctuations underlying RSFC were not simply a crude and poorly temporally resolved measure of fast neuronal spiking activity; rather, these fluctuations were a distinct and intrinsically slow physiological process in the brain (He et al., 2008; Mitra & Raichle, 2016). The specific physiological and functional significance of such a process, however, was less clear.

Around this same time, emerging neurotechnologies began to permit high-density, brain-wide measurements of single-neuron activity in awake behaving animals (e.g., (Jun et al., 2017)). Despite the ability to record from large neuronal populations, the structure of this activity turned out to be surprisingly low-dimensional: in particular, these studies were invariably finding that brain-wide activity was dominated by global activity that slowly fluctuated with arousal state over tens of seconds (e.g., (Garcia-Junco-Clemente et al., 2019; Stringer et al., 2019)). The slow timescale of this global activity motivated investigation of a potential link between these arousal-related fluctuations and spontaneous BOLD signal fluctuations. The difficulty in pursuing this

question was that arousal fluctuations, its physiological correlates (e.g., fluctuations in cardiorespiratory activity), and more generally, globally shared signal variance, were (and still are) generally viewed as signals of non-interest, or even artifact, in the neuroimaging community (e.g., (Birn, 2012; Power et al., 2017)). The principal concern is that blood oxygen correlates of these factors reflect systemic physiological processes unrelated to the neuronal activity that is presumably of interest. But, by removing global variance and physiological "nuisance," were we overlooking a potentially interesting and important piece of the story?

What unfolded from this pursuit was, I believe, much broader in scope than anticipated. Arousal increasingly appeared to be not just a missing piece, but a missing context that – once reintroduced – allowed for a parsimonious account of much of the literature pertaining to RSFC. But, even further, we realized that arousal also connects RSFC and intrinsic activity to a much broader literature on physiology and psychology. Or, at least, I was finding that ideas from these fields were proving immensely helpful for my own understanding of what we were observing. I now feel that this broader literature is vital to proper conceptualization of intrinsic brain activity; this has motivated a more theoretical chapter (Chapter 2) that engages with this broader literature to articulate at length an integrative perspective on arousal and brain function. Writing Chapter 2 was a very helpful exercise to me in thinking about the many pieces relevant to this story. I hope that it might be similarly useful to others.

Summary of Thesis

The research contributions of this thesis are presented as three main chapters. The first of these, Chapter 2, introduces a theory of arousal and intrinsic brain activity. This theory predicts a latent physiological process that spatiotemporally regulates global brain function – via modulation of

brain states and brain networks – in congruence with body and behavior. The theory leads to two principal hypotheses whose empirical investigation is pursued in Chapters 3 and 4. Thus, Chapter 3 will validate the prediction of a topographically structured, brain-wide traveling wave process that spatiotemporally organizes brain-wide activity in relation to arousal. This phenomenon forms the basis for a framework that I will propose as a parsimonious account for several major themes in the RSFC literature.

Chapter 4 will recast this activity from a dynamical systems perspective, which – as I will argue in Chapter 2 – offers several advantages for understanding the coupling among various measurements of intrinsic brain activity, body, and behavior. This viewpoint falls in line with a longer tradition of understanding physiological processes as smooth phase space trajectories unfolding on low-dimensional manifolds (Goldbeter, 1996; Nicolis & Prigogine, 1989; Winfree, 1980). Consistent with the predictions of Chapter 2, the traveling wave phenomenon will be shown to intimately relate to the notion of brain state dynamics (e.g., (McGinley et al., 2015)). We will further validate the prediction of a latent "brain state" variable that continuously cycles along an intrinsic attractor manifold; movement along this manifold manifests physically as movement of activity across the brain – i.e., the wave propagation discussed in Chapter 3. Thus, brain state dynamics and RSFC will be absorbed into a common, parsimonious framework.

Concluding remarks are provided in Chapter 5. I will briefly discuss lingering questions and future directions, as well as further testable hypotheses relating to the theoretical framework pursued in this thesis.

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Chapter 2

On the Internal Regulation of Brain Function

2.1 Abstract

Biological brains act in concert with body-wide physiology and behavior to maintain internal states within a tenable range. At the same time, the neurophysiological processes underlying brain function are part and parcel of these internal states. These simple facts motivate theoretical consideration of how global brain function and its underlying physiology are internally regulated. I approach this question by contextualizing themes in the empirical systems neuroscience literature with concepts and principles borrowed from theoretical biology, psychophysiology, ethology, and cybernetics. The chief proposal emerging from this integration is the existence of a latent arousal cycle entraining brain, body and behavior. I will argue that this cycle acts as a spatiotemporal regulatory process for global brain function, lawfully transitioning among functional regimes of the brain that are instantiated temporally, in the form of brain states, and spatially, as large-scale functional systems. I posit that a considerable fraction of so-called spontaneous or intrinsic brain activity may be parsimoniously attributed to this spatiotemporal regulatory process. Further implications and specific hypotheses are discussed.

2.2 Introduction

2.2.1 A brief synopsis

Physiological states vary in the extent to which they leave an organism prepared to contend with an environmental threat. Given the fundamental imperative to survive, let us assume that

organisms seek to minimize the likelihood of encountering a threat whilst in a suboptimal state. Statistical structure in the environment affords some (limited) predictability toward this end, enabling anticipatory regulation of physiological states. However, active organisms have the additional ability to render their environments (including risk of encountering adverse environmental conditions) more predictable by simply behaving in a regular manner – e.g., alternating between active, exploratory, environment-engaging states, and inactive or "offline" states. This dynamic naturally fosters coordinated cycles among body, behavior, and environment: a circular causation of those very environmental regularities that come to entrain an organism's internal states and behavior.

What is seldom appreciated is that – to the extent that internal states of the *brain* also vary in their suitability for dealing with environmental threats – global brain *function* must itself be internally regulated and kept in synchrony with body and behavior.

This brief synopsis is intended to intuitively motivate the principal argument of this essay. Brain function exhibits global temporal and spatial organization in relation to active and inactive states; consequently, it is argued, internal regulatory processes are likely to place significant constraints on brain-wide spatiotemporal dynamics and, hence, global brain function. I suggest that the orchestration of this internal regulation is likely to account for a considerable fraction of so-called "spontaneous" or intrinsic brain activity.

The remainder of this essay motivates this account by appealing to and building upon essential concepts from several relevant disciplines that are, unfortunately, sparsely represented in the experimental systems neuroscience literature. I review these concepts in attempt to provide an integrative perspective on the internal regulation of brain function. I begin by reviewing the

concepts of homeostatic (Cannon, 1932) and allostatic (Sterling, 2012) physiological regulation, which I proceed to connect to the notion of global organismic states (LeDoux, 2012) – coordinated states of body-wide physiology and behavior. An extension to global organismic *dynamics* is motivated by connecting these states to ethological accounts of goal-directed behavior, which recognize stereotyped "appetitive-consummatory" behavioral sequences (Craig, 1917). I proceed to argue that these global organismic dynamics are embedded within a cyclic trajectory of a "generalized arousal" process (Calderon et al., 2016). Finally, within this context, I review a body of evidence on intrinsic brain activity that spans multiple poorly integrated systems neuroscience communities. The argument is made that much of intrinsic brain activity studied across these contexts is associated with a latent regulatory process that spatiotemporally organizes brain-wide dynamics in relation to ongoing arousal cycles.

2.3 Physiological primer

2.3.1 Homeostatic regulation

The most essential characteristic of all organisms is the ability to resist decay of internal states to the surrounding environment (Bernard, 1974; Friston, 2013; Schrödinger, 1945). These internal states include essential physiological variables such as fluid balance, temperature, blood pressure, and blood glucose. The active maintenance of these variables within physiological range – i.e., *homeostasis* (Cannon, 1932) – is the most fundamental imperative of biological systems.

Intuitively, homeostatic regulation may be understood as preservation of a mostly static internal milieu. Indeed, historically, regulation of the internal state has been cast in terms of closed-loop regulatory mechanisms that detect and respond to the deviation of essential variables from their

corresponding setpoints. But, as bluntly put by Ross Ashby – a central figure in the "cybernetics" movement inspired by Walter Cannon's work on homeostasis – "Error-controlled regulation is in fact a primitive and demonstrably inferior method of regulation" (Conant & Ashby, 1970). Thus, as would be noted by Sterling (Sterling, 2012), error-driven homeostatic regulation is at odds with another essential principle of biology: the principle of natural selection.

2.3.2 Allostatic regulation

As previously noted (Schulkin & Sterling, 2019; Sterling, 2012), the seminal work of Claude Bernard (Bernard, 1974) – introducing the essence of what Walter Cannon would term *homeostasis* – emerged contemporaneously with Darwin's principle of natural selection (Darwin, 1881). Consequently, considerations of efficiency and selective pressures were hardly factored into the notion of retaining the "constancy of the internal milieu" (Bernard, 1974), nor its subsequent elaboration by Cannon.

Given the competitive advantages amidst limited resources, natural selection will tend to favor more efficient regulation. Although negative feedback and error-driven regulation play a vital role in the maintenance of the internal milieu (Ramsay & Woods, 2014), in practice, much of physiological regulation is *predictive* – i.e., acting to *anticipate* deviations from physiological conditions, ideally avoiding those conditions from actually occurring (Barrett & Simmons, 2015; Kalat, 2019; Ramsay & Woods, 2016). We stop drinking water well before our fluid balance is restored. Insulin secretion begins to promote glucose uptake well before a meal induces a rise in blood sugar – in fact, even before the first bite of food! Likewise, muscles are warmed and cardiovascular activity upregulated at the very onset of exercise – far in advance of the need for such extensive physiological changes (Krogh & Lindhard, 1913). In short, physiological systems

make use of *presystemic* or *cephalic* signals in cueing regulatory processes (Ramsay & Woods, 2014; Stricker & Hoffmann, 2007). This anticipatory regulation of homeostasis has come to be referred to as *allostasis* (Sterling, 1988, 2012).

Allostatic regulation further enables exploitation of dynamic energetic tradeoffs (Sterling, 2012). Thus, complex physiological regulatory dynamics manage a suite of tradeoffs on the basis of predicted need. (The natural emergence of such tradeoffs is perhaps simpler than one might imagine (Liu et al., 2017).) The ongoing nature of these tradeoffs is readily apparent from the coordinated fluctuations observed across a multitude of physiological measures (Schulkin & Sterling, 2019; Sterling, 2012).

This account thus deviates from a more static picture of homeostasis resting on closed-loop error-correction; instead, we see dynamic, anticipatory tradeoffs that facilitate efficiency and flexibility even in the absence of immediate homeostatic challenge. Such flexible regulation is more well-equipped for the dynamic and unpredictable environments that lifeforms have come to inhabit.

2.3.3 From physiology to behavior: global organismic states

The homeostatic potential of internal regulation alone, orchestrated by the autonomic nervous system, is woefully limited. On a cold winter day, most of us will not rely exclusively on shivering or upregulating our metabolism to increase our body temperature. Instead, quite likely, we will also seek out a warmer environment, or simply put on a sweater. In other words, in addition to regulating internal states, we may change our *behavior* – our interaction with the environment – in pursuit of desired internal states (Cisek, 2019; Friston, 2010, 2013; Seth, 2015). From this perspective, we can appreciate *generalized* homeo- (or allo-) stasis as the very basis

for adaptive behavior (Ashby, 1952; Powers, 1973). This notion of coordinated, anticipatory (allostatic) regulation of physiology and behavior is not a new one; indeed, it was integral to the Nobel Prize-winning work of Ivan Pavlov (Pavlov & Thompson, 1902)

In sum, we see that both autonomic internal regulation and (allostatic) actions on the external word are complementary means to achieving desired internal conditions (Friston, 2010; Kalat, 2019) (or, more formally, minimization of interoceptive prediction errors (Friston et al., 2010; Gu & FitzGerald, 2014; Seth, 2015)). Put simply, "The homeostatic mechanisms thus extend from those that work wholly within the animal to those that involve its widest-ranging activities; the principles are uniform throughout" (Ashby, 1952) (p. 61). This pursuit of homeostasis manifests as "global organismic states" (LeDoux, 2012) (cf. "central motive states" (Bindra, 1969)), comprising coordinated and integrated physiological and behavioral modes (Duffy, 1957).

2.3.4 Global organismic dynamics: goal-directed physiological and behavioral sequences

Progression toward homeostatic conditions implies a sequenced logic to physiology and behavior. In 1906, on the basis of behavioral observations, Sir Charles Sherrington – in his seminal, "The Integrative Action of the Nervous System" – makes the distinction between "precurrent" and "consummatory" phases of behavioral sequences (Sherrington, 1947). A decade later, a similar distinction would be argued for by Wallace Craig (Burghardt & Burkhardt, 2018; Craig, 1917), who described a characteristic progression from "appetitive" to consummatory phases. The goal-seeking, appetitive phase is eventually terminated once the goal is obtained – marking the beginning of the consummatory phase (i.e., *consummation* of the goal-seeking behavior). Consummatory behaviors then involve interaction with the sought-after goal. This

appetitive-consummatory construct has received considerable attention and remains a widely used basis for understanding organismal behavior (Anderson, 2016; Berridge, 2004). The recognition and investigation of this lawful unfolding of behavior is now being revived in the field of computational ethology (Anderson & Perona, 2014; Datta et al., 2019; Mathis et al., 2018).

In consideration of the above arguments, it becomes clear that appetitive-consummatory sequences must be extended to body-wide physiology. We arrive at purposive (Rosenbleuth et al., 1943; Sherrington, 1947; Tolman, 1932), goal-directed (Ashby, 1952), global organismic *dynamics*: orderly sequences of global organismic states, each constituting its own body-behavior dynamical regime best suited for the predicted need.

2.3.5 Generalized arousal

Perhaps our most familiar sense of coordinated behavioral and physiological change is our subjective experience of "fight-or-flight" versus "rest-and-digest" states. This intuitive sense of an overall level of physiological and behavioral "activation" is captured by the notion of generalized arousal (Calderon et al., 2016; Moruzzi & Magoun, 1949). Thus, arousal state has been indexed according to a wide range of physiological measures (e.g., heart rate, muscle tone, the electroencephalogram (more on this below), galvanic skin response, etc.). Notwithstanding evidence for specific, differentiated neural and physiological processes contributing to this overall activation (e.g., (Cacioppo et al., 2017)), the notion of a generalized arousal – "or whatever you wish to call it" ((Hebb, 1955), p. 249) – reflecting the overall responsivity of an organism (Calderon et al., 2016) has played an essential role in the theories and ideas put forth by numerous influential psychophysiologists (Calderon et al., 2016; Duffy, 1957; Hebb, 1955)

(for an integrative review of this literature and the associated neurobiology, see (Pfaff, 2006)). The importance of recognizing such a general component – and the diverse evidence supporting such a concept (Calderon et al., 2016) – has been noted repeatedly over the years (Duffy, 1957; Hebb, 1955).

I suggest that appetitive-consummatory cycles have a natural relationship to ongoing arousal fluctuations occurring within the awake state (McGinley, Vinck, et al., 2015). Such a relationship is implied by the intimate connections between arousal, motivation, and drive-reduction models of goal-directed behavior (reviewed in (Berridge, 2004)). Likewise, Craig describes the appetitive phase of behavior as a "readiness to act" or an "agitation", contrasting with a consummatory period of "relative rest" (Craig, 1917). Further connecting these ideas is the notion that certain triggers, such as threats, initiate a generalized arousal response, with an ensuing goal-directed behavioral sequence unfolding as part of a stereotyped "survival circuit" (LeDoux, 2012). In all these cases, appetitive-consummatory sequences are accompanied by an increase and gradual reduction in generalized arousal.

2.4 Creeping up on brain function

2.4.1 Self-organization of global brain function

We have so far posited that body-wide physiology and behavior evolve in accordance with ongoing arousal cycles. At this point, it is worth considering how a brain might function within this dynamic. A tacit assumption is that, privileged with an autonomic regulatory system and brainstem control centers that can handle the dirty work, brains are afforded the opportunity to operate independently from an imperative so fundamental as maintaining the internal milieu. In contrast, and perhaps counterintuitively, I suggest that brain function is not divorced from, but

rather, intimately intertwined and structured upon these cycles (Goldstein & Kopin, 2017; Porges, 2007; Varela et al., 2016).

The *apparent* dichotomy of these two perspectives is nicely resolved in Claude Bernard's treatment of the subject. Thus, although the "constancy of the internal environment is the condition for free and independent life," Bernard goes on to clarify that, "Far from being indifferent to the external world, the higher animal is on the contrary in a close and wise relation with it, so that its equilibrium results from a continuous and delicate compensation established as if by the most sensitive of balances" (Bernard, 1974) (p. 84). Pavlov would go on to express a similar view: of complex organisms, he asserts that "If the organism were not in exact correspondence with its environment it would, sooner or later, cease to exist" (Pavlov, 2010) (p.138).

These arguments hint at the very essence of biological organisms: thermodynamically open systems that, through continuous interaction (energy exchange) with – rather than independence from – their environment, sustain themselves in a nonequilibrium steady-state (Nicolis & Prigogine, 1977; Schrödinger, 1945).

Both Bernard and Pavlov credit the brain with ultimate regulatory control of this body-environment balance. Similarly, early cybernetic theories on brain function emphasize the role of the brain in internal regulation (Ashby, 1952; Conant & Ashby, 1970), and this perspective has enjoyed growing recognition in modern theoretical neuroscience (Pezzulo et al., 2015; Seth, 2015; Smith et al., 2017). Thus, through a predictive coding lens, brains are tasked with learning the statistical contingencies of their sensory environments *for the ultimate purpose* of regulating the internal milieu.

Yet, if we carry this perspective with us as we seek to understand the functioning of the brain, then – accepting the brain as effectively a predictive organ (Clark, 2013, 2015) – we are led to an interesting corollary. Specifically, when we speak of the brain's environment, we are speaking of the exteroceptive, proprioceptive, and interoceptive sensoria (Sherrington, 1947) – the same sensoria whose dynamics and statistical structure have come to be molded according to the arousal cycle, owing to the entrainment of behavior and sensory sampling. Thus, circular causal flows entrain body, behavior, and – consequently – the sensory environment (Corcoran et al., 2020; Karl, 2012; Varela et al., 2016). The statistical structure imparted upon the environment via behavior, in turn, is manifested in the sensorium; it is this same statistical structure to which the brain must adapt.

Thus, recognizing the circular causalities that tie the statistical regularities of the sensorium back to behavior (Chiel & Beer, 1997; Cisek, 1999, 2019), we are motivated to take a broader view on the relation of brain function and internal regulation. Rather than a purely unidirectional or hierarchical perspective on the role of the brain in internal regulation, I suggest that the circular flows coupling physiological, behavioral and environmental fluctuations are a likely catalyst of brain self-organization (Goldbeter, 2018; Karl, 2012; Nicolis & Prigogine, 1977; Varela et al., 2016). In other words, there will be a natural tendency for the brain to take advantage of – by adapting its own functioning in relation to – the cycling of arousal that entrains the dynamics of the body, behavior, and environment.

2.4.2 Regulating the regulator

Of course, as an organ, the brain is itself subjected to the same allostatic regulatory processes we have been discussing. Crucially – to the extent that brain function has come to self-organize

according to the abovementioned appetitive-consummatory arousal cycles – the regulation of brain physiology according to these cycles will amount to a regulation of brain *function*. Thus, in contrast to organs such as the heart, which maintain a single functionality that is effectively up- and downregulated according to arousal, arousal regulation of the brain would amount to qualitative changes in its functionality as arousal cycles unfold. Although neural mechanisms of arousal and physiological regulation have long been an active area of research, this possibility that global brain function is structured and, indeed, regulated in accordance with arousal and global organismic states has received surprisingly little attention.

Of course, this is all contingent on the extent to which brain function is intrinsically segregated according to arousal cycles. As we will see below, there is in fact a broad literature on this topic; I believe the foregoing perspective informs how we might interpret it.

2.5 Brain function, intrinsic activity, and arousal

2.5.1 Brain state dynamics: the temporal regulation of brain function

The birth of electroencephalography (EEG) in the 1920s brought with it a recognition of the preponderance of spontaneous, ongoing, intrinsic brain activity (Berger, 1929). The global and state-dependent nature of these electric potentials was recognized early on, with clear links to arousal state (Berger, 1929; Moruzzi & Magoun, 1949; Steriade, 2000). These globally coordinated dynamics include, for example, ~1-4 Hz delta waves – the gold standard for defining epochs of slow-wave sleep. Most recently, a considerable literature now casts these changes in oscillatory dynamics between wake and sleep as two extremes, with ongoing changes along this landscape occurring in awake behaving animals – in particular, rodents (Harris & Thiele, 2011; McGinley, Vinck, et al., 2015; Poulet & Crochet, 2018).

Leveraging recent tools for cortex- and brain-wide imaging in awake behaving rodents, a series of studies have gone on to link ongoing arousal fluctuations with changes in brain-wide dynamics (e.g., (Musall et al., 2019; Salkoff et al., 2020; Stringer et al., 2019)). A commonly expressed viewpoint is that these brain-wide dynamics encode or are driven by spontaneous behaviors (e.g., (Drew et al., 2019; Kaplan & Zimmer, 2020; Musall et al., 2019; Stringer et al., 2019)); however, the extent of integrative physiological changes accompanying these arousal fluctuations would appear to suggest that behavior is itself a manifestation of some underlying, fundamental state change. Thus, processes time-locked to ongoing fluctuations in arousal include not only local field potential oscillations (Gervasoni et al., 2004; Harris & Thiele, 2011), neuromodulator activity (Collins et al., 2021; Lee & Dan, 2012; Reimer et al., 2016) and brain-wide spiking activity of excitatory units (Stringer et al., 2019), but also the specific activities of molecularly distinct inhibitory interneuron cell types (Barson et al., 2020; Garcia-Junco-Clemente et al., 2019; Reimer et al., 2014) and glial cells (especially astrocytes (Paukert et al., 2014; Poskanzer & Yuste, 2016; Wang et al., 2018), though recent evidence even hints at active contributions from microglia (Mercan & Heneka, 2019)), as well as metabolic processes (Natsubori et al., 2020; Zuend et al., 2020) and changes in the extracellular ionic environment (Rasmussen et al., 2019) and temperature (Csernai et al., 2019; Fernandez & Lüthi, 2020). Furthermore, a parallel line of work has understood “brain states” in terms of states of the hippocampus, with arousal fluctuations associated with alternation between a theta state, associated with exploratory behavior and locomotion, and a sharp-wave ripple state – supporting, e.g., memory consolidation – that emerges during reduced arousal states (Buzsáki, 2015; Harris & Thiele, 2011; Kay & Frank, 2019; McGinley, David, et al., 2015).

Considering the extent and diversity of endogenous neurophysiological processes varying with ongoing arousal fluctuations, I propose that this evidence points to an internal temporal regulation of brain function in relation to arousal. As we have discussed for body-wide physiological states, we can readily appreciate that different dynamical regimes of brain-wide activity and physiology are best-suited for particular behavioral or anticipated environmental states. Given their temporal evolution in synchrony with arousal, I propose that brain states are tuned to particular phases along a canonical appetitive-consummatory arousal cycle.

2.5.2 Brain state dynamics and the arousal cycle

In an extensive review of hippocampal sharp-wave ripple physiology and function, György Buzsáki draws a connection between sharp-wave ripples (SWRs) and the aforementioned consummatory phases of behavior. The fidelity of this correspondence even leads Buzsáki to propose SWRs as a brain state index of consummatory behavior (Buzsáki, 2015). More generally, Buzsáki casts the hippocampal theta-SWR dichotomy as a brain state corollary of the preparatory- (appetitive-) consummatory dichotomy. Considering the close correspondence of hippocampal and neocortical states (Harris & Thiele, 2011; Kay & Frank, 2019), I suggest a further generalization of this perspective to encompass brain-wide dynamics. Thus, I propose that global brain state dynamics unfold according to appetitive-consummatory arousal cycles.

Putting a cyclic “spin” on brain state dynamics, though not the predominant view, is consistent with evidence for stereotyped temporal sequences of changes in brain oscillations – and the progression of these neural sequences in lockstep with gross, overt behavioral sequences (Gervasoni et al., 2004; Liu et al., 2015). Moreover, goal-directed behavioral sequences entrain brain-wide activity in much the same way as arousal (Allen et al., 2019; Allen et al., 2017; Peters

et al., 2021). Further supporting this view is mounting evidence that – despite the lack of an overt periodicity to these cycles – the *phase* of ongoing arousal fluctuations appears to be specifically relevant for brain state dynamics (Okun et al., 2019; Reimer et al., 2014; Reimer et al., 2016). Of course, phase can only be defined in relation to some overall cyclic process. This implies that brain state dynamics are inherently cyclic; this topic will be revisited below and in the specific hypothesis put forth at the end of this essay.

2.5.3 Spatial organization of brain function: Large-scale functional anatomy as an embedding of a goal-directed behavioral sequence

Having described an intrinsic temporal organization of brain function and its intimate relationship to appetitive-consummatory cycles, we will now turn to an entirely complementary organization of global brain function: namely, the *spatial* segregation of brain function – the object of study in the centuries-long endeavor of (human) brain mapping (Raichle, 2009a).

Human brain mapping in particular was greatly accelerated following the advent of modern neuroimaging tools – e.g., positron emission tomography and, in particular, functional magnetic resonance imaging (fMRI). These tools enable brain-wide monitoring (with millimeter scale resolution) of regional (metabolic or blood-oxygen) activity changes in response to various cognitive tasks. This line of work has converged upon a characterization of mammalian brains in terms of multiple anatomically segregated, large-scale functional systems (e.g., somatomotor, visual, and higher-order cognitive systems (Petersen & Sporns, 2015)). These functional-anatomic systems are arranged along a continuous axis extending from unimodal (e.g., somatomotor and visual) to transmodal (higher-order) systems (Huntenburg et al., 2018; Margulies et al., 2016). At the broadest scale, this axis separates the brain into two complementary “macro” systems: an “extrinsic” system more directly linked to the immediate

sensory environment, and an "intrinsic" system, whose activity preferentially relates to changing higher-level, internal context (Cioli et al., 2014; Golland et al., 2008; Hacker et al., 2017). This extrinsic-intrinsic axis – or more commonly, unimodal-transmodal, sensorimotor-association, or principal axis – describes systematic variation of a remarkably diverse set of structural and functional properties (for a wide-ranging overview, see (Sydnor et al., 2021)).

Without extensive treatment of this literature, we can readily appreciate that this spatial axis of brain function bares resemblance to the segregation of functionality occurring across an appetitive-consummatory cycle. A convenient meta-analytic result is provided in (Margulies et al., 2016), demonstrating systematic variation from interaction with the immediate sensory environment to self-referential, internally-oriented functions (e.g., "autobiographical memory", "emotion, and "reward-based decision") as one moves along the sensorimotor-to-association axis.

In this context, it is worth recalling the widely used conceptualization of generalized arousal as an index of "reactivity" (e.g., (Calderon et al., 2016)), thus intuitively connecting high arousal states to sensorimotor and attention-related networks. In turn, the relegation of "social" functions to low arousal periods resonates with the incompatibility of (low arousal) social and (high arousal) defensive behavioral states – a concept central to Porges' polyvagal theory (Porges, 2007, 2009). Likewise, even in Sherrington's original account of "precurrent" (appetitive) and consummatory behaviors, it is the latter that he strongly identifies with affective experiences (Sherrington, 1947), p. 330).

More generally, low arousal and consummatory behavior recall the functionalities that have come to be associated with the so-called "default mode network" (Fox et al., 2018; Raichle,

2015), situated furthest from early sensorimotor regions (Margulies et al., 2016; Smallwood et al., 2021) (interestingly, although the default mode network is not typically discussed in relation to arousal per se, this connection was noted in the initial observations supporting the existence of this brain network (Shulman et al., 1997)). Collectively, these functionalities have been assembled into a unifying view of default mode function as opposite that of "goal-directed behavior". Though seemingly in contradiction with the present argument, broadly construed, such goal-directed antagonism is quite compatible with the upregulation of default network activity during the consummatory phase of goal-directed behavior – i.e., a state in which the goal has already been obtained. Understanding default mode function within the context of goal-directed behavioral cycles may offer broader perspective on its activity, which – like consummatory behaviors – reliably ensues upon cessation of the goal-directed task (Hugdahl et al., 2019).

If we view the functional anatomy of the brain as the embodiment of a generative model of its sensorium (Friston & Buzsáki, 2016; Karl, 2012; Parr et al., 2020), the proposal on offer is that the greatest spatial scale of brain functional organization is matched to the most fundamental (predictable) segregation of behavior and sensation, which occurs along appetitive-consummatory cycles. Thus, to first approximation, an appetitive-consummatory progression is systematically reflected along the principal functional coordinate. Thus, the principal functional coordinate may be viewed as the anatomical embedding of the same dimension manifested in arousal cycles (glossing over precise distinctions for the sake of drawing parallels, we may view this dimension as the segregation of consummatory vs. appetitive, rest vs. activity, explore vs. exploit, or internal vs. external orientation).

The relationship between large-scale functional anatomy and appetitive-consummatory behavioral sequences implies that functional systems should be dynamically engaged in a systematic manner in relation to ongoing arousal cycles. We will now see how intrinsic activity may endogenously regulate brain function by supporting this dynamic engagement of functional systems.

2.5.4 Resting-state functional connectivity: the spatial organization of intrinsic activity

A paradigm shift in brain mapping gradually emerged following recognition that spatially organized activity motifs resembling large-scale functional networks emerged spontaneously – i.e., even in the absence of experimental stimulus (Raichle, 2009b). Crucially, these ongoing activity patterns cannot be explained in terms of unconstrained cognition – see (Laumann & Snyder, 2021) for a recent summary of this argument – but reflect in large part bona fide intrinsic processes. An extensive body of work has since exploited this physiology (Fox & Raichle, 2007), under the label of "resting-state functional connectivity" (RSFC), to map the global organization of brain function. This paradigm seeks to map out the strength of functional relationships between regions based on their the correlation of their spontaneous activity (i.e., spontaneous BOLD signal fluctuations) (Fox & Raichle, 2007).

RSFC approaches, informed by decades of brain mapping studies, have arrived at a consensus description of global brain function in terms of several large-scale functional anatomic systems (represented by "FC networks") with partially separable functionality (Power et al., 2011; Yeo et al., 2011). The spatial structure of this organization is grossly conserved across individuals of a species and remarkably invariant to various task or behavioral states (Gratton et al., 2018; Vincent et al., 2007). These networks derived from intrinsic activity recapitulate patterns of

evoked activity in the brain (Salvo et al., 2021; Smith et al., 2009). The approach has also proven invaluable for functional mapping of subcortical structures that are less accessible to most other minimally invasive brain recording methodologies; these studies reveal large-scale functional systems organization that topographically parallels that of the neocortex (e.g., (Buckner et al., 2011; Choi et al., 2012; Greene et al., 2019; Zhang et al., 2010)).

Recent focus in RSFC has shifted from precise functional localization (e.g., (Glasser et al., 2016)) to mapping of latent global structure. Thus, by examining brain-wide coordinates (via manifold learning) instead of discrete networks, Margulies et al. found that functional connectivity structure indeed recapitulates the sensorimotor-association principal axis (Margulies et al., 2016). Similar structure has been obtained through a variety of analytic decompositions (Morrissey et al., 2021; Sepulcre et al., 2012; Zhang et al., 2019). Subsequent studies have established topographically mirrored gradients occurring also in subcortical structures (Marquand et al., 2017; Tian et al., 2020; Yang et al., 2020) and the cerebellum (Guell et al., 2018). Notably, other features of intrinsic brain activity are also observed to vary systematically along this axis – including the characteristic spatial scale of functional connectivity (Sepulcre et al., 2010) and, consistent with theoretical predictions (Chaudhuri et al., 2015; Hasson et al., 2015; Kiebel et al., 2008), intrinsic timescale (Ito et al., 2020; Müller et al., 2020; Raut et al., 2020). Taken together, these observations indicate that intrinsic activity strongly distinguishes between positions along the sensorimotor-association axis.

2.6 Putting the pieces together

2.6.1 Brain states and brain networks: a unifying perspective on intrinsic activity

Surprisingly, there is no general framework explicitly linking the above discussed temporal and spatial descriptions of functional segregation in the brain. That is, to date, systems neuroscience has separately established both temporal and spatial organization of global brain function, but *spatiotemporal* mechanisms integrating these two organizational principles are lacking. Nonetheless, several lines of evidence point to the existence of such a mechanism.

Firstly, despite their widespread use in functional localization, spontaneous BOLD signal fluctuations also exhibit richly organized dynamics (e.g., (Majeed et al., 2011; Matsui et al., 2016; Mitra et al., 2014; Preti et al., 2017; Thompson & Fransson, 2016; Vidaurre et al., 2017; Wu et al., 2013)), with a multitude of behavioral and electrophysiological correlates (e.g., (Han et al., 2019; Kucyi et al., 2018; Magri et al., 2012; Mantini et al., 2007; Sadaghiani & Kleinschmidt, 2013)). These results are consistent with an underlying spatio*temporally* organized dynamical process, although a unifying physiological and theoretical account of spontaneous BOLD signal fluctuations remains lacking.

Second, as implied by the above discussion, the spatial and temporal modes have clear functional overlap – particularly when viewed within the context of a basic arousal cycle. Indeed, in recent years, the functional similarities of SWRs and the default mode network (most thoroughly studied in the human neuroimaging literature, but see, e.g., (Buckner & DiNicola, 2019; Fox et al., 2018; Smallwood et al., 2021; Whitesell et al., 2021)) have been noted (O'Callaghan et al.,

2021) and experimentally corroborated (Higgins et al., 2020; Kaplan et al., 2016; Karimi Abadchi et al., 2020; Norman et al., 2021).

Third, having discussed the diversity of cell types and physiological processes that are temporally regulated according to arousal, we may now consider that many of these features are expressed to a degree that systematically varies along the sensorimotor-association axis – e.g., the densities of pyramidal cells and their synapses, interneurons and glial cells. Indeed, the first principal component of transcriptional variation maps onto the principal coordinate (Burt et al., 2018; Wang, 2020). Hence, because these cell types and physiological processes are temporally regulated according to arousal, their respective functions will inherently contribute to *spatio*temporal organization of brain activity in relation to arousal.

To further generalize, a central argument of this essay is that phases within a canonical arousal cycle are represented as both temporal and spatial modules of brain function (Fig. 2.1). As these organizational modes are apparent from intrinsic, ongoing brain activity, the implication is that intrinsic activity serves to internally regulate global brain function in anticipation of behavioral and physiological demand. Thus, I propose that a significant fraction of intrinsic brain activity reflects a highly organized, intrinsic regulatory function.

If this account is valid, different large-scale functional systems must be preferentially engaged at different phases within the canonical arousal cycle. Further, because of the gradient-like organization of the sensorimotor-association axis (Margulies et al., 2016), it follows that this process should be instantiated as a traveling wave along this axis. The existence of topographically parallel axes in thalamus, striatum, and cerebellum implies such a wave process must also occur simultaneously in subcortical structures.

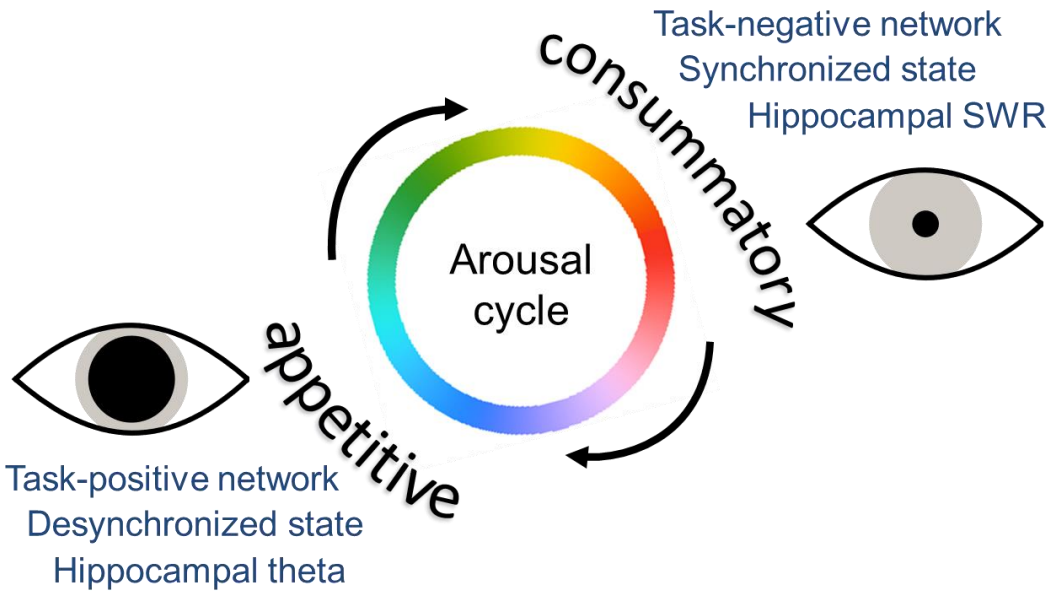

Figure 1. A canonical arousal cycle. High arousal states are associated with the appetitive behavioral phase (Craig, 1917), the "task-positive" network (opposing the default mode network) (Fox et al., 2005), desynchronized cortical state (Harris & Thiele, 2011; Moruzzi & Magoun, 1949), and the hippocampal theta state (Buzsáki, 2015). In turn, low arousal states are associated with consummatory behavior, the default mode or "task-negative" network, low-frequency synchronization, and hippocampal sharp-wave ripples.

Furthermore, in theory, this wave process should be cyclic, potentially involving a role for rotating waves (Winfree, 1980) (in fact, this possibility is supported by recent observations using widefield imaging of calcium activity in mouse neocortex (Vanni et al., 2017)). Functionally, such a cyclic process implies that consummatory phases inform the next appetitive phase. This appeals to the notion that the combined retro- *and antero*-grade (Ingvar, 1985) functionalities supported by hippocampal SWRs and DMN function (Buckner & Vincent, 2007; Buzsáki, 2015; Diba & Buzsáki, 2007; Schacter et al., 2012), including reward-related information obtained during the consummatory phase, serve to guide and contextualize the next goal-directed behavioral sequence.

Finally, as already implied, internally generated brain activity unfolds over nested spatiotemporal scales (Buzsáki & Draguhn, 2004). Thus, the key argument here is for the existence of a *regulatory* process operating on the temporal and spatial modes of brain function; the functionality of such a process is secondary (Bich et al., 2016) to the primary functionalities presumably instantiated by specific cellular- and circuit-level neural mechanisms, the nature of which are not addressed here. The physiology and function of intrinsic brain activity are widely debated and include, e.g., multidimensional sensory coding (Stringer et al., 2019), instantiation of priors (Pezzulo et al., 2021; Ringach, 2009), and synaptic homeostatic cascades (Laumann & Snyder, 2021). The present account is hardly in conflict with any of these accounts; rather, the presence of an intrinsic regulatory process is presumed to dynamically regulate each of these processes, which I suggest, are at some level temporally locked to a latent arousal cycle.

In short, intrinsic activity is inclusive of myriad processes. The present argument is that a substantial amount of this intrinsic activity directly reflects a hypothesized internal regulatory process. I will now suggest that this regulatory process may correspond to what has come to be termed “infra-slow” brain activity.

2.6.2 Infra-slow activity and the intrinsic regulation of brain function

Although there has been minimal concerted research effort on infra-slow (~0.01 to 0.1 Hz) brain activity, which remains a fairly poorly understood phenomenon (or phenomena) (Watson, 2018) (but see (Aladjalova, 1964)), this activity is ubiquitous in the neurophysiology literature (for excellent reviews, see (Fernandez & Lüthi, 2020; Palva & Palva, 2012; Watson, 2018)). I will briefly note several features of this activity that make it a likely candidate for the endogenous, spatiotemporal regulatory process hypothesized herein.

Firstly, a recent line of research has implicated infra-slow activity as the specific physiological process reflected in spontaneous BOLD signal fluctuations and RSFC (Grooms et al., 2017; He et al., 2008; Mitra et al., 2018; Palva & Palva, 2012). Notably, this marks a departure from the conventional view of BOLD signal fluctuations as a vascular and effectively low-pass filtered recapitulation of brain activity occurring on millisecond timescales. To the extent that this interpretation is supported, we may conclude that an infra-slow regulatory process maintains an intrinsic, large-scale spatial organization of brain function.

Furthermore, accumulating evidence now suggests that infra-slow activity is intimately linked to brain state dynamics and arousal (Lecci et al., 2017; Okun et al., 2019). Hippocampal SWRs (McGinley, David, et al., 2015; Sirota et al., 2003) and sleep spindles (Fernandez & Lüthi, 2020; Lecci et al., 2017) appear to be modulated at infra-slow frequencies, and the phase of infra-slow potentials couples to the amplitude of higher-frequency neural oscillations that are associated with distinct phases of arousal (He et al., 2010; Mitra et al., 2018; Monto et al., 2008). There further exists (relatively scattered) evidence for a slight periodicity of infra-slow activity close to .02 Hz (Csernai et al., 2019; Lecci et al., 2017; McGinley, David, et al., 2015; Novak et al., 1992; Penttonen et al., 1999) – overlapping an autonomic-specific frequency range (Söderström et al., 2003) – and other properties consistent with a quasi-rhythmic nature of infra-slow activity (Palva & Palva, 2012; Palva & Palva, 2018). This work connects to an even broader literature on brain and body that has discussed an “ultra-slow” or “overall myogenic rhythm” (Baðsar, 2011; Başar, 2008) (see also, e.g., (Azzalini et al., 2019; Rebollo et al., 2018)). These rhythmic features are consistent with a connection between infra-slow activity and arousal *cycles.* On the other hand, the general lack of a strict period for appetitive-consummatory cycles is consistent with the broad frequency content of infra-slow dynamics (conventionally studied from ~0.01 to 0.1 Hz).

Taken together, the evidence is consistent with a view of infra-slow activity in supporting the quasiperiodic regulation of the brain's temporal and spatial modes in relation to ongoing arousal cycles. From this perspective, it is intriguing that early work strongly implicated the hypothalamus in infra-slow brain activity (Aladjalova, 1964). Given the sophistication of modern tools for neurobiological circuit dissection, this relationship may be greatly elaborated through a coordinated research effort on infra-slow brain activity.

2.7 Summary

2.7.1 Propositions

For clarity, I will summarize the above points as a set of propositions, followed by several specific hypotheses. Thus, we have:

Proposition 1: Appetitive-consummatory phases of goal-directed behavior are inclusive of body-wide physiology.

Proposition 2: The appetitive and consummatory phases of these "global organismic dynamics" are embedded within a canonical arousal cycle.

Proposition 3: Brain state dynamics reflect quasi-rhythmic temporal evolution along this latent arousal cycle.

Proposition 4: Large-scale functional anatomy may be viewed as a spatial embedding of this canonical arousal cycle.

Proposition 5: Brain-wide traveling waves spatiotemporally instantiate the latent arousal cycle across large-scale functional anatomy.

Proposition 6: “Infra-slow” brain activity is a physiological mediator of this spatiotemporal regulation of global brain function.

2.7.2 Hypotheses

Two core hypotheses will be examined in this thesis. First, I predict the existence of brain-wide, topographically organized traveling waves, observable with any macroscopic measure of large-scale brain activity (e.g., fMRI, EEG/MEG, widefield imaging). As elaborated upon in the following chapter, while heretofore unrecognized, such a global process could, in fact, be entirely consistent with the known properties of BOLD time series.

The second core hypothesis is that “brain state” continuously evolves along a latent, quasiperiodic arousal cycle: traveling waves and stereotyped sequences of oscillatory dynamics are two reflections of this continuous cycling. Importantly, this view casts intrinsic brain dynamics as being far more predictable, low-dimensional, and spatiotemporally organized than is currently appreciated (e.g., (Shimaoka et al., 2018; Stringer et al., 2019)). This hypothesis will be examined in Chapter 4.

2.9 Extensions and implications

2.9.1 Non-mammalian vertebrates

I have focused on mammalian vertebrates due the extent of available literature on intrinsic brain activity in mammals. Nonetheless, parallel descriptions of intrinsic brain activity and behavior are increasingly appearing in non-mammalian vertebrates. This has been most clear in the larval zebrafish, whose popularity as a model organism in neuroscience is rapidly growing. Thus, larval zebrafish similarly exhibit substantial internally-generated fluctuations over tens of seconds (Ahrens et al., 2013). As in mammals, these fluctuations temporally organize brain-wide

dynamics according to alternating explore-exploit behavioral states (Marques et al., 2020). The extent to which these fluctuations exhibit spatiotemporal organization in accordance with homologous functional anatomy as in mammals remains unclear. However, the neuromodulator circuitry underlying these fluctuations exhibits clear homology with that seen in mammals (Lovett-Barron et al., 2017), suggesting that the intrinsic global dynamics in the two species are homologous processes. Similarly, the intrinsic activity of these species is known to exhibit large-scale spatial organization (Betzel, 2020; Chen et al., 2018) analogous to RSFC as studied in mammals. Finally, this work is nicely complemented by a recent line of work from Gilles Laurent and colleagues establishing cyclic modulations of brain arousal and sleep-related physiology in reptiles (Norimoto et al., 2020; Shein-Idelson et al., 2016). The evidence appears consistent with an evolutionarily conserved, infra-slow neuroregulatory process throughout vertebrate evolution.

2.9.2 Invertebrates

Slow fluctuations in brain-wide activity and intimate couplings of brain, body, and behavioral dynamics have similarly been described in invertebrates (Kaplan & Zimmer, 2020). In *C. elegans*, as in mammals, a behavioral cycle is similarly manifest in the intrinsic brain dynamics – notably, even after prevention of motor expression of the associated behavioral cycle (Kato et al., 2015). In drosophila, similarly coupled global brain-behavior dynamics are readily observed (Aimon et al., 2019; Mann et al., 2021); crucially, the same slow dynamics give rise to a correlation structure that recapitulates large-scale functional neuroanatomy in this species (Mann et al., 2017), once again paralleling the RSFC literature most extensively developed through human neuroimaging. My inference based on this literature, though speculative, is that the

intrinsic spatiotemporal regulation of brain function via arousal is an evolutionarily ancient physiological principle predating the split of vertebrate and invertebrate lineages.

2.9.3 Outlook

A few specific lines of future inquiry will be reserved for the final chapter of this dissertation (so that I have something to write about there). Instead, here, I will focus on motivating a perspective that will inform results presented in the next two chapters (Chapter 4 in particular). Namely, in light of the remarkably physiologically integrative dynamics reviewed in this chapter, how should we go about studying their coupling?

One approach is to focus on obtaining a detailed, mechanistic understanding of unidirectional physiological interactions. I believe that the prospects of such an approach in systems neuroscience are limited. Indeed, this ideological approach has already stifled the extent of integration across methods and subfields of neuroscience. How long more will neurovascular uncoupling remain incompletely understood, and how long more should that preclude integration of resting-state fMRI literature with systems neurophysiology more broadly?

An alternative approach is to understand intrinsic, latent dynamical laws of brain, body, and behavior (Barack & Krakauer, 2021; Chiel & Beer, 1997). From this perspective, we may seek to understand the causal relations among physiological variables by virtue of their coupling to the same governing dynamics (Rulkov et al., 1995; Sugihara et al., 2012). In the present case, the arousal cycle constitutes one such (hypothetical) dynamical process; this perspective will be pursued in Chapter 4 of this thesis.

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Chapter 3

Global Waves Synchronize the Brain's Functional Systems with Fluctuating Arousal

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3.1 Abstract

We propose and empirically support a parsimonious account of intrinsic, brain-wide spatiotemporal organization arising from traveling waves linked to arousal. We hypothesize that these waves are the predominant physiological process reflected in spontaneous fMRI signal fluctuations. The correlation structure ("functional connectivity") of these fluctuations recapitulates the large-scale functional organization of the brain. However, a unifying physiological account of this structure has so far been lacking. Here, using fMRI in humans, we show that ongoing arousal fluctuations are associated with global waves of activity that slowly propagate in parallel throughout neocortex, thalamus, striatum, and cerebellum. We show that these waves can parsimoniously account for many features of spontaneous fMRI signal fluctuations, including functional connectivity. Finally, we demonstrate similar, cortex-wide propagation of neural activity measured with electrocorticography in macaques. These findings suggest that traveling waves spatiotemporally pattern brain-wide excitability in relation to arousal.

3.2 Introduction

Organisms continuously regulate multiple physiologic variables. This regulation is supported by autonomic arousal fluctuations that coordinate body-wide physiology in relation to anticipated behavioral demands, e.g., cycling between “fight-or-flight” versus “rest-and-digest” modes (Sterling, 2012). Accumulating evidence indicates that global brain function is also temporally structured in relation to these arousal fluctuations (McGinley, Vinck, et al., 2015). Thus, in awake rodents, fluctuations in physiological (e.g., pupil size) and behavioral (e.g., locomotor activity) variables over tens of seconds are correlated with changes in global brain state, indexed by neural oscillations, incidence of sharp-wave ripples, or the extracellular environment (McGinley, Vinck, et al., 2015; Rasmussen et al., 2019; Zuend et al., 2020). Recently, massively parallel neural recordings have demonstrated that these ongoing arousal fluctuations account for a substantial fraction of variability in single-unit firing rates throughout the brain (Okun et al., 2019; Stringer et al., 2019). These findings appeal to a broader literature implicating an endogenous, infra-slow (<~0.1 Hz) neuromodulatory process that temporally organizes brain-wide function in relation to arousal (Lecci et al., 2017; Watson, 2018).

A separate line of investigation has described the spatial organization of brain function. Thus, mammalian brains have been characterized in terms of multiple anatomically segregated functional systems (e.g., somatomotor, visual, and higher-order cognitive systems (Petersen & Sporns, 2015)). These functional-anatomic systems are arranged along a continuous axis extending from unimodal (e.g., somatomotor and visual) to transmodal (higher-order) systems (Huntenburg et al., 2018; Margulies et al., 2016). At the broadest scale, this axis separates the brain into two complementary “macro” systems: an “extrinsic” system more directly linked to the immediate sensory environment, and an “intrinsic” system, whose activity preferentially

relates to changing higher-level, internal context (Cioli et al., 2014; Golland et al., 2008). It is unclear how this spatial organization relates to the infra-slow arousal regulation of brain-wide function.

Notably, the current understanding of spatially segregated function has been informed by spontaneous infra-slow fluctuations of the blood oxygen level-dependent (BOLD) functional MRI signal (Fox & Raichle, 2007; Power, Schlaggar, et al., 2014). These fluctuations are correlated within brain regions to an extent that reflects their functional relatedness (functional connectivity; FC). Thus, BOLD FC is widely used to hierarchically partition the brain into functional modules ("networks") at multiple granularities (e.g., 2, 7, 17 FC networks (Lee et al., 2012; Yeo et al., 2011)). Apart from functional mapping, substantial evidence indicates that spontaneous BOLD signal fluctuations exhibit globally organized structure (e.g., (Margulies et al., 2016; Power et al., 2011; Sepulcre et al., 2012)) and dynamics (e.g., (Majeed et al., 2011; Matsui et al., 2016; Mitra et al., 2014; Preti et al., 2017; Vidaurre et al., 2017)), with a multitude of behavioral and electrophysiological correlates (e.g., (Kucyi, Tambini, et al., 2018; Magri et al., 2012; Sadaghiani & Kleinschmidt, 2013)). Yet, to date, this expansive literature lacks a unifying physiological and phenomenological theoretical framework.

We propose that the available behavioral, electrophysiological, and neuroimaging evidence is consistent with a model in which coordinated cortical and subcortical traveling waves spatiotemporally pattern brain-wide excitability in relation to infra-slow arousal fluctuations. This parsimonious account is motivated by mounting evidence of an endogenous physiological process underlying infra-slow fluctuations in electrophysiology and in the BOLD signal (Grooms et al., 2017; Mitra et al., 2018; Palva & Palva, 2012). Accordingly, this model constitutes a

generative account of the canonical spatiotemporal features of spontaneous BOLD signal fluctuations, including the global organization of FC.

Four major predictions follow from this traveling wave model. First, BOLD signal fluctuations throughout the brain should be coherent with arousal fluctuations. Second, regional phase shifts of the BOLD signal, relative to physiological indices of arousal, should be organized according to FC network identity. Third, these phase shifts should systematically vary along the principal, unimodal-transmodal axis of FC (Margulies et al., 2016). Fourth, similarly organized traveling waves should also be apparent in electrophysiological recordings. We provide novel support for each of these predictions, presenting converging evidence across multiple human fMRI datasets, multiple indices of arousal, and hemisphere-wide electrocorticography in macaque monkeys. We characterize several additional features of these waves that, taken together, offer a parsimonious account for many spatiotemporal features of spontaneous BOLD signal fluctuations, including large-scale FC structure. In sum, our results suggest that infra-slow arousal waves are a physiologically integrative process supporting an intrinsic spatiotemporal organization of brain-wide excitability.

3.3 Theory

Fig. 1 illustrates our proposed framework, which casts infra-slow arousal fluctuations as a (quasiperiodic (Palva & Palva, 2018)) spatiotemporal cycle that endogenously regulates brain-wide physiology (Fig. 1A). Global brain states and behavior vary according to the phase of ongoing arousal fluctuations (McGinley, Vinck, et al., 2015). Likewise, we hypothesize that different phases within a canonical arousal cycle are associated with different topographies of enhanced excitability. These different topographies should be organized according to the major

functional systems of the brain (Fig. 1A), which systematically vary along the unimodal-transmodal axis in their relation to the immediate sensory environment (Margulies et al., 2016). Accordingly, the proposed spatiotemporal process comprises large-scale, topographically organized patterns of excitability (involving coordinated metabolic and electrophysiological changes) that evolve over tens of seconds in parallel with arousal. Importantly, we propose that this topographically organized modulation is the predominant physiological process that is reflected in spontaneous, spatially patterned fluctuations in the BOLD signal. For this reason, the proposed spatiotemporal arousal process, described below, also amounts to a generative mechanism underlying BOLD FC.

An immediate question follows from our assertion that spontaneous BOLD signal fluctuations reflect, to large extent, a global arousal process. Namely, how can a global process account for the classical picture of segregated FC networks? We hypothesize that this global arousal process is instantiated by topographically organized traveling waves. Traveling waves are a ubiquitous source of spatiotemporal organization in nature (Muller et al., 2018; Winfree, 2001). Fig. 1B-D illustrates how global wave propagation can account for spatially organized FC structure.

Fig. 1B takes, as a starting point, the familiar representation of FC as discrete networks. FC networks are defined as sets of regions that share temporally coincident BOLD signal fluctuations, assessed by the strength of zero-lag correlation (i.e., FC) (Power, Schlaggar, et al., 2014). Discrete networks are often obtained by first representing all pairwise FC relationships as a graph, with nodes corresponding to brain regions and edges corresponding to time-averaged correlations (Power, Schlaggar, et al., 2014). This graph representation can then be subjected to

clustering or community detection algorithms that assign brain regions to one of several modules ("FC networks"), such that edges are stronger within rather than between modules (Fig. 1B).

Such modular descriptions of FC have proven useful for mapping large-scale functional systems (e.g., see canonical FC networks shown in Fig. 1A-B (Yeo et al., 2011)). However, emphasis on identifying discrete FC networks obscures the global and spatially embedded nature of FC organization. Thus, canonical networks exhibit organized FC and anatomical positions in relation to one another (Margulies et al., 2016; Power et al., 2011) (Fig. 1C). These aspects of FC are well captured by analyses that do not enforce modular descriptions (e.g., manifold learning). Such analyses have described a principal, unimodal-to-transmodal axis of global FC organization (e.g., (Guell et al., 2018; Margulies et al., 2016; Sepulcre et al., 2012)) (Fig. 1C). From this perspective, canonical FC networks are understood as sets of regions that occupy characteristic positions along cortex-wide spatial gradients. Thus, the "principal functional gradient" (i.e., the first coordinate of a low-dimensional embedding of FC structure (Coifman & Lafon, 2006; Margulies et al., 2016)) maps gradual variation in FC to gradual changes over anatomical space. A dynamical process underlying this correspondence has not been proposed.

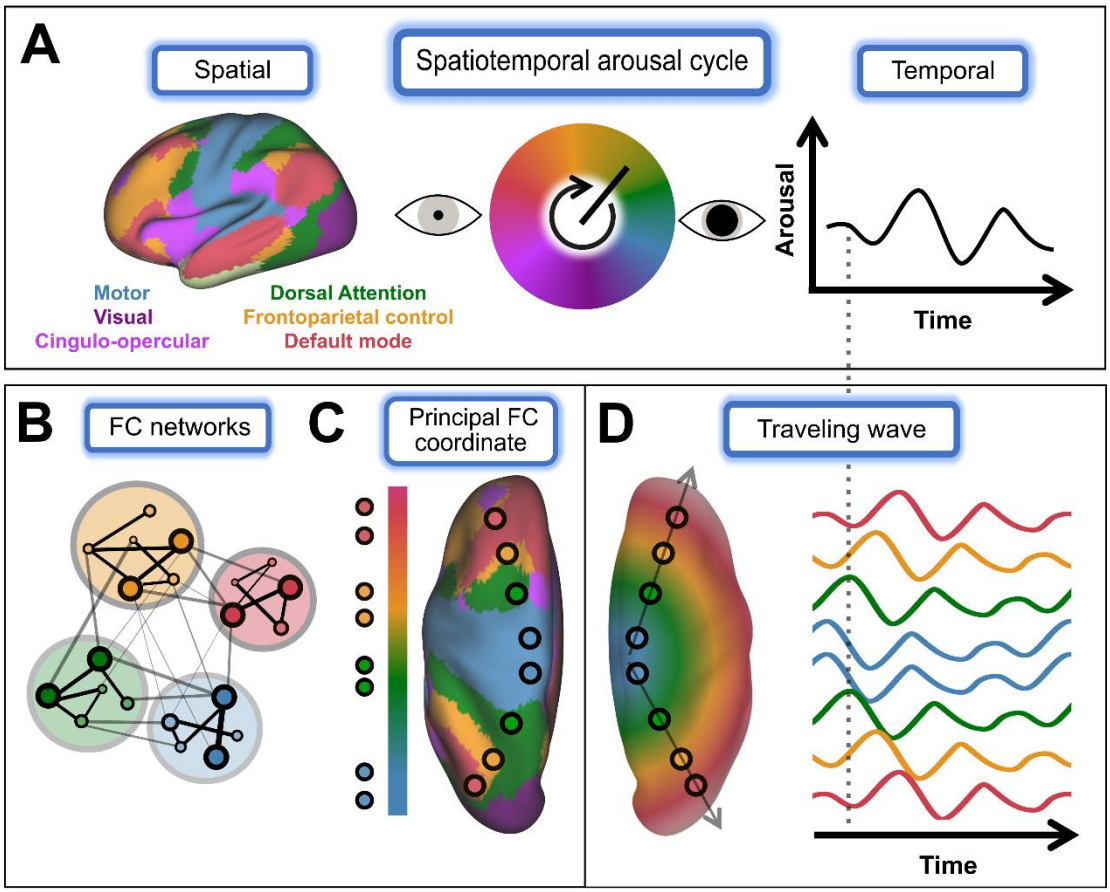

Figure 1. Infra-slow arousal fluctuations as a global, spatiotemporal process. (A) We propose that infra-slow arousal fluctuations can be understood as a spatiotemporal cycle, within which different temporal phases correspond to different spatial patterns of enhanced excitability. These spatial patterns correspond to the major functional systems of the brain (left; (Yeo et al., 2011)), such that activity within each system fluctuates over tens of seconds in accordance with arousal (right). **(B-D)** The proposed mechanism linking FC networks to global arousal fluctuations. **(B)** FC networks are often defined using tools from graph theory (Power, Schlaggar, et al., 2014), where "edges" are defined by the strength of zero-lag correlation (FC) between the spontaneous BOLD fluctuations observed in any two regions. Brain regions (here, small circles) are assigned to modules (large circles) such that connections are stronger within rather than between modules. Module assignments (e.g., those shown in A) do not preserve global (i.e., inter-module) relationships. **(C)** Without enforcing modularity, FC is seen to evolve along a principal, cortex-wide "coordinate"; this principal FC coordinate corresponds to the unimodal-transmodal axis of brain functional organization (Margulies et al., 2016). Canonical FC networks occupy characteristic positions along this continuous axis, as apparent from the dorsal view shown here. Notably, process does not enter to this picture of FC. **(D)** This continuous, gradient-like organization of FC can be parsimoniously explained by traveling waves. A global wave would introduce propagation delays that gradually increase with distance from the wave source.

Thus, activity would be in-phase (i.e., strongly correlated at zero-lag) between regions that are approximately equidistant from the source (compare with (C)). The vertical dashed line highlights various in-phase and out-of-phase relationships between brain regions. Finally, if this wave process is linked to arousal fluctuations, then different sets of regions (i.e., networks) will be preferentially active at different phases of arousal (A, above).

We suggest that this global, gradient-like picture of FC can be parsimoniously explained by traveling waves that propagate along the unimodal-transmodal axis (Fig. 1D). In this simple model, the FC between two regions (i.e., the degree to which their fluctuations are temporally coincident) will vary inversely with difference in propagation delay (arrival time) of the global wave at these regions. In turn, the difference in propagation delay between any two regions will reflect the difference in anatomical position of these two regions in relation to the wave source (Matsui et al., 2016). Accordingly, wave propagation along the unimodal-transmodal axis (Fig. 1C) would instantiate a topographic spatial gradient of time delays (phase shifts (Gutierrez-Barragan et al., 2019)) (Fig. 1D) and, consequently, a spatial gradient in FC structure. Finally, in this model, global waves are linked to neuromodulators that underlie arousal fluctuations (Reimer et al., 2016). Consequently, global waves would temporally segregate functional systems within a canonical arousal cycle (effectively, propagation along the unimodal-transmodal axis spatiotemporally instantiates the canonical arousal cycle). In this way, a global, spatiotemporal process can parsimoniously link the spatial patterns described by FC and global arousal fluctuations.

The proposed model serves as a guiding framework for the novel results presented in the remainder of this paper. These results include empirical support for the following core predictions of the model: 1) BOLD signal fluctuations are globally coherent with arousal, 2)

phase shifts of the BOLD signal relative to arousal are network-dependent in cortical and subcortical structures, 3) these phase shifts are ordered along unimodal-transmodal gradients, and 4) these phase relations also manifest in electrophysiology. We describe additional properties of arousal waves that highlight their explanatory potential as a parsimonious, theoretically grounded, mechanistic account of many previously described features of resting-state fMRI time series. We anticipate that future studies will more systematically examine various properties of these waves and their relation to an expansive resting-state fMRI literature.

3.4 Results

BOLD fluctuations exhibit brain-wide coherence with arousal

Our model predicts that spontaneous BOLD signal fluctuations should be coherent with physiological indices of arousal throughout the brain. This hypothesis concerns spontaneous BOLD fluctuations in general; it is not a hypothesis concerning specific brain regions that we believe to regulate arousal. We examined coherence between BOLD signals and autonomic activity in a large dataset comprising simultaneously collected resting-state fMRI and physiological data (the Human Connectome Project (Glasser et al., 2013)). First, we examined BOLD signal fluctuations averaged within canonical large-scale networks (Fig. 2A). Consistent with our predictions, spectral analysis revealed strong, broadband coherence of BOLD signal fluctuations with infra-slow fluctuations in respiratory volume (respiratory variation, RV), present across cortical networks (Fig. 2B). Notably, RV coherence exhibited a broad peak centered on ~0.025 Hz, consistent with prior reports of a biphasic cross-correlation between arousal measures and spontaneous BOLD signal fluctuations (e.g., (Birn, 2012)). This coherence peak at 0.025 Hz was not observed in relation to the global BOLD signal (Fig. S1), implying that

it is specific to the relation between BOLD signals and arousal (and is not a consequence of inability to resolve very low frequency peaks in BOLD fMRI runs of finite duration (15 mins)). Thus, the low frequency coherence peak is consistent with an intrinsically rhythmic, autonomic-related infra-slow process (Lecci et al., 2017; McGinley, David, et al., 2015; Söderström et al., 2003; Watson, 2018).

Next, we examined the phase of coherence across networks. Inspection of RV phase spectra confirmed a topographic organization of coherence phase: throughout the canonical infra-slow frequency range (0.01 to 0.1 Hz), functional networks maintained substantial phase shifts *relative to one another* in their relation to RV. Notably, this result indicates that phase relations among networks, rather than time delays, are preserved across infra-slow frequencies (Supplementary Note 1). Network phase shifts generally progressed from unimodal cortex ["Motor" (includes primary somatomotor, somatosensory, and auditory cortices (Yeo et al., 2011)) and "Visual" networks] to transmodal (e.g., "Frontoparietal control" and "Default mode" networks). Similar patterns were observed in relation to two other measures of autonomic activity: heart rate variability (Fig. 2C) and, in an independent dataset (Yellin et al., 2015), pupil size (Reimer et al., 2016) (Fig. 2D). Thus, the temporal structure of spontaneous BOLD fluctuations appears to reflect an association with general physiological arousal.

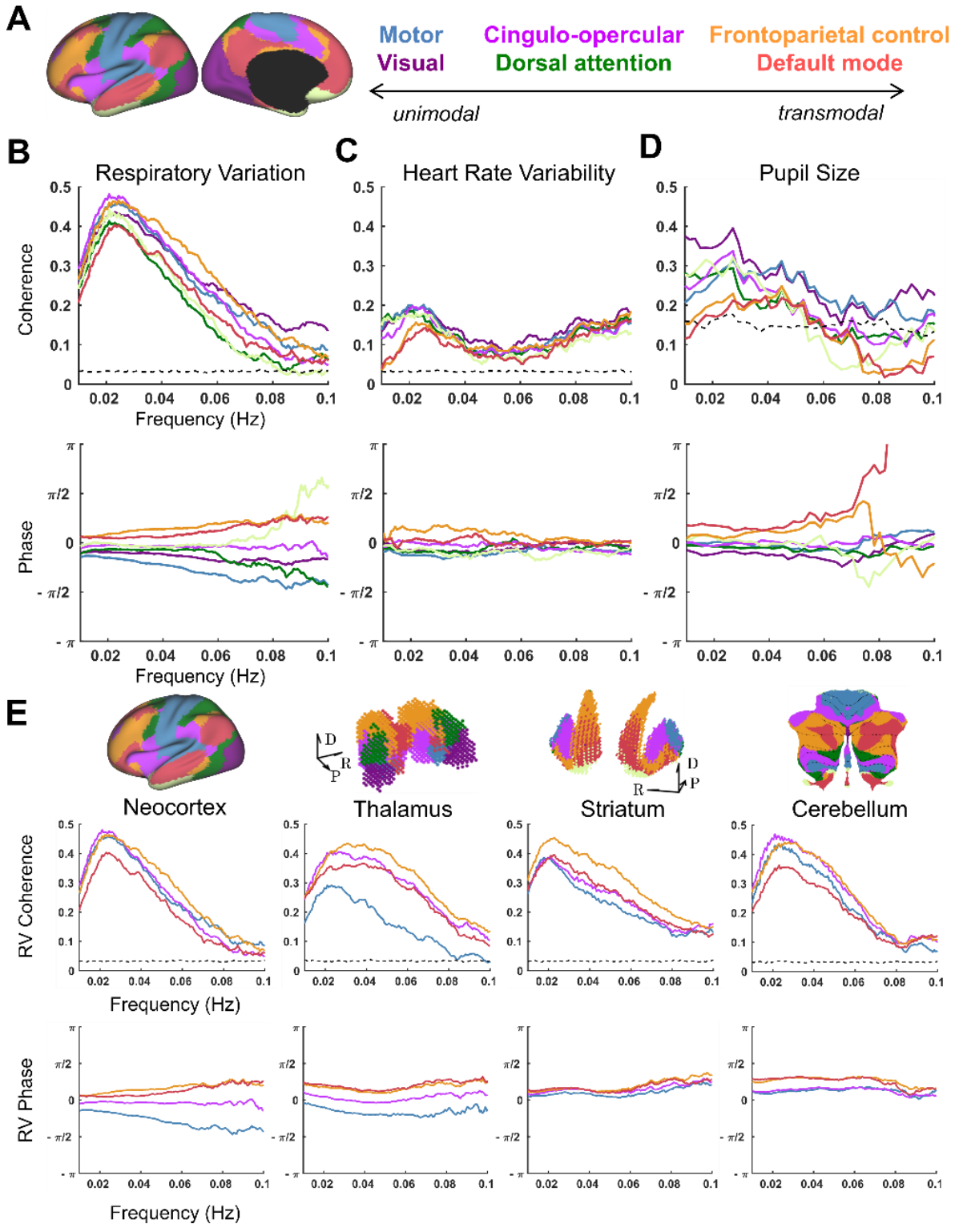
A
Motor
Visual
Cingulo-opercular
Dorsal attention
Frontoparietal control
Default mode
unimodal
transmodal
B
Respiratory Variation
C
Heart Rate Variability
D
Pupil Size
Coherence
Phase
Frequency (Hz)
E
Neocortex
Thalamus
Striatum
Cerebellum
RV Coherence
RV Phase
Frequency (Hz)

Figure 2. Global and topographically organized coherence with fluctuating arousal. (A) Functional organization of brain structures as previously estimated from FC (7-network parcellation) (Yeo et al., 2011). **(B)** Group-average coherence magnitude (upper) and phase (lower) of cortical network-averaged signals in relation to respiratory variation (RV). RV was computed as the temporal standard deviation of respiratory belt data over 6-second sliding windows. Cross-spectra were averaged across a large sample (N = 190 subjects). The displayed phase spectra are shifted to remove a constant (frequency-independent) ~-7 second lag (BOLD preceding RV). Note substantial phase shifts over a broad frequency range. **(C)** Same as in (B), but for heart rate variability (HRV), measured as the (inverse) mean beat-to-beat interval derived from pulse oximetry within 6-second sliding windows. Data obtained from the same N = 190 subject sample as in (A). Note that weaker HRV coherence is likely related to technical factors (see Methods); BOLD:HRV coherence is similar in magnitude to RV:HRV coherence (Fig. S1E). **(D)** Same as in (B) but for pupil size. Data were acquired in an independent sample (N = 20) (Yellin et al., 2015). **(E)** Same as in (B) but for four major networks in neocortex, thalamus, striatum, and cerebellum. FC network parcellations obtained from prior studies (Buckner et al., 2011; Choi et al., 2012; Raut et al., 2020; Yeo et al., 2011). Black dashed lines in coherence plots indicate 99th percentile of the null distribution computed from 500 random shuffles. Direction labels indicate dorsal (D), posterior (P), and anatomical rightward (R). Three-dimensional maps of subcortical structures were generated from MNI152 voxel coordinates. A flatmap representation is shown for the cerebellum (following (Guell et al., 2018)).

Finally, we asked whether phase relationships with arousal measures are similarly mirrored in subcortical structures. Of the physiological measures, cortical coherence was strongest with RV; accordingly, subsequent analyses focused on this measure. We found that the thalamus, striatum, and cerebellum each exhibit strong coherence with RV (Fig. 2E). Phase spectra in these structures also indicated appreciable phase shifts over a broad frequency range that topographically parallel neocortex. Thus, BOLD time series are globally coherent with fluctuating arousal, but phase-shifted in a consistent order according to network identity.

Global waves recapitulate FC structure

We next sought to test our hypothesis that BOLD signal phase shifts, relative to arousal, are spatially organized as traveling waves. To investigate this possibility, we obtained regional phase shifts of BOLD fluctuations relative to RV using Hilbert transform analysis within the frequency range of strongest coherence ($0.01 < f < 0.05$ Hz) (Fig. 3A). This procedure allows us to infer traveling waves from time-averaged phase relationships in spontaneous activity, relative to RV, rather than from the delay times of evoked responses. Indeed, the RV phase map revealed parallel, coordinated unimodal-to-transmodal waves within cerebral cortex, thalamus, striatum, and cerebellum (Fig. 3B).

The phase shifts shown in Fig. 3B indicate propagation delays on the order of several seconds (see Fig. 3B caption). Such long delays are consistent with our model in which slowly propagating waves can account for features of BOLD FC measured at zero-lag. More specifically, we hypothesized that propagating waves can account for the gradient-like structure of FC (Fig. 1C). Accordingly, we assessed the spatial correspondence between the RV phase map (Fig. 3B) and the principal FC coordinate described by Margulies et al. (Margulies et al., 2016) (Fig. 3C).

We confirmed that cortical RV phase map is strongly correlated with the principal FC coordinate in the neocortex (spatial Spearman's rho = .78) (Fig. 3D). Importantly, our model further predicts topographically consistent wave propagation in the thalamus, striatum, and cerebellum. To investigate this possibility, we computed the principal FC coordinate within thalamus, striatum, and the cerebellum based on their FC with neocortex. Principal FC coordinates were obtained via diffusion map embedding (Coifman & Lafon, 2006), as in (Margulies et al., 2016) (see *Diffusion*

maps in Methods). In each structure, we found strong spatial correlation between the principal FC coordinate and the RV phase map (Fig. 3C) (Spearman's rho = .88, .69, .80 in thalamus, striatum, and cerebellum, respectively; $p<.01$ in each structure following correction (see Methods)).

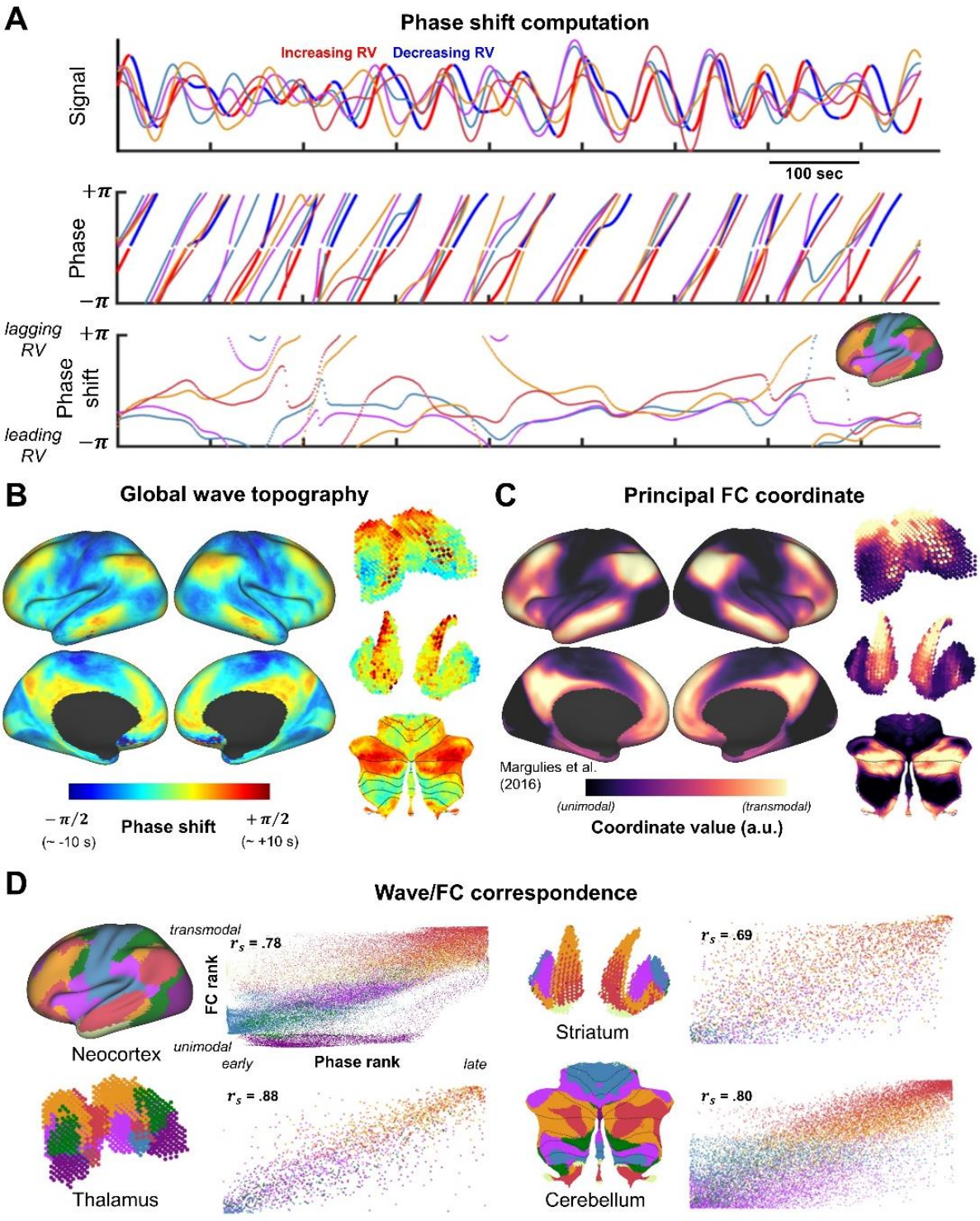

Figure 3. Arousal-related global waves closely relate to large-scale FC structure. (A) Phase shift analysis for a representative time epoch from a single subject. The upper panel shows RV (color-coded red and blue according to phase) and multiple network-averaged BOLD time series

(color-coded by networks shown in Fig. 2A) after filtering between 0.01 and 0.05 Hz. These time series were Hilbert transformed to extract instantaneous phase values (middle). The RV minus BOLD phase differences (modulo 2π) are shown in the lower part of panel A. Thus, lower panel of A depicts time series of instantaneous phase shifts of network-averaged signals relative to RV. **(B)** Time- (and subject-) averaged maps of instantaneous phase shifts relative to RV (zero-centered). The equivalence between a phase shift of and a time delay of ~10 seconds reflects that this analysis was conducted on narrowband signals centered at ~0.025 Hz. **(C)** Principal neocortical, cortico-striatal, cortico-thalamic, and cortico-cerebellar FC diffusion coordinates (Coifman & Lafon, 2006) ("principal functional gradients"). Principal coordinate in cerebral cortex was obtained from (Margulies et al., 2016). Coordinates in thalamus, striatum, and cerebellum were computed de novo (see Diffusion maps, Methods). The unimodal-transmodal gradient is reflected in the gradual increase in coordinate values progressing from primary sensorimotor regions (black) to higher-order association regions (yellow). **(D)** Correspondence between maps shown in (B) and (C). Voxels sorted by FC coordinate rank (vertically) and phase rank (horizontally), and color-coded according to FC network identity. Color codes shown in Fig. 2A. r_s denotes Spearman's rank correlation coefficient.

Brain-wide propagation dynamics

The preceding results suggest that global arousal waves can account for the principal organizational feature of FC; namely, the unimodal-transmodal axis of FC organization (Margulies et al., 2016). However, traditionally, FC structure has been understood in terms of discrete, hierarchically nested networks with (proportionately) sharp boundaries (Wig et al., 2014; Yeo et al., 2011). Thus, FC most strongly distinguishes between two major, distributed functional brain systems (Golland et al., 2008; Lee et al., 2012): an extrinsic system comprising sensorimotor and "task-positive" (Fox, Snyder, Vincent, et al., 2005) regions; and an intrinsic system comprising the default mode network ("task-negative") and frontoparietal regions that preferentially respond to changing task conditions (Marek & Dosenbach, 2018). How might global waves account for this feature?

To answer this question, we sought to visualize wave propagation across a canonical arousal cycle. Thus, rather than obtaining an average RV phase value for each voxel (as in Fig. 3B), we

computed an average spatial map of the BOLD signal at each RV phase (discretized into 40 phase bins). The resulting sequence of maps describes the evolution of voxelwise BOLD signals in relation to RV phase. These maps reveal a succession of spatially distributed motifs resembling canonical FC networks (Fig. 4A,B; Movie S1). As suggested by voxelwise maps of average phase (Fig. 3B), FC network motifs are embedded in waves that propagate from somatomotor and higher-order visual cortices (Supplementary Note 2) toward transmodal, association cortex. In parallel, unimodal $\rightarrow$ transmodal propagation occurs within the thalamus, striatum and cerebellum. In line with previous observations, global waves begin with suppression of activity in the midline thalamus arousal center (Liu et al., 2018; Logothetis et al., 2012). Hippocampal and brainstem activity similarly exhibit organized activity patterns that are time-locked to these waves (Fig. S3; Movie S2).

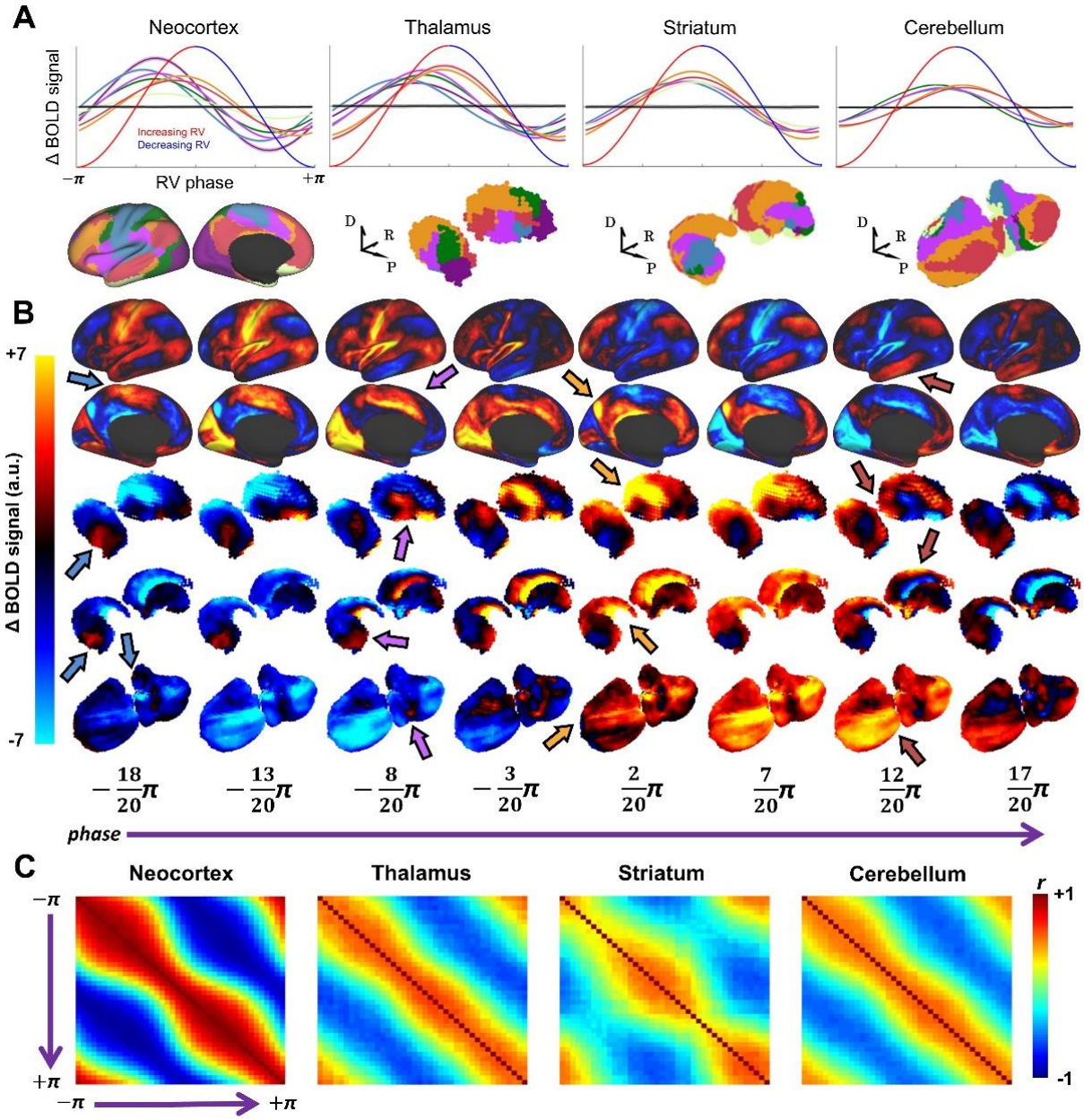

Figure 4. Visualizing propagation dynamics. (A) Mean FC network BOLD signals averaged (across time and subjects) within each of 40 equally spaced RV phase bins and subsequently plotted as a canonical RV cycle (see Fig. 3A). Black lines at the center of each plot indicate 99th percentile values from null distribution (500 random shuffles of physiological and BOLD time series across subjects). Color-coded network topographies below. Increasing and decreasing RV broadly correspond to sympathetic and parasympathetic activity, respectively (although note that interpretation of BOLD vs. RV timing may not be straightforward). **(B)** Group-averaged BOLD signal maps shown for 8 (of 40) evenly-spaced phase bins across the canonical RV cycle. This

illustrates the temporal evolution ("animation" of the BOLD signal topography over a canonical arousal cycle. Each column displays the average BOLD signal topography at a particular arousal phase. To enhance spatial specificity (for visualization only), the global mean time course across all phase bins was subtracted from the time course at each voxel. Thus, for a given phase, (B) illustrates how each voxel differs from the brain-wide mean BOLD value at that phase. Color-coded arrows highlight canonical FC network topographies (motor, cingulo-opercular, frontoparietal control, and default mode) appearing simultaneously across cerebral cortex, thalamus, striatum and cerebellum. **(C)** Frame-by-frame spatial correlation matrices computed from (B). Each element in these matrices represents the spatial correlation of BOLD maps at two different phase bins. Thus, these matrices represent spatial correlations between temporal units (in contrast to conventional FC matrices, which represent temporal correlations between spatial units). Matrices indicate relatively smooth progression (i.e., strong correlations surrounding diagonals) between anti-correlated topographies (blue off-diagonal regions). However, the narrowing of the diagonal near the middle of this matrix (where phase ~=0), particularly in the neocortex, indicates that most time is spent with one of the two anti-correlated topographies). Positive correlation in corners reflects intrinsic periodicity (Majeed et al., 2011) (data in (C) were unfiltered beyond a gentle .0005 Hz temporal high-pass (Smith et al., 2013)).

Fig. 4C illustrates propagation between the abovementioned intrinsic and extrinsic brain systems. Such propagation between complementary topographies occurs in both cortical and subcortical structures, with intrinsic periodicity of ~40 s (Majeed et al., 2011). Notably, the BOLD signal topography changes relatively rapidly during the transition between the extrinsic and intrinsic systems (Fig. 4C; Movie S2). This observation is consistent with prior accounts of the extrinsic and intrinsic systems as two temporal "metastates" (Majeed et al., 2011; Vidaurre et al., 2017), such that activity gradually increases in one state before rapidly switching to the other (Yellin et al., 2015).

Transitions between the extrinsic and intrinsic topographies appear to involve multiple coordinated, rotating waves within cortex and subcortex (Fig. 4B; Movie S1-2), which are less apparent from the RV phase map shown in Fig. 3B. We characterized these complex propagation features in two ways. First, we applied optical flow analysis to the cortical dynamics shown in Fig. 4B (i.e., the canonical RV cycle) (Horn-Schunck algorithm; Methods). The resulting flow

fields revealed vortex- or spiral-like propagation in several locations (Fig. 5A). For example, on the lateral surface, propagation from motor cortex broadly follows a clockwise trajectory – sequentially passing through insula, inferior frontal regions, and dorsolateral prefrontal cortex – before propagating back towards motor cortex (Fig. 5A). Thus, a transmodal → unimodal propagation pattern completes the spatiotemporal cycle.

To further characterize rotation, we represented the "movie" in Fig. 4B as a new phase function, $\psi(r, t)$, where r indexes voxels and t indexes time points (i.e., RV phase bins). ψ, defined via Hilbert transform (Methods), represents each frame of the RV movie as a spatial map of instantaneous phase shifts (Bray et al., 2001). After referencing each frame of ψ to a common region (the visual network), the (circular) mean of ψ across movie frames (Fig. 5B) captures the dynamics of brain regions in relation to one another (thus, "Relative phase") within a canonical RV cycle, rather than peak times in relation to RV. Fig. 5B reveals, embedded within the globally coherent wave process, many sharp phase boundaries. Notably, these include several apparent phase singularities (i.e., centers of pinwheel-like structures, at which all phases come arbitrarily close together (Winfree, 2001)), e.g., in the anterior insula, premotor cortex, and angular gyrus. (Effectively, Fig. 5B represents the curl of the flow field (Bray et al., 2001); divergence of the flow field identifies sources in several nearby, attention-related regions (Fig. S6)).

If phase within this global wave cycle determines FC structure (as in the proposed framework), phase should be most variable at locations where FC is also most variable. Indeed, by computing local variability of ψ (i.e., circular standard deviation within a 10mm radius; Methods), greatest phase variability is observed at the boundary separating the extrinsic and intrinsic systems (Fig.

5B). Thus, similar to FC, phase within the global wave cycle is most variable at the boundaries circumscribing the default mode (red) and frontoparietal control (yellow) FC networks (Fig. 5D). Importantly, the principal FC coordinate also changes abruptly at these boundary regions (Margulies et al., 2016) (Fig. 5D). Accordingly, the globally coherent wave process, as well as the unimodal-transmodal coordinate of FC, preserve the sharp distinction between the extrinsic and intrinsic systems.

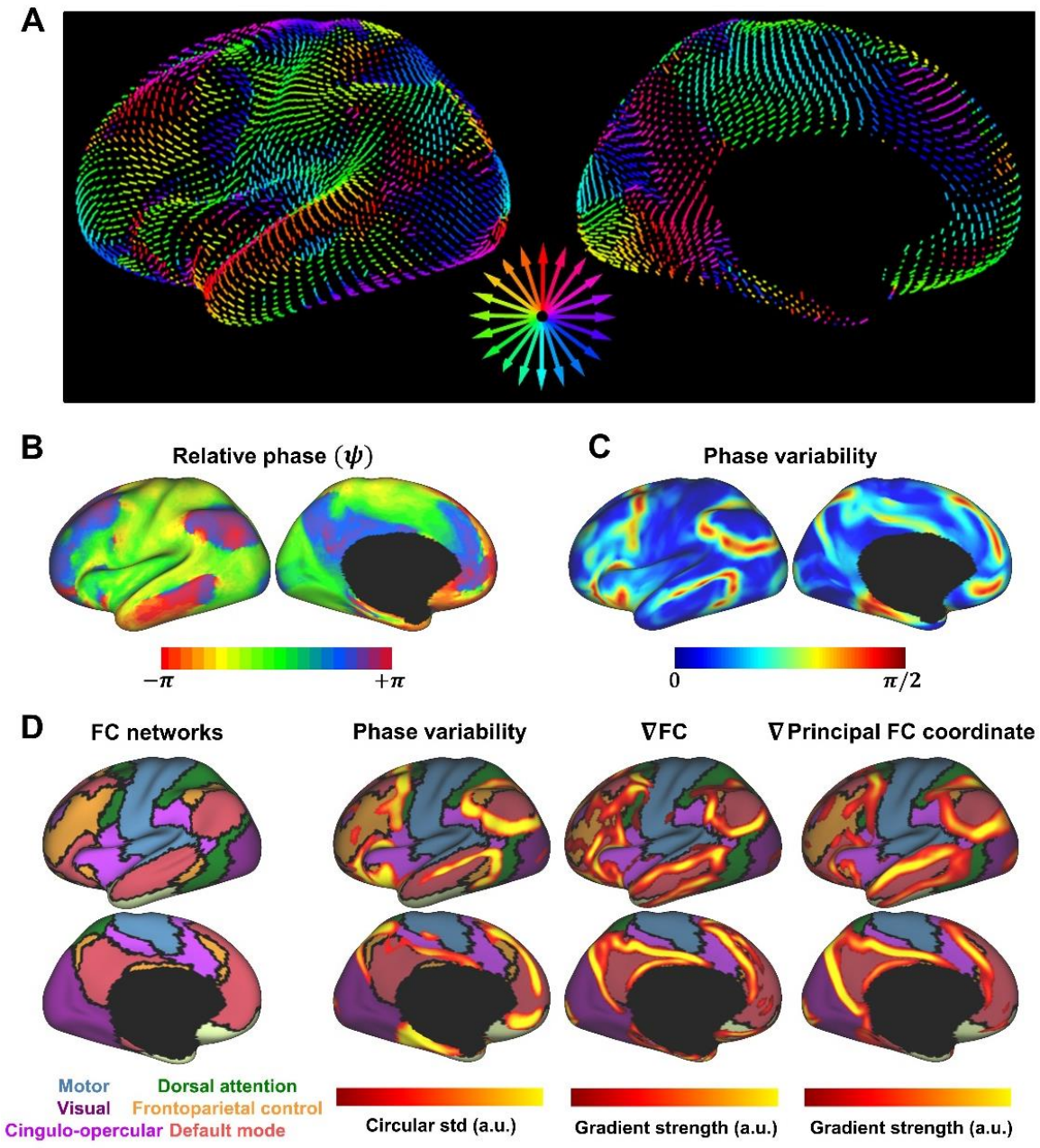

Figure 5. Wave decomposition. (A) Flow fields computed from (Fig. 4B), using optical flow analysis (Methods). Arrow magnitude and orientation indicate the local velocity and direction of propagation within three-dimensional Euclidean space. To facilitate visualization, arrows are color-coded according to direction within the 2-D plane of the page based on color wheel at center. See also Movies S1-S2. **(B)** Phase mapping of movie shown in Fig. 4B. ψ illustrates the rotating nature of the propagation dynamics (effectively, curl of the vector field; divergence shown in Fig. S6). Phase maps were referenced to a common region; hence, exact phase value in this map is arbitrary. Note pinwheel-like structures where many phases come together in close

proximity (e.g., anterior insula, premotor cortex, and angular gyrus). **(C)** Local phase variability of the map shown in (B). Phase variability is computed as the (circular) standard deviation of phase values within a 10mm radius of each vertex. **(D)** Regions with high phase variability (C) overlap regions where FC exhibits abrupt changes – in particular, at the boundary dividing the extrinsic and intrinsic systems. From left to right: canonical FC networks (Yeo et al., 2011); thresholded version of map shown in (C); spatial gradient of the FC similarity matrix (Wig et al., 2014); and spatial gradient of the principal FC diffusion coordinate (shown in 3C) (Margulies et al., 2016). ∇ is the differential operator indicating gradient computation.

Global waves in macaque electrocorticography

The preceding analyses link topographically organized BOLD signal fluctuations to global arousal fluctuations indexed by RV, heart rate variability, and pupil size. Similar results are also obtained in relation to spontaneous head movements, which are intimately linked to arousal (see Supplementary Text and Fig. S5). The interpretation of BOLD signal fluctuations linked to these indices is a matter of ongoing debate (e.g., (Birn, 2012; Chen et al., 2020; Power, Mitra, et al., 2014; Tong et al., 2017); see Discussion). However, our model posits that propagating BOLD signal fluctuations observed with fMRI are physiologically coupled to electrophysiological waves reflecting neuronal activity. Accordingly, the question now emerges as to whether the results obtained on the basis of BOLD fMRI signals can also be demonstrated with infra-slow electrophysiology.

The power envelope of broadband "gamma" (40-100 Hz) local field potentials is a reliable correlate of the BOLD signal (e.g., (Nir et al., 2007; Shmuel & Leopold, 2008)). Gamma band-limited power (BLP) exhibits spontaneous, infra-slow fluctuations that are closely coupled to infra-slow electrical potentials (<0.1 Hz) (which are not typically recorded in conventional electrophysiology) (Palva & Palva, 2012). These power fluctuations mirror the long-distance

coordination characteristic of BOLD FC (e.g., (Kucyi, Schrouff, et al., 2018) and references therein). Thus, our model predicts that the FC topographies of gamma BLP are embedded within globally propagating arousal waves.

Importantly, a series of studies in macaque monkeys have defined an electrophysiological index of arousal transitions, involving cortex-wide fluctuations in gamma BLP recorded with electrocorticography (ECoG) (Liu, Yanagawa, Leopold, Chang, et al., 2015). These gamma BLP fluctuations occur as part of a stereotypical temporal sequence of changes to >1 Hz cortical spectral content, termed sequential spectral transitions (SSTs), and are closely linked to global fluctuations observed with fMRI (reviewed in (Gu et al., 2019)). Taken together, SSTs emerge as a likely electrophysiological correlate of infra-slow arousal waves. Accordingly, although SSTs are currently understood to be globally synchronous events, we hypothesized that the gamma component of SSTs should manifest as a traveling wave.

Testing this hypothesis requires large-scale electrophysiological recordings of sufficient spatial resolution and coverage. Accordingly, we examined spontaneous cortical activity measured from hemisphere-wide ECoG arrays in two highly-sampled macaques (Yanagawa et al., 2013). We identified SST events using previously described criteria (Liu, Yanagawa, Leopold, Chang, et al., 2015). Averaging over SST events (N = 1,145 events total; Monkey 1, N = 656; Monkey 2, N = 489), we found that fluctuations in gamma BLP propagate as traveling waves across macaque neocortex (Fig. 6A-C). Propagation dynamics strongly resembled results obtained by analysis of human fMRI data, specifically, propagation from sensorimotor regions to distributed association regions in frontal, parietal, and temporal cortices (Fig. 6D; Movies S3-S4).

Similar to fMRI results in humans, we examined correspondence of propagation patterns to the principal diffusion coordinate of the FC matrix in each monkey. We found that principal FC coordinates obtained from gamma BLP (Fig. 6C) varied from unimodal to transmodal cortex. Thus, the principal FC coordinate obtained with macaque electrophysiology was homologous to the principal, fMRI-derived functional gradient in humans (Fig. 3C), and corresponded well with previous descriptions of structural and functional connectivity gradients across macaque neocortex (Margulies et al., 2016; Oligschläger et al., 2019). As in the human fMRI data, we observed strong correlation between propagation delays and functional gradients in both monkeys (Fig. 6C). These results demonstrate an electrophysiological basis for slowly propagating waves that spatiotemporally pattern high-frequency neuronal dynamics in relation to arousal.

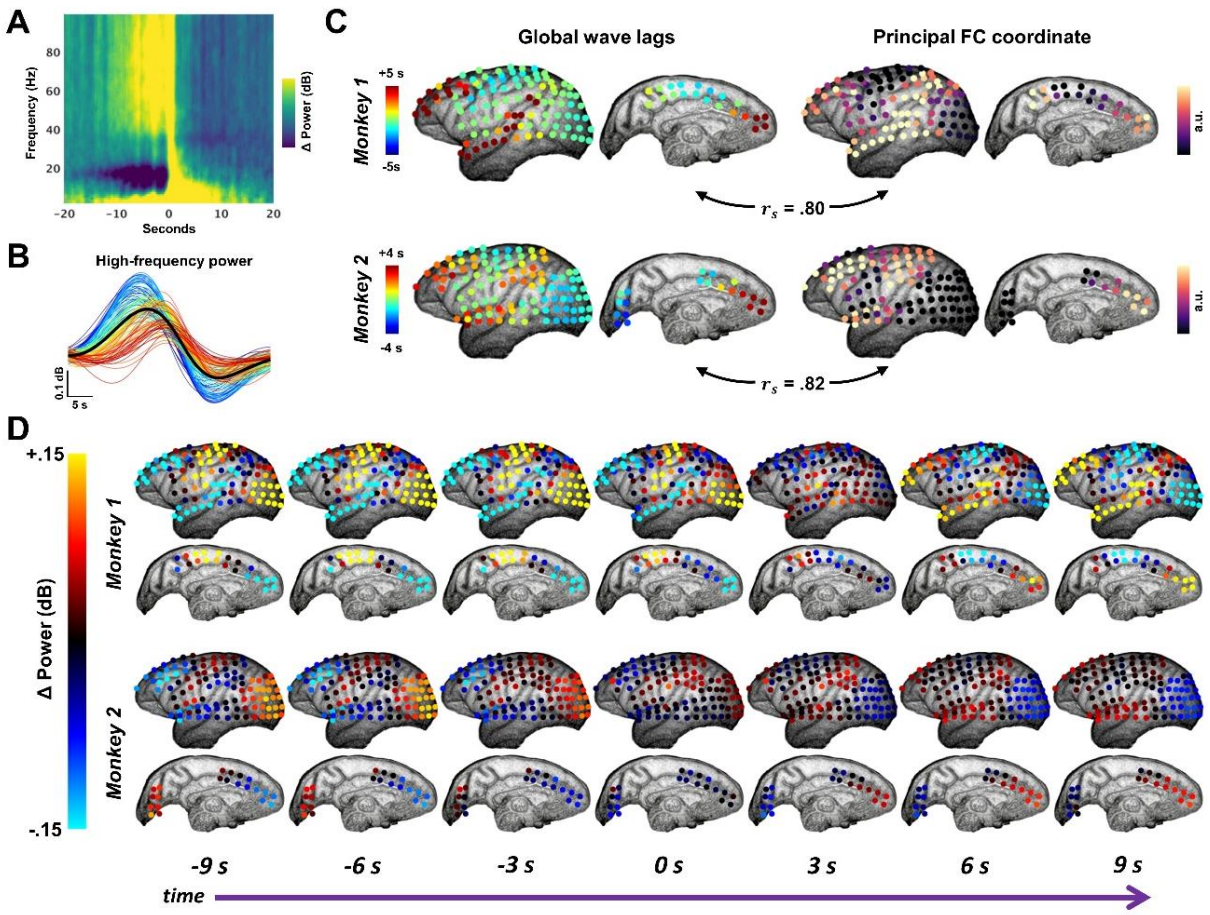

Figure 6. Electrophysiological arousal transients propagate as global waves across macaque neocortex. (A) Spectrogram depicting a sequential spectral transition (SST) event (Liu, Yanagawa, Leopold, Chang, et al., 2015) averaged over hemisphere-wide electrodes (128) in two macaque monkeys across several awake recording sessions (N = 1,145 events in total). SSTs comprise a stereotypical sequence of changes in power within multiple frequency bands. **(B)** The high-frequency portion of the mean SST spectrogram (gamma; 40-100 Hz), plotted as a separate time series for each electrode in one monkey. Time series (color-coded by mean latency) reveal a range of time delays. **(C)** (Left) Lag maps of global high-frequency power during SST events, derived from cross-correlation, follow gradients that indicating large-scale traveling waves. In each monkey, this propagation delay map strongly correlates with the principal functional gradient obtained from diffusion embedding of the FC matrix computed across all electrodes (similar to Fig. 3C). r_s denotes Spearman's rank correlation coefficient. **(D)** Spatiotemporal evolution of high-frequency power during SST events in two monkeys. Global mean time course subtracted from (D) for visualization only (as in Fig. 4B). As in human fMRI, activity propagates over several seconds from sensorimotor regions to association areas in frontal, parietal, and temporal cortices. See also Movies S3-S4.

3.5 Discussion

Herein, we have proposed an intrinsic, infra-slow physiological process that spatiotemporally patterns brain-wide excitability in relation to arousal. We have empirically confirmed the central prediction of this model: topographically organized traveling waves that slowly propagate in cortical and subcortical structures in synchrony with arousal fluctuations. We suggest that these waves are the predominant, intrinsic physiological process reflected in spontaneous BOLD signal fluctuations. Accordingly, infra-slow arousal waves constitute a generative mechanism of FC and spatiotemporal structure as assessed with resting-state fMRI.

A key feature of these waves is that they link together, within a unifying physiological framework, many previously described features of resting-state fMRI time series. Thus, arousal waves relate to and may provide a parsimonious account of large-scale FC structure (Lee et al., 2012; Margulies et al., 2016), anti-correlated systems (Fox, Snyder, Vincent, et al., 2005; Golland et al., 2008; Lee et al., 2012), quasiperiodic patterns (Abbas et al., 2019; Majeed et al., 2011) and BOLD temporal sequences described at multiple timescales (Gutierrez-Barragan et al., 2019; Mitra et al., 2014; Vidaurre et al., 2017), SSTs (Gu et al., 2019; Liu, Yanagawa, Leopold, Chang, et al., 2015), “transition zones” in the neocortex (discussed below) (Mennes et al., 2010; Power et al., 2013), as well as the BOLD correlates of head motion: global and temporally extended signal changes, and distance-dependent FC changes (Power, Mitra, et al., 2014). To be clear, many of these features reflect properties of large-scale functional anatomy (e.g., functional systems, structural connectivity, spatial embedding). Waves offer a mechanistic account of how this functional anatomy manifests in BOLD spatiotemporal structure (e.g., zero-lag FC). [Note

that FC is sometimes assessed via coherence (i.e., not necessarily zero-lag), particularly in electrophysiology (e.g., (Hipp et al., 2012)). The present paper uses "FC" interchangeably with "zero-lag correlation", which is the primary measure of interest in resting-state fMRI research (Power, Schlaggar, et al., 2014))].

Phase singularities may link together several additional themes in the literature. Singularities lie at the boundary of the extrinsic and intrinsic systems (a similar observation was recently described in mouse cortex (Vanni et al., 2017)). Regions proximal to this boundary have been implicated in diverse contexts relating to integration (e.g., (Assem et al., 2020; Power et al., 2013); see (Raut et al., 2019) for further discussion and results in individuals). Attention and salience-related regions (Corbetta et al., 2008; Menon & Uddin, 2010) may drive rotation about these singularities (Fig. S6): recent studies indicate that the structural connectome intrinsically biases propagation to occur along the unimodal-transmodal axis (Seguin et al., 2019), whereas attention-related regions are well-positioned to flexibly re-route propagation along this axis (Vézquez-Rodríguez et al., 2020). Such regions may have the ability to interrupt (effectively, phase-reset) an ongoing infra-slow arousal cycle (Palva & Palva, 2018; Rajkai et al., 2008). Notably, this potential for phase resetting suggests one way in which global waves may significantly contribute to observed task-evoked brain responses (Fox, Snyder, Barch, et al., 2005).

Regardless of their functional interpretation, phase singularities provide a parsimonious account for multiple FC-related observations. Thus, if FC network assignments are determined by phase shifts in relation to global waves, then the phase singularities of these waves – where all phases converge – should correspond to regions where many networks appear to converge. Relatedly,

regions lacking a well-defined phase shift should also lack a reliable FC network affiliation, even in individuals. These interpretations appear consistent with published results (Golland et al., 2008; Lee et al., 2012; Power et al., 2013; Yeo et al., 2014) (for results in individuals, see (Raut et al., 2019) and Figs. S10-11 in (Kong et al., 2018)). Finally, because regions of poorly defined phase lie at the junction between two anti-correlated systems, interindividual variability in the precise location of these points (likely determined by gyral patterns (Santos et al., 2014; Winfree, 2001)) is expected to yield highly variable FC patterns across individuals. Indeed, interindividual variability in FC is maximal at the boundary between the extrinsic and intrinsic systems (Ren et al., 2020; Seitzman et al., 2019). This adds nuance to the notion that phylogenetically recent transmodal regions exhibit greatest interindividual FC variability (Mueller et al., 2013). Notably, boundary regions also hold greatest explanatory value in studies relating interindividual variability in FC to interindividual variability in behavioral measures (Mueller et al., 2013) or task-evoked BOLD responses (Mennes et al., 2010).

The second-order statistics of BOLD signal fluctuations (e.g., correlation structure and spectral content) index arousal on a timescale of minutes (referred to here as “vigilance”, to avoid confusion) (Liu & Falahpour, 2020). These slower changes are consistent with increasing magnitude of spontaneous waves during lower vigilance states. Thus, reduced vigilance is marked by increased BOLD signal amplitude and FC within sensorimotor cortex (consistent with dispersive propagation beginning in these locations), increased “global signal” amplitude, and decreasing anti-correlations between the default mode network and attention systems (reviewed previously (Gu et al., 2019; Liu & Falahpour, 2020; Tagliazucchi & van Someren, 2017)). These slower fluctuations in vigilance have emerged as an important explanatory factor for time-varying FC, as well as its behavioral and electrophysiological correlates (Gu et al., 2019). We

suggest that these results are consistent with relative suppression of spontaneous waves during higher-vigilance states, recapitulating the widely observed negative relationship between spontaneous and task-evoked brain activity (e.g., (Churchland et al., 2010; He, 2013)). Nonetheless, we expect that the persistence of these waves during task states is likely to account for a substantial fraction of variability observed in task-evoked brain responses and behavioral performance (Gilden, 2001; McGinley, Vinck, et al., 2015; Palva & Palva, 2012).

The full explanatory potential of this framework, and the extent to which additional intrinsic physiological processes need to be invoked, remains to be determined. The present study focuses on a dominant global wave pattern and its association with arousal. Resting-state BOLD signal fluctuations also include contributions from other wave patterns with state-dependent probability (Mitra et al., 2018; Mitra et al., 2015), and other mechanisms may contribute to more fine-scale FC structure (Cabral et al., 2017). These mechanisms include experimentally unconstrained evoked activity (i.e., not an intrinsic physiological process). Nonetheless, we note that the spatiotemporal dependencies inherent to traveling waves pose a widely recognized challenge to spatiotemporal decomposition. Conventional decomposition techniques, which typically assume spatial and/or temporal independence, can be expected to assign different features of these waves to statistically (but not phenomenologically) independent components, thereby inflating the estimated dimensionality (and, correspondingly, underestimating the amount of variance attributable to the propagating wave) (Brunton & Kutz, 2019; Hindriks et al., 2019).

Implications for BOLD imaging

The BOLD signal reports local changes in blood oxygenation. These changes are tightly linked to millisecond-scale neuronal activity through a complex neurovascular cascade. However, many

biochemical agents (e.g., blood gases) can influence cerebral hemodynamics outside of this classical cascade. As these factors all are regulated to some extent by autonomic activity, the BOLD correlates of autonomic fluctuations are generally regarded as nuisance variables, particularly in the context of functional brain mapping. In contrast, our proposed framework follows from accumulating, multimodal evidence demonstrating that systemic physiological processes are fundamentally linked to infra-slow neural activity (Fernandez & Lüthi, 2020; Okun et al., 2019; Watson, 2018). This evidence has emerged against a backdrop of empirical and theoretical support for the centrality of autonomic processes to global brain function (e.g., (Azzalini et al., 2019) and references therein; see (Calderon et al., 2016) for historical overview of arousal, behavior, and the brain). These results warrant a more nuanced view of physiological variables in fMRI.

The coordination of neural, metabolic, and systemic physiology underlies the success of BOLD-based imaging in the study of human brain function. It is not surprising, then, that infra-slow neurophysiology is intimately related to each of these factors. The relevant biology is wide-ranging and likely includes many metabolic and non-neuronal process that slowly modulate neuronal excitability (see (Palva & Palva, 2012; Watson, 2018) and references therein). Although reference limits preclude proper treatment of this literature, we note likely essential roles for redox metabolism (Natsubori et al., 2020; Vern et al., 1997), ion fluxes (Krishnan et al., 2018; Rasmussen et al., 2019), and glial physiology (including upstream of the neurovascular cascade (Wang et al., 2018; Zuend et al., 2020)). These interrelated factors are each influenced by neuromodulators that track behavioral state over infra-slow timescales (Moore & Cao, 2008;

Reimer et al., 2016; Zuend et al., 2020). More generally, our work builds upon substantial evidence implicating infra-slow oscillations in the autonomic-related coupling of brain and body (reviewed in (Başar, 2008; Fernandez & Lüthi, 2020)).

This extent of integrative physiology raises practical and, more importantly, theoretical challenges for distinguishing "neuronal" versus "non-neuronal" sources of BOLD signal fluctuations. Global waves are inherently associated with physiological variables and head movements, yet are likely to significantly contribute to the spatiotemporal features of interest in BOLD time series, and are apparent from electrophysiology (Fig. 6). Further, the broad distribution and frequency-invariance of regional phase shifts (Fig. 2) implies that removal of widely shared variance (e.g., with global signal regression), though useful for enhancing spatial specificity (Murphy & Fox, 2017), alters rather than eliminates the manifestation of global waves in BOLD time series. The available evidence supports this interpretation (Abbas et al., 2019; Chen et al., 2020; Matsui et al., 2016). Our results pose a challenge to the commonly held view that BOLD associations with physiological variables, even if related to neuronal activity, are purely a "nuisance" in investigations not explicitly concerned with fluctuating arousal. The possibility should be considered that autonomic activity is fundamental to spontaneous infra-slow brain activity.

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3.7 Methods

Datasets

Dataset 1: Human Connectome Project (fMRI and physiology)

Simultaneously collected resting-state fMRI and physiological data were analyzed from a previously described subset of 190 subjects (Chen et al., 2020) from the WU-UMinn Human Connectome Project (HCP) 1200 Subject Release. Details regarding the HCP dataset are published elsewhere (Smith et al., 2013; Van Essen, Ugurbil, et al., 2012). Two 15-minute, eyes-open resting-state fMRI sessions (multi-band factor = 8, TR = 0.72 s; 2.0 mm isotropic voxels, one left-to-right and one right-to-left phase encoding direction) were obtained at each of two experimental sessions, for a total of four runs per subject. Physiological data were collected at 400 Hz via a bellow placed around the chest (respiration) and a pulse oximeter placed on the fingertip (pulse). We analyzed all runs from the 190 subjects that included full duration BOLD and physiological time series (22 of 760 possible scans were omitted from RV analyses; 31 were omitted from HRV analyses).

Dataset 2: Weizmann Institute dataset (fMRI and pupil size)

Simultaneously collected resting-state fMRI and eye-tracking data were acquired from 22 subjects as part of the main (i.e., "Rest-fixation") experiment described in Yellin et al. (Yellin et al., 2015). Briefly, each subject provided one 8-minute, eyes-open resting-state scan (TR = 2.0 s, 3.0 x 3.0 x 4.0 mm voxels). Pupil diameter was acquired at 500 Hz using an MR-compatible infrared Eyelink-100 (SR Research, Osgoode, ON, Canada) eye-tracker. Two subjects were excluded based on excessive movement or eye-tracking artifacts (Yellin et al., 2015), leaving 20 subjects for analysis in the present work.

Dataset 3: Genomics Superstruct Project (fMRI)

We additionally analyzed resting-state fMRI data from 1,139 individuals of the Harvard-MGH Brain Genomics Superstruct Project (GSP). Details regarding the GSP dataset are published elsewhere (Holmes et al., 2015; Yeo et al., 2011). Two six-minute fMRI runs (TR = 3.0 s, 3.0 mm isotropic voxels) were acquired per subject included in the present analyses.

Dataset 4: Neurotycho (ECoG)

Resting-state electrophysiological data were obtained from a publicly available database (neurotycho.org) (Nagasaka et al., 2011). We used ECoG data from two macaque monkeys each chronically implanted with a subdural, 128-channel electrode array spanning the cerebral cortex of the left hemisphere. Details of this recording system (Nagasaka et al., 2011) and this particular dataset (Liu, Yanagawa, Leopold, Chang, et al., 2015; Yanagawa et al., 2013) are published elsewhere. As previous studies find that arousal shifts most closely associated with the fMRI global signal are most prominent in the eyes-closed state (Liu, Yanagawa, Leopold, Chang, et al.,

2015; Schölvinck et al., 2010), we analyzed data obtained during the awake, eyes-closed resting-state. A total of 8 sessions were used for Monkey 1 ("Chibi") and 9 sessions for Monkey 2 ("George"), each lasting 10-20 minutes.

Data processing and analysis

Physiological data preprocessing

Respiratory variation (RV) and heart rate variability (HRV) were computed as previously (Chen et al., 2020). Thus, temporal standard deviation of the respiratory trace and mean beat-to-beat interval were computed within 6-second sliding windows centered on each TR (i.e., every 0.72 s). Beat-to-beat interval was estimated using the built-in *findpeaks* MATLAB function. Physiological traces did not undergo detailed manual inspection (as previously discussed (Glasser et al., 2019)). Hence, magnitude of BOLD coherence with physiological measures (Fig. 2) are likely underestimated (for HRV in particular, which was obtained via pulse oximeter).

Pupil size estimates were obtained from the Eyelink system and pre-processed as previously (Yellin et al., 2015). Briefly, periods of missing pupil data (due to blinks or other acquisition issues) were interpolated via an inverse-distance weighting algorithm, *Z*-normalized, and resampled to the match the fMRI resolution (0.5 Hz).

fMRI preprocessing

GSP and Weizmann BOLD data were preprocessed to reduce artifact, maximize cross-session registration, and resample to an atlas space, following a previously described procedure (Mitra et al., 2014). Briefly, scans underwent correction for odd-even slice intensity differences stemming from interleaved acquisition of slices within a volume, correction for within-volume slice-

dependent time shifts, and intensity normalization to a whole brain mode value of 1000. Rigid body correction for head movement was included with affine transformation in a single resampling that generated volumetric time series in 3 mm isotropic Talairach atlas space. Processed time series were transformed to MNI152 space prior to surface mapping. For each subject, the atlas-transformed T1-weighted image was nonlinearly warped to the MNI152 template using FSL's FNIRT (Jenkinson et al., 2012) and the resulting transform was applied to BOLD runs. Preprocessed data were mapped to individually constructed cortical surface meshes using the standard HCP pipeline incorporating FreeSurfer (Fischl, 2012) and Caret (Van Essen et al., 2001) tools (using the ribbon-constrained sampling procedure (Glasser et al., 2013)). The final time series were aligned to 32k fs_LR atlas space (Van Essen, Glasser, et al., 2012). GSP surface time series were minimally geodesically smoothed along the subject-specific cortical surface (2mm FWHM), and volumetric data were not smoothed. Because of the limited sample size (N = 20 subjects), pupil data were geodesically smoothed with a 10 mm FWHM Gaussian kernel (volumetric subcortical data were not analyzed). Nuisance regression was restricted to the six motion parameters and no motion censoring was performed.

HCP data were preprocessed using the minimal preprocessing pipeline (Glasser et al., 2013). For main analyses, we used publicly available HCP data that had undergone ICA-FIX denoising (Salimi-Khorshidi et al., 2014), although this denoising pipeline had minimal influence on the results (e.g., Fig. S4). HCP data did not undergo slice-timing correction (Glasser et al., 2013), which in principle introduces systematic bias in latency estimates on the order of the TR (0.72 s). In practice, this bias is negligible in the present study given that HCP analyses were primarily focused on much longer delays (e.g., Figs. 3-4). Moreover, we averaged over scans collected

using left-to-right and right-to-left phase encoding, thereby considerably reducing temporal biases due to slice-timing.

All fMRI data were analyzed in CIFTI format, which represents cortical voxels as vertices on a surface mesh while retaining volumetric time series from the subcortex and cerebellum (Marcus et al., 2011). We used the standard HCP "grayordinate" parcellation, comprising 59K cortical vertices and 66K subcortical/cerebellar gray matter voxels (Glasser et al., 2013).

Network parcellations

Neocortical, thalamic, striatal, and cerebellar network parcellations, defined on the basis of zero-lag FC, were obtained from previously published works (Buckner et al., 2011; Choi et al., 2012; Raut et al., 2020; Yeo et al., 2011).

Coherence analysis

Cross-spectral analysis of BOLD and physiological data was performed using multitaper spectral estimates (Bokil et al., 2010). Time series were averaged within networks and complex-valued cross power spectral density (CPSD, P_{xy}) was computed at the subject level (time-bandwidth product = 6 (10), number of tapers = 6 (12) for HCP (Weizmann) data; network phase sequences were robust to these parameter choices) and subsequently averaged across subjects. Magnitude and phase of coherence were derived from the group-averaged PSD and CPSD estimates. Specifically, magnitude squared coherence was computed as:

$$C_{xy}(f) = \frac{\left|P_{xy}(f)\right|^2}{P_{xx}(f)P_{yy}(f)}, \tag{3.1}$$

and phase spectra were computed as the four-quadrant inverse tangent of imaginary over real parts of the CPSD:

$$\theta_{xy}(f) = \tan^{-1}\left(\frac{\mathrm{Im}\left(P_{xy}(f)\right)}{\mathrm{Re}\left(P_{xy}(f)\right)}\right) \tag{3.2}$$

A null distribution of coherence estimates were obtained by shuffling physiological time series across subjects and recomputing the group-averaged CPSD. This procedure was repeated 500 times.

All group-level phase spectra contained a group delay term of ~7 seconds corresponding to the temporal lag of the physiological time series relative to BOLD fluctuations. To emphasize between-network phase shifts, this delay was removed from network phase spectra by subtracting out the group-level global signal phase spectrum (relative to the relevant physiological term).

Phase maps

To generate phase maps shown in Fig. 3, physiological and BOLD time series were filtered between 0.01 and 0.05 using a 4th-order zero-phase Butterworth filter. Instantaneous phase was computed via Hilbert transform. Mean phase shifts were computed for each voxel as the circular mean of instantaneous phase shifts (relative to the physiological time series) across all time points and subjects. Thus,

$$\mathrm{PLV}_n = \frac{1}{T}\left|\sum_{t=1}^{T} \exp\left(i\left(\theta_{RV,t} - \theta_{n,t}\right)\right)\right|, \tag{3.3}$$

where $\theta_{RV,t}$ and $\theta_{n,t}$ are the instantaneous phases, at time t, of RV and the BOLD signal at a given voxel n. PLV is the complex phase-locking value (Lachaux et al., 1999; Tass et al., 1998), which is subsequently averaged across subjects. Fig. 3B displays the angle of the group-average PLV; magnitude of the group-average PLV is shown in Fig. S2.

Phase-locked dynamics

Movies of a canonical arousal cycle (Fig. 4) were obtained by averaging BOLD signals within 40 phase bins spanning the interval $(-\pi, \pi]$ based on the instaneous phase of the filtered RV time series (similar to (Reimer et al., 2014; Reimer et al., 2016)). For Results shown in Fig. 4A and B, BOLD data were additionally filtered between 0.01 and 0.05 Hz and the resulting 40-frame movie was smoothed using a sliding-window average of three phase bins in either direction. Finally, subcortical and cerebellar voxels were smoothed with a 4mm Gaussian kernel (following the above steps). These maneuvers did not materially change the results; propagation dynamics without ICA-FIX denoising, temporal filtering, or averaging across phase bins are shown in Fig. S4. Propagation displays (both image frames and videos) are shown following subtraction of the global mean time course from the final, group-level result, to aid visualization of spatial specificity.

Optical flow estimation and wave decomposition

Vector flow fields (Fig. 5A) were constructed via optical flow analysis. Optical flow was estimated from the spatial and temporal derivatives of the RV "movie" shown in Fig. 4B (Movie S1-S2) using the Horn-Schunck algorithm (Horn & Schunck, 1981). Here, flow fields are used primarily as a visualization technique, with Fig. S6 (divergence) being the only analysis performed directly on the flow field. The reader is referred to recent detailed descriptions of

optical flow algorithms and their application to spatiotemporal data in neuroscience (Afrashteh et al., 2017; Townsend & Gong, 2018). We briefly summarize our application of this algorithm to fMRI data below.

The Horn-Schunck algorithm estimates the "movement" of pixels between consecutative frames, in terms of a velocity vector field defined at each pixel (voxel), by solving an optimization equation satisfying two constraints (Horn & Schunck, 1981). First, a "brightness constancy" constraint assumes preservation of image itensity I at each spatial location (x, y, z) between consecutive frames t and $t + dt$. Thus,

$$I(x + u, y + v, z + w, t + dt) - I(x, y, z, t) = 0, \tag{3.4}$$

where $I(x, y, z, t)$ is the image intensity (here, BOLD percent signal change (a.u.)) at location (x, y, z) and time t, and $I(x + u, y + v, z + w, t + dt)$ is the image intensity after spatial displacements u, v and w in the x, y and z directions, respectively, following time step dt (here, $2\pi/40$). Thus, error in brightness constancy, ε_b, can be expressed as

$$\varepsilon_b = I_x u + I_y v + I_z w + I_t \,, \tag{3.5}$$

where I_x, I_y, and I_z are the spatial derivatives, and I_t the temporal derivative, of $I(x, y, z, t)$. A second constraint is placed on spatial smoothness, such that the velocity vectors specify smooth and continuous motion where possible. Thus, smoothness error, ε_s, can be expressed as the sum of the squared gradient magnitudes of the velocity components:

$$\varepsilon_s = |\nabla u|^2 + |\nabla v|^2 + |\nabla w|^2, \tag{3.6}$$

where ∇ denotes gradient operation (i.e., $\nabla f = \frac{\partial f}{\partial x} + \frac{\partial f}{\partial y} + \frac{\partial f}{\partial z}$). Thus, solving for u, v, w amounts to numerically solving the following minimization problem:

$$\min_{u,v,w} \left\{ \iiint ({\varepsilon_b}^2 + \alpha {\varepsilon_s}^2)\, dxdydz \right\} \tag{3.7}$$

where α determines the relative weighting of the two constraints.

For the present application, optical flow must be constrained to the two-dimensional cortical sheet. Thus, spatial derivatives I_x, I_y, and I_z were computed by first "unfolding" the cortical sheet at each vertex such that, in practice, gradients were computed in two spatial directions (orthogonal to the surface normals) and backprojected to anatomical x, y, z coordinates. This strategy was implemented in tandem with geodesic smoothing along the cortical sheet (Glasser et al., 2013) using the built-in "cifti-gradient" functionality in Connectome Workbench, described in detail previously (Glasser et al., 2016). Subsequent analyses were based on a publicly available implementation of the Horn-Schunck algorithm (https://www.mathworks.com/matlabcentral/fileexchange/22756-horn-schunck-optical-flow-method), as described previously (Afrashteh et al., 2017) (present results obtained with $\alpha = 2$). Finally, u, v and w were averaged across all movie frames to obtain a mean vector field $\mathrm{V}(x, y, z) = \big(u(x, y, z), v(x, y, z), w(x, y, z)\big)$. Thus, V, shown in Fig. 5A, displays the mean flow field averaged across all 40 phase bins within the RV cycle.

Divergence of V was computed from spatial derivatives obtained again via the cifti-gradient functionality. Thus,

$$\mathrm{div}\ \mathrm{V} = \frac{\partial \mathrm{V}_x}{\partial x} + \frac{\partial \mathrm{V}_y}{\partial y} + \frac{\partial \mathrm{V}_z}{\partial z}\ , \tag{3.8}$$

where V is first normalized by vector magnitude (suppressing high values at anatomical boundaries). The divergence map is shown in Fig. S6.

The rotational component of propagation was obtained by defining a new phase function $\psi(r,t)$ via Hilbert transform of the RV cycle shown in Fig. 4B (Movie S1-S2), where r indexes cortical vertex and t indexes "movie" frame. (Note that this procedure does not make use of the flow field computed above.) To summarize as a single map, the phase topography at each time point of ψ was referenced to a common region (the visual network) and subsequently averaged across the 40 frames. This procedure is similar to that illustrated in Fig. 3A (Eq. 3.3), except that BOLD phase shifts were subtracted from the phase of the visual network, rather than phase of the RV time series. The resulting map, ψ_{avg}, is shown in Fig. 5B.

The extent of local phase variability (Fig. 5C) was quantified by computing the circular standard deviation of ψ_{avg} within a 10mm radius centered on each vertex. Thus,

$$\mathrm{std}_{\mathrm{circ}} = \sqrt{-2\ln \bar{R}}\,, \tag{3.9}$$

where $\bar{R}$ is the resultant mean vector length (Mardia & Jupp, 2000) (analogous to the magnitude of the PLV in Eq. 3). Note that this measure is not intended to isolate phase singularities per se (i.e., the precise point of convergence of a full 2π cycle), which is of secondary importance in the present context. Rather, more generally, this measure identifies regions where phase is highly variable within a small region of the cortex.

Finally, spatial gradients in Fig. 5D were computed using the cifti-gradient procedure described above. This procedure was applied to 1) a FC "similarity matrix", as previously (Glasser et al., 2016), where the similarity matrix was computed from the publicly available HCP S1200 subject

release group average FC matrix (available from https://db.humanconnectome.org); and 2) to the principal FC coordinate defined in (Margulies et al., 2016).

Head motion analyses

Framewise displacement (FD) is an instantaneous measure of head motion, defined as the L1 norm of the temporal derivatives of realignment estimates (Power et al., 2012). The phase distribution in Fig. S5A is the histogram of instantaneous RV phase values corresponding to time points at which FD exceeded each HCP subject's 99th percentile FD value (thus, each subject contributed roughly the same number of values). Statistical significance of this phase distribution was assessed by computing modulation index as described by Tort et al. (Tort et al., 2010), which measures KL-divergence from a uniform phase distribution, and comparing it to a null distribution of modulation index values obtained by shuffling FD time series across subjects and recomputing the RV phase distribution.

For the BOLD:FD analysis shown in Fig. S5B, cross-correlation was computed between FD time series and mean cortical network signals, both low-pass filtered at 0.1 Hz, and the resulting cross-correlation functions were averaged across HCP runs and subjects. The same procedure was used to compute group-averaged BOLD:RV cross-correlation functions also shown in Fig. S5B.

A threshold of FD = 0.2 mm is often used to flag high-motion frames for exclusion from FC analysis (Power, Mitra, et al., 2014). Accordingly, we used frames in which FD exceeds 0.2 mm as events of interest in order to study arousal dynamics in an independent dataset (GSP). For this

analysis, following preprocessing, GSP BOLD time series were low-pass filtered at 0.1 Hz. Then, 40-second windows centered on high-motion frames (unfiltered FD > 0.2 mm) were averaged within and across runs to yield a group-level head motion-triggered average. For overlapping windows, only the highest motion frame was used to define the 40-second period. The global mean time course was subtracted from the final, group-level result shown in Fig. S5C to visualize spatial specificity.

ECoG processing and analysis

Two channels from Monkey 2 ("George") were excluded (as previously (Liu, Yanagawa, Leopold, Chang, et al., 2015)) based on anomalous spectral content. Notch filtering at 50 Hz and harmonics was used to remove line noise. Sequential spectral transition (SST) events were identified on the basis of a low-frequency synchronization index following an identical procedure as in (Liu, Yanagawa, Leopold, Chang, et al., 2015). Thus, spectrograms were generated for each channel via a multitaper time-frequency transformation (Bokil et al., 2010) (1 second window, 0.2 second step size, 5 tapers), yielding time series of 1-100 Hz power in 1 Hz frequency bins. Power was converted to decibels (dB) following a logarithmic transformation, and the temporal mean of power was subtracted from each frequency bin. Band-limited power (BLP) was computed for each channel by averaging the mean-subtracted spectrograms across frequencies within a given frequency band. A low-frequency spatial synchronization index was defined as the fraction of channels at each time point (every 0.2 s) whose delta (1-4 Hz) BLP exceeded +1 standard deviation. SSTs were defined as the 40-second period surrounding time points at which the low-frequency synchronization index surpassed a threshold of 0.4 (i.e., 40% of channels showing increased delta power). Threshold crossings occurring within three seconds of a preceding crossing were excluded. In total, 1,145 SST events were identified across sessions

(Monkey 1, N = 656; Monkey 2, N = 489). SSTs were averaged within and across sessions to yield an average SST spectrogram for each channel in each monkey.

Broadband gamma (40-100 Hz) BLP was similarly averaged across all SST instances to yield dynamics shown in Fig. 6D. Gamma BLP waveforms at each channel were cross-correlated with the mean waveform averaged across channels (analogous to “global signal”; Fig. S1) to yield a time delay for each channel (Fig. 6C). A global mean SST spectrogram (Fig. 6A) was obtained by averaging SST spectrograms across channels and monkeys.

Diffusion maps

We obtained principal FC coordinates via diffusion map embedding (Coifman & Lafon, 2006), as in (Margulies et al., 2016). Diffusion maps provide a framework for nonlinear feature extraction and dimensionality reduction. A global, low-dimensional embedding of the original data points (here the FC "seed map" of each voxel/electrode) is obtained by constructing a random walk on the graph representation of the data, in which edges are given by some a priori definition of pairwise similarity. The eigenvectors of a transition probability matrix based on this graph can be understood as coordinates of the data (diffusion coordinates). Thus, the (topological) distance between data points is defined as the Euclidean distance between these data points within a low-dimensional manifold whose coordinates are defined by the principal eigenvectors of the transition matrix (i.e., "diffusion distance") (Coifman & Lafon, 2006; Coifman et al., 2005).

The principal FC diffusion coordinate for neocortex, previously derived by diffusion map embedding of fMRI FC, was obtained from publicly available results from Margulies et al. (Margulies et al., 2016). Similarly, we used diffusion maps to obtain a principal coordinate for

cortico-striatal, cortico-thalamic, cortico-cerebellar FC, using the publicly available HCP S1200 subject release group average FC matrix (available from https://db.humanconnectome.org). Further, a principal FC coordinate was defined for each macaque monkey using FC matrices constructed from broadband gamma power. Gamma FC matrices were constructed by filtering the full-run time series into the broadband gamma range (40-100 Hz), extracting the Hilbert amplitude envelope, and subsequently filtering into the infra-slow frequency range (0.01 to 0.1 Hz). Zero-lag pairwise correlations were computed for each session, Fisher-z transformed, and averaged across sessions.

Human fMRI and macaque ECoG FC matrices were used to construct a symmetric affinity matrix L, measuring angular similarity (cosine similarity scaled to [0,1] (Vos de Wael et al., 2018)) between each pair of FC "seed maps" **x** and **y**:

$$\text{similarity}(\mathbf{x},\mathbf{y}) = \cos\theta = \frac{\mathbf{x}\mathbf{y}^{\boldsymbol{T}}}{\|\mathbf{x}\|\|\mathbf{y}\|} \tag{3.10}$$

$$L = 1 - \frac{\cos^{-1}\big(\text{similarity}(\mathbf{x},\mathbf{y})\big)}{\pi}, \tag{3.11}$$

where $\|\cdot\|$ denotes Euclidean norm. L was subsequently subjected to the diffusion map algorithm to obtain a new asymmetric kernel, $L^{(\alpha)}$, and its normalized graph Laplacian, P. Thus,

$$L^{(\alpha)} = D^{-\alpha} L D^{-\alpha} \tag{3.12}$$

$$P = \left(D^{(\alpha)}\right)^{-1} L^{(\alpha)}, \tag{3.13}$$

where D is a diagonal matrix containing the sum along each row in L (i.e., $D_{i,i} = \sum_j L_{i,j}$; $D^{(\alpha)}{}_{i,i} = \sum_j L^{(\alpha)}{}_{i,j}$), P functions as the transition matrix of a Markov chain determined by L, and the diffusion parameter α is set to 0.5 such that the density of the data points on the

underlying manifold is factored into the random walk (approximating the long-term behavior of a stochastic process (Nadler et al., 2006)) (Coifman & Lafon, 2006). The eigenvectors of *P* are the diffusion map coordinates (whose weights can be scaled by a diffusion time parameter (Coifman & Lafon, 2006)), and the topography of the principal FC coordinate is given by the first non-constant eigenvector. Our principal coordinate for cortico-cerebellar FC (Fig. 3C) showed good correspondence with prior results using this algorithm (Guell et al., 2018). In addition, our principal FC coordinate derived from macaque ECoG (Fig. 6C) showed good correspondence with previously published FC results from these monkeys (Liu, Yanagawa, Leopold, Fujii, et al., 2015), and with previously described structural and functional connectivity gradients across macaque neocortex (Margulies et al., 2016; Oligschläger et al., 2019).

Statistical analyses

All spatial correlations were computed as Spearman's rho values. Statistical significance of spatial correlation values was evaluated in all cases by comparison against a null distribution obtained from maps with similar spatial autocorrelation. We assessed spatial correspondence by comparison with a null distribution (500 random shuffles) obtained via Moran spectral randomization (Vos de Wael et al., 2020; Wagner & Dray, 2015). This algorithm generates randomizations of the feature vector that preserve the original spatial autocorrelation. The algorithm requires a weight matrix that captures the spatial relationships between all region pairs. We used (inverse) geodesic distance for human cortex, and (inverse) Euclidean distance for human volumetric structures as well as macaque electrodes. Statistics were computed on a single (left) hemisphere to avoid distance computations across hemispheres.

Data visualization

Cortical surface displays were rendered using Connectome Workbench software (Marcus et al., 2011) and are shown on the "very inflated" Conte-69 atlas surface (Van Essen, Glasser, et al., 2012). Three-dimensional maps of subcortical structures were generated from MNI152 voxel coordinates. Cerebellar flatmap representations were generated using the SUIT toolbox (Diedrichsen & Zotow, 2015) and used for display purposes only. Spatial maps of macaque ECoG arrays were downloaded from neurotycho.org (Nagasaka et al., 2011). Flow field computation is described under the heading "*Optical flow estimation and wave decomposition"*.

3.8 Supplementary Appendix

Supplementary Notes

Supplementary Note 1

A fixed time delay between signals yields a phase spectrum with constant slope, i.e., $-d\phi/d\omega = \text{constant} = \tau$, where ϕ, ω, τ are phase, angular frequency ($2\pi f$), and time delay (in physics terminology, phase delay = group delay = constant). In other words, if a disturbance propagates with no change in waveform, then the phase shift measured at each frequency must decrease linearly with decreasing frequency (increasing period). In contrast, the results shown in Fig. 2 indicate dispersive propagation (i.e., gradual spreading with attenuation (see (Nunez & Srinivasan, 2006)). The near frequency-independence of infra-slow phase shifts has been previously observed across multiple recording techniques (Mitra et al., 2018; Okun et al., 2019). The physiology underlying this phenomenon requires further investigation.

Supplementary Note 2

Notably, propagation within the visual system departs from propagation across systems in that activity propagates from classically higher-order visual areas to V1, in parallel with unimodal → transmodal propagation across systems (Fig. 3B) (Hindriks et al., 2019). The functional significance of this observation is not clear at present. However, sharp boundaries between primary and higher-order visual cortex (Fig. 3B), as well as slow, peripheral → foveal propagation within visual cortex (Fig. 4B) are both consistent with the known features of intra- and inter-network visual cortex FC (Buckner & Yeo, 2014; Griffis et al., 2017) (see also (Arcaro & Kastner, 2015)).

Supplementary Text

Systematic head motion signal changes recapitulate global brain state dynamics

Spontaneous in-scanner "micro" head movements (as small as a tenth of a millimeter) are associated with systematic BOLD signal changes (Power, Mitra, et al., 2014) and are widely regarded as a major obstacle to FC-based functional mapping (Ciric et al., 2017). However, head movements often coincide with physiological events (e.g., deep breaths) and global BOLD signal fluctuations (Power et al., 2017). More generally, recent studies in behaving rodents reveal intimate associations between locomotion (including head micro-movements (Musall et al., 2019; Salkoff et al., 2020; Stringer et al., 2019)), arousal, and brain state (Drew et al., 2019; Liu et al., 2020; Nelson & Mooney, 2016; Reimer et al., 2016) (see also (Ramot et al., 2011)). These relationships suggest that the systematic BOLD signal correlates of head movements may not reflect motion artifact per se, but rather, global arousal dynamics that co-occur with head movements.

Fig. S5 confirms that spontaneous head movements during the resting-state are tightly linked to instantaneous RV phase. Moreover, cross-correlation of BOLD signals in relation to either RV or instantaneous head motion yields similar, topographically organized temporal structure (Fig. 5B), suggesting that head movements coincide with brain state fluctuations (Gu et al., 2020). This tendency for head movements to co-occur with global arousal waves, which recapitulate large-scale FC structure, has clear practical implications for the interpretation of head motion "artifacts" in fMRI. However, the arousal dependence of head movements carries an intriguing corollary: that spontaneous head movements may themselves be used as an index of arousal, enabling examination of global arousal waves even in resting-state fMRI data that was not collected with simultaneous physiology measurements (i.e., vast majority of datasets).

To test this hypothesis, we examined an independent, widely used dataset (Genomics Superstruct Project (Yeo et al., 2011)), in which we treated spontaneous head movements as events of interest. Event-triggered averaging of BOLD signals surrounding spontaneous head movements revealed topographic spatiotemporal structure persisting over more than 20 seconds (Fig. S5). These spatiotemporal dynamics closely recapitulated those of arousal waves described in relation to RV (Fig. S5D-E). Thus, systematic signal changes that accompany head movements – which have been presumed to reflect artifact (or evoked responses of non-interest) – are dominated by patterned arousal waves.

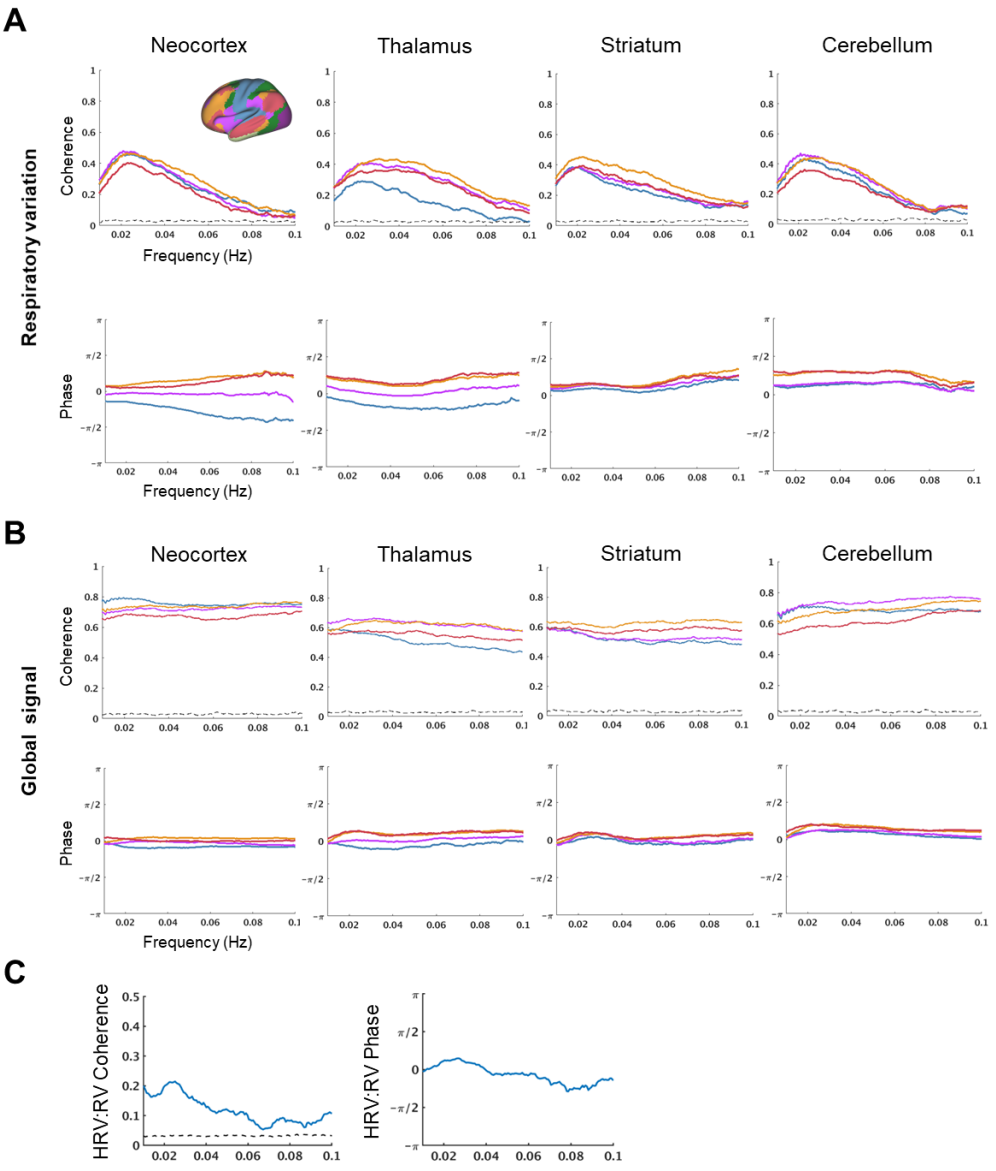

Figure S1. BOLD coherence with respect to global signal. Group-average magnitude (upper plots) and phase (lower plots) of coherence for network-averaged signals in relation to **(A)** respiratory variation (same as in Fig. 2B) and to **(B)** the global signal, computed in the same dataset (HCP; N = 190 subjects). Global signal phase shifts are generally smaller than RV phase shifts, and global signal coherence lacks frequency-specificity. **(C)** Group-average magnitude (left) and phase (right) of coherence between HRV and RV**.**

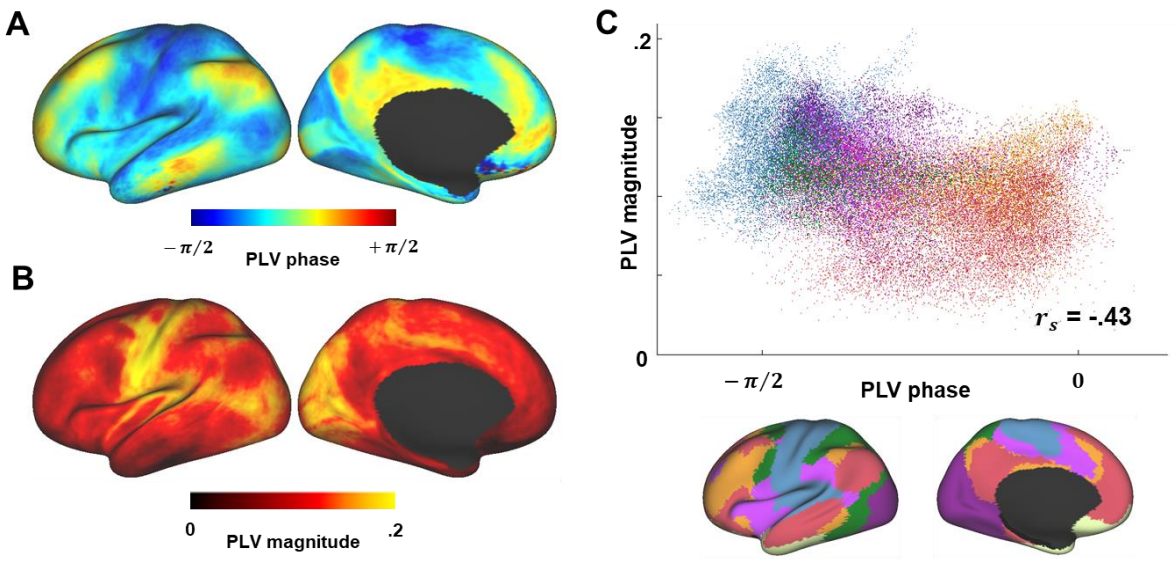

Figure S2. Close relationship between magnitude and phase of RV coherence. (A) Time- (and subject-) averaged maps of instantaneous phase shifts relative to RV (same as Fig. 3B). Phase is reported as the angle of the circular mean of phase shifts, i.e. angle of the complex phase-locking value (PLV) (Lachaux et al., 1999). **(B)** PLV magnitude (strength of coherence). **(C)** Decreasing coherence with increasing phase shift, suggesting dispersive propagation (see also cortical topographies shown in (Liu et al., 2018; Power et al., 2017)). Data points are cortical vertices color-coded by network identities below. r_s denotes Spearman's rank correlation coefficient. Limbic network (white) is excluded due to low SNR (Yeo et al., 2011) (for this analysis only).

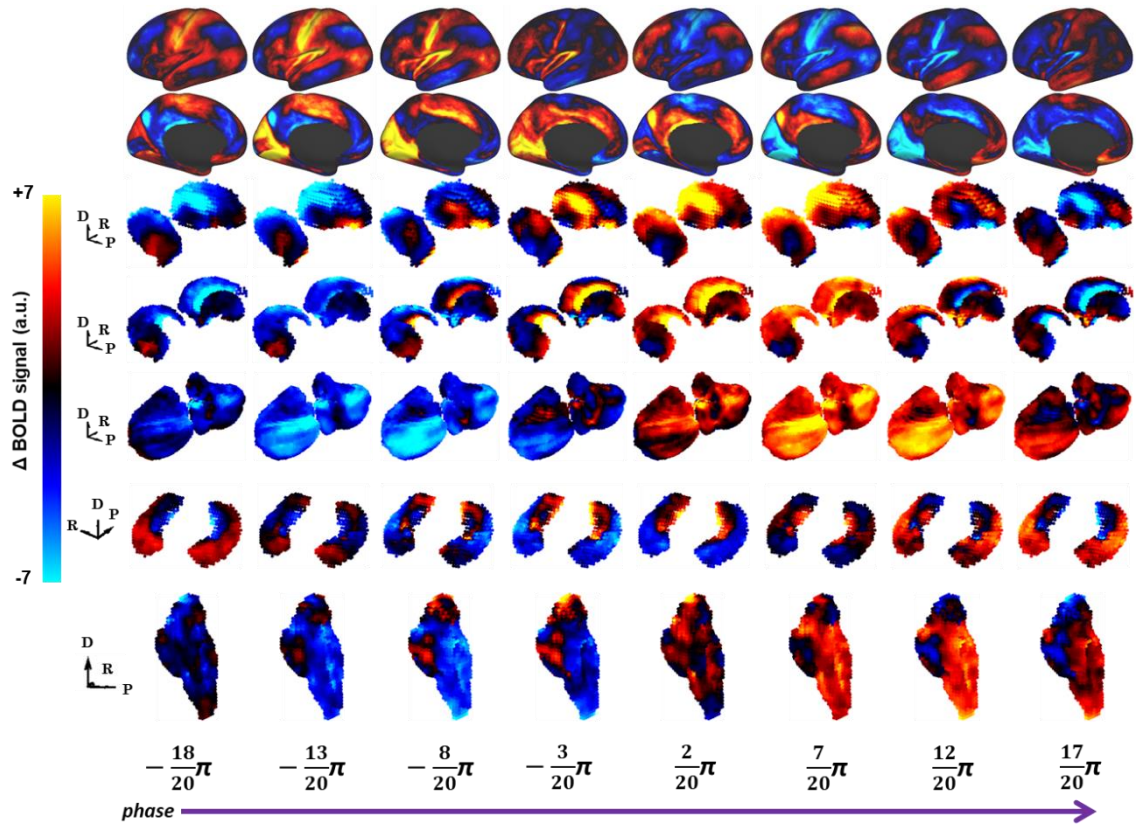

Figure S3. Visualizing propagation dynamics. Group-averaged BOLD signal maps shown for 8 (of 40) evenly-spaced phase bins across the canonical RV cycle. Same as in Fig. 4B but including hippocampus and brainstem (second-to-last and last row, respectively). D, P, R, denote dorsal, posterior, and anatomical rightward directions. See also Movie S2.

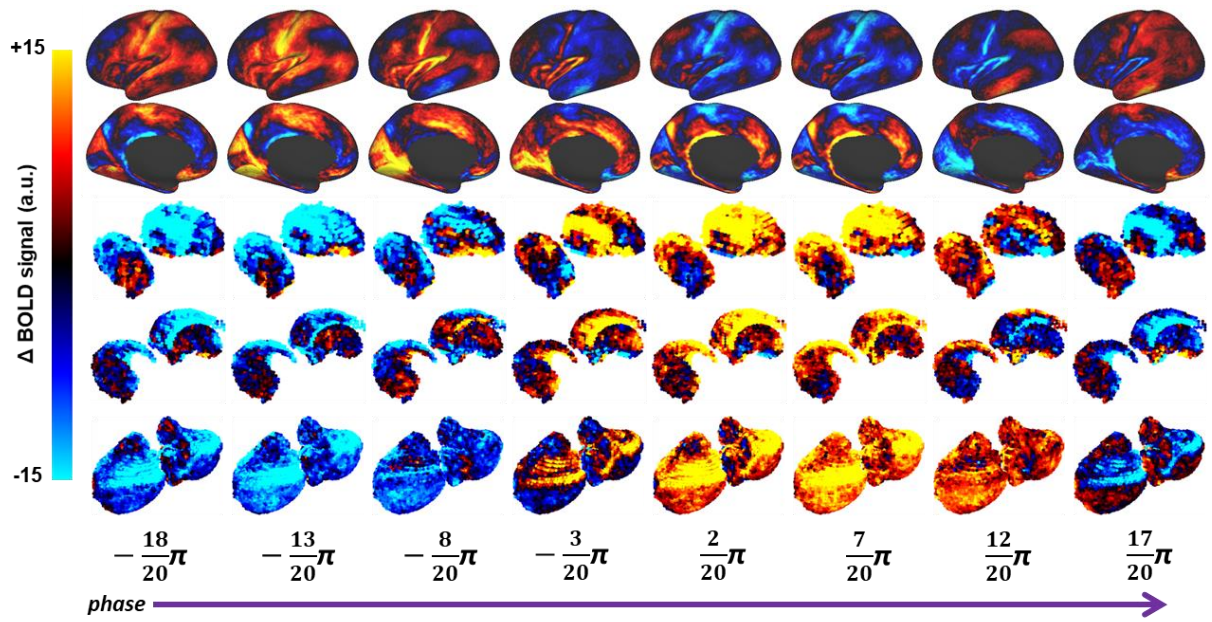

Figure S4. Propagation dynamics with minimal preprocessing. Group-averaged BOLD signal maps shown for 8 (of 40) evenly-spaced phase bins across the canonical RV cycle. Same as in Fig. 4B but without ICA-FIX denoising, spatial smoothing, temporal filtering, or smoothing across phase bins.

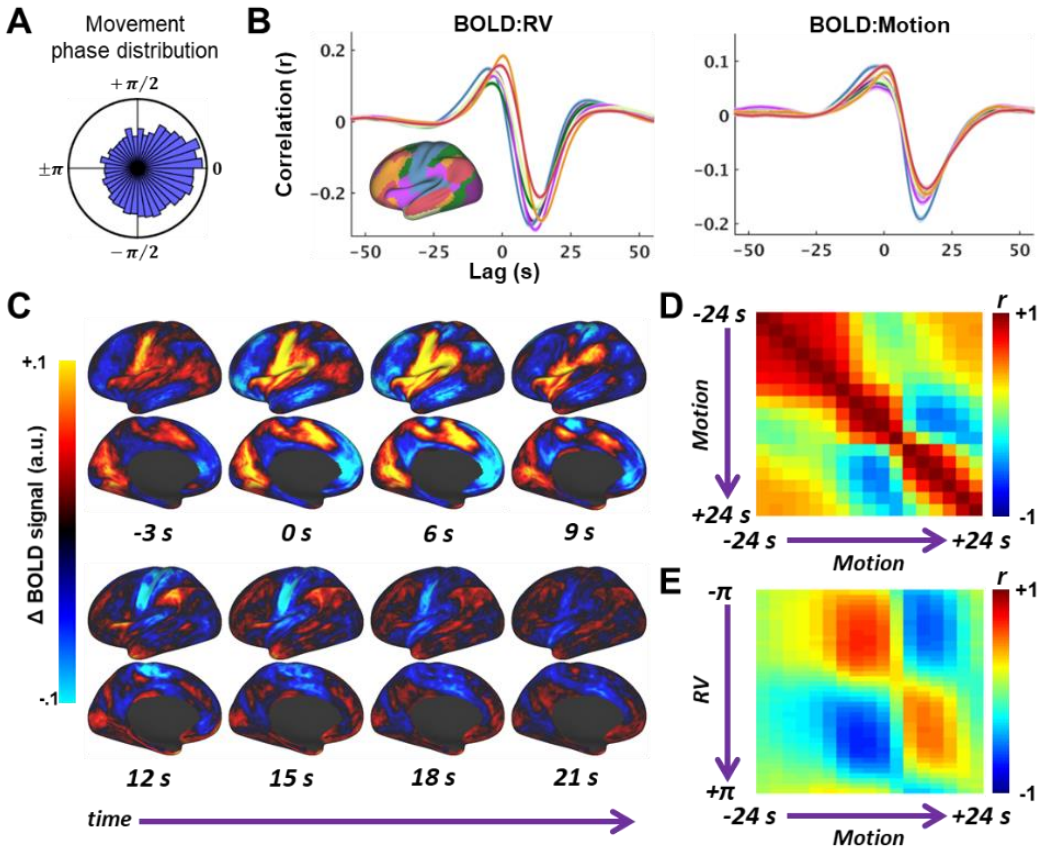

Figure S5. Systematic head motion-associated BOLD signal changes reflect brain state dynamics. (A) Distribution of RV phases, summed over all subjects (N = 190), corresponding to head movements (framewise displacement values (Power, Mitra, et al., 2014)) exceeding each subject's 99th percentile value. Phase dependence significantly deviated from a null distribution obtained by shuffling motion time series across subjects ($p < .001$; Methods). **(B)** Cross-correlation of BOLD cortical network signals with respect to RV (left) or head motion (framewise displacement) time series. Negative lags indicate BOLD leading. A similar biphasic pattern, led by the motor network, is evident in both plots. **(C)** Head movement triggered-average in an independent dataset (GSP dataset; N = 1139 subjects). Head movements were defined according to framewise displacement values exceeding 0.2 mm, a threshold widely used to flag high-motion frames for removal (Power, Schlaggar, et al., 2014). Global mean time course has been subtracted from the movie for visualization only (as in Fig. 4B). **(D)** Frame-by-frame spatial correlation matrix (as in Fig. 4C) of head movement-triggered average. Positive correlation in upper-right/lower-left corners indicates intrinsic periodicity (data were not high-pass filtered). **(E)** Frame-by-frame spatial correlation matrix between RV cycle and head movement-triggered average. Each element represents the spatial correlation of the group-averaged BOLD signal map at a given RV phase bin and motion-triggered average time point. A similar transition between anti-correlated topographies is observed for both arousal and motion-triggered dynamics.

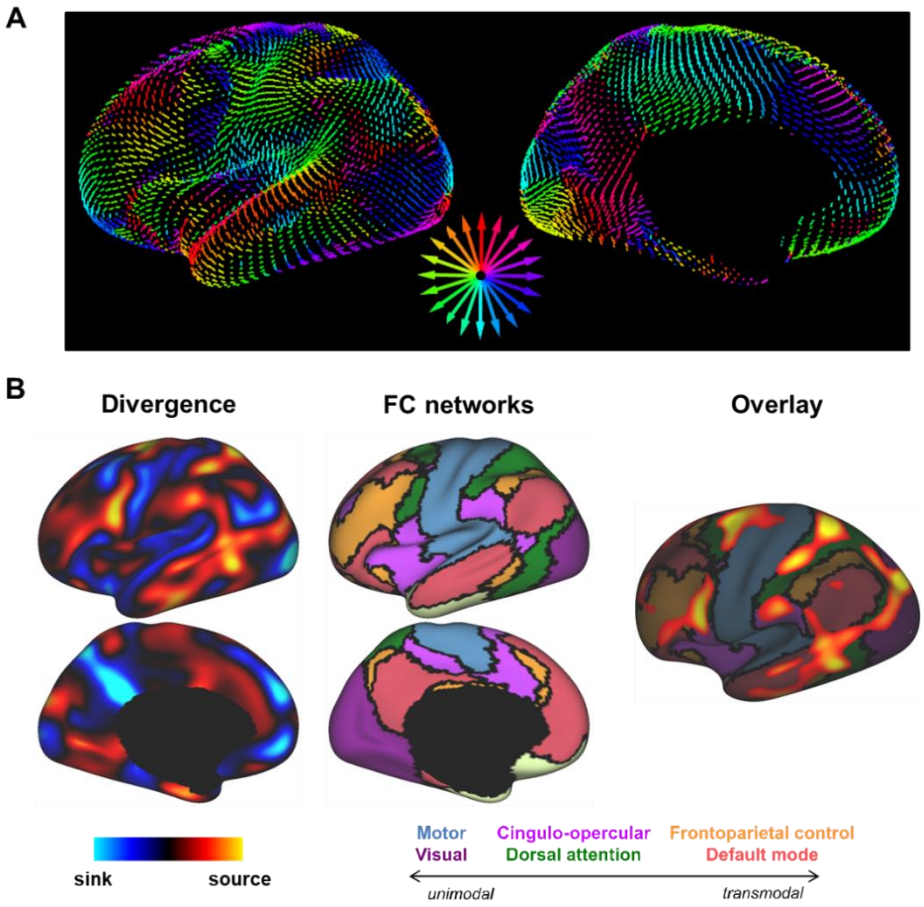

Figure S6. Wave decomposition. (A) Flow fields computed from (Fig. 4B), using optical flow methodology (Horn & Schunck, 1981) (same as Fig. 5A). Arrow magnitude and orientation indicate the local velocity and direction of propagation within three-dimensional Euclidean space. To facilitate visualization, arrows are color-coded according to direction within the 2-D plane of the page based on color wheel at center. See also Movies S1-S2. **(B)** Flow field divergence. This map captures the local source- and sink-like behavior of the vector field. Sources appear to overlap regions of the dorsal attention network (right). Sinks are most conspicuous in the default mode network, consistent with many prior works (e.g., (Liao et al., 2010; Yan & He, 2011)).

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Chapter 4

A spatiotemporal cycle for brain state dynamics

4.1 Abstract

The organizing principles, physiology and function of intrinsic brain activity have received significant attention across multiple neuroscience research communities employing diverse measurements and model organisms. Here, we propose a latent physiological process bridging several existing accounts of intrinsic activity. Across three species (mice, monkeys, and humans), four brain recording methodologies (widefield calcium imaging, electrocorticography, magnetoencephalography, and functional MRI), and multiple behavioral and physiological indices of arousal, we provide converging evidence for the continuous evolution of global brain state along a latent arousal cycle. Cyclic movement along this intrinsic attractor is associated with propagation of large-scale, topographically structured rotating waves. We suggest that much of the apparent spatial and temporal variability of intrinsic brain activity may emerge from this simple spatiotemporal process.

4.2 Main Text

Intrinsic brain activity has been studied using a plethora of experimental techniques and physiological measurements. In recent years, many such studies – particularly in awake behaving mice – have reported a wide range of physiological changes occurring throughout the brain in association with ongoing arousal fluctuations and locomotion (e.g., (McGinley et al., 2015; Rasmussen et al., 2019; Zuend et al., 2020)). The spatiotemporal dynamics of these state fluctuations have defied simple organizational principles (Shimaoka et al., 2018; Stringer et al.,

2019). On the other hand, a separate literature has described spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal whose correlation structure closely recapitulates the large-scale functional organization of the brain (Power et al., 2014). Thus, there remains considerable debate and lack of clarity surrounding the sources and properties of intrinsic brain activity, the principles governing its spatiotemporal evolution, and the relationship between neural, physiological, and behavioral measures collected across modalities and species (Drew et al., 2019; McCormick et al., 2020; Shimaoka et al., 2018; Stringer et al., 2019; Winder et al., 2017).

To address these issues, we propose a latent physiological process that parsimoniously links the above accounts of intrinsic activity. Specifically, we propose that the internal state of the brain continuously evolves along a latent arousal cycle (Fig. 1A). We hypothesize that the broad range of neural, physiological, and behavioral measures associated with arousal evolve in time according to this latent dynamical process. Moreover, recently, a traveling wave process giving rise to large-scale correlation structure was shown to couple to ongoing arousal fluctuations (Raut et al., 2021); here, we predict that this phenomenon is similarly a continuous, ongoing process governed by the same, latent arousal cycle. Together, this account motivates an understanding of the interrelationships of brain-wide spatiotemporal dynamics, body, and behavior by virtue of their coupling to the same governing dynamics (cf. (Chiel & Beer, 1997; Rulkov et al., 1995; Sugihara et al., 2012)).

To test this account, we require a method allowing us to index instantaneous phase along a (hypothetical) arousal cycle. Subsequently, we may assess the consistency of phase relations among various indices of arousal over time. Importantly, in contrast to standard measures of temporal dependence (e.g., correlation and coherence), which may be inflated by large-amplitude

events occurring simultaneously across time series, the proposed procedure enables assessment of the extent of continuous phase synchrony among variables (Lachaux et al., 1999) along state space trajectories (Pikovsky et al., 1997; Rulkov et al., 1995).

To visualize latent trajectories of arousal indices, we pursued a data-driven approach to reconstruct the state space of arousal dynamics based upon time-delayed snapshots of univariate time series (Packard, 1980; Takens, 1981). Thus, we began by projecting mouse pupil size (Reimer et al., 2016) to a three-dimensional state space spanned by its principal time-delay coordinates (Methods) (Broomhead & King, 1986; Brunton et al., 2017). To index progression along the hypothesized canonical arousal cycle, we assigned to each time point a "latent phase" based upon recurrence times in this state space (e.g., (Pikovsky et al., 1997)) (Fig. 1C). We applied this procedure to pupil size measurements concatenated across seven mice. This procedure revealed, qualitatively, continuous orbits of varying size through the state space, permitted a continuous index of arousal phase (Fig. 1D).

We next sought to assess the extent to which this data-driven approach yields similar state trajectories across two additional measures coupled to arousal: whisker motion (Stringer et al., 2019) and the mean signal obtained from widefield imaging of neuronal calcium activity (Wang et al., under review) (Methods). Fig. 1E-F illustrates the resulting attractors, color-coded according to latent phase obtained from pupil size in Fig. 1B. Thus, similar color gradients across trajectories provide a qualitative picture of the synchronized motions of these three indices of arousal state along a latent arousal cycle.

To quantitatively assess this synchronization, we computed the phase locking value (Lachaux et al., 1999; Tass et al., 1998) (PLV, ranging from 0, completely incoherent, to 1, perfectly

coherent) among latent phase estimates obtained along the data-reconstructed attractors of these measures. We found that the three measures evolve with considerable phase synchrony (pupil-whisker PLV = .59, pupil-brain PLV = .44, whisker-brain PLV = .47; all $p > .001$ following comparison with phase randomized null distributions). These results establish phase synchronization among brain, body, and behavioral states according to a latent arousal cycle.

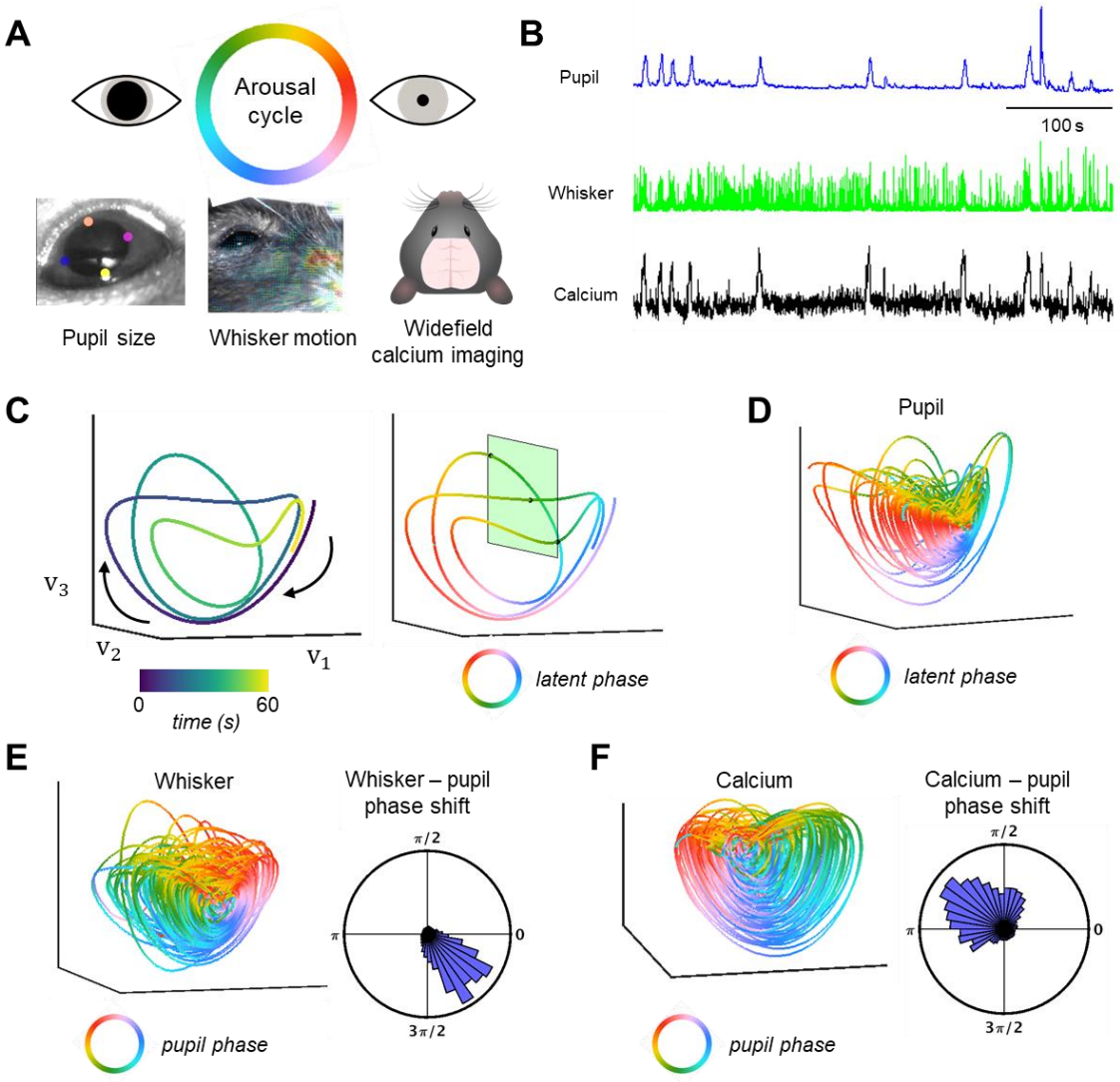

Figure 1. Phase synchronization of brain, body, and behavior. (A) (upper) Proposed model of brain state dynamics. We hypothesize that intrinsic brain activity evolves spatiotemporally according to a latent arousal cycle (Raut et al., 2021). (lower) Arousal indices included pupil size

(estimated via DeepLabCut (Mathis et al., 2018)), whisker motion estimated via optical flow analysis, and widefield calcium imaging of the dorsal neocortex; see Methods. **(B)** Example time series for the three indices of arousal (arbitrary units). Note presence of large transients in addition to small fluctuations, e.g., in the pupil size time series. **(C)** Illustration of delay embedding and latent phase assignment. Univariate time were embedded via lagged copies to obtain principal component delay coordinates (Broomhead & King, 1986; Brunton et al., 2017). Latent phase was assigned to each point of the state space trajectories extraction by interpolating between intersections with a two-dimensional plane define transverse to the flow (i.e., the Poincaré recurrence times). **(D)** Attractor for pupil size following time series concatenation across 7 animals (10 mins per mouse). Latent phase assigned as in (C). **(E)** Attractors for whisker motion (left) and calcium imaging (right). Attractors are colored according to instantaneous pupil phase; coherent coloring facilitates visualization of phase-locked trajectories. Histograms summarize distribution of instantaneous phase differences between pupil and whisker motion (left) or calcium imaging (right) across the seven mice (pupil:whisker PLV = .59; pupil:brain PLV = .44).

Next, we sought to examine the spatiotemporal correlates of this process. At present, brain state dynamics are understood to be highly spatiotemporally heterogenous and dependent upon the duration of spontaneous behavioral episodes (e.g., locomotion) (Shimaoka et al., 2018). In theory, this structure may be accounted for by a quasiperiodic traveling wave process previously observed with human fMRI (Raut et al., 2021). Here, we propose, as a general principle, a similar phase locking of brain-wide physiology to a latent arousal cycle.

To test this possibility, we examined large-scale spatiotemporal dynamics linked to a latent arousal cycle across several modalities and species. We applied the same procedure in Fig. 1 to the mean brain signal obtained from widefield calcium imaging in mice, electrocorticography in macaque monkeys, and magnetoencephalography and functional MRI in humans (for fMRI, this procedure was applied to respiratory variation time series, as – likely due to limited SNR – the same approach applied to mean fMRI time series failed to produce the attractor structure).

By averaging brain dynamics according to latent arousal phase (Reimer et al., 2016), we observed spatiotemporal dynamics that were highly coherent across a canonical arousal cycle

(Fig. 2). Spatiotemporal dynamics appeared closely homologous across the three species. A common observation across all measurements was alternation between two main states. In humans and non-human primates, this observation corresponds to the distinction between the "task-positive" and "task-negative" (or default mode (Buckner & DiNicola, 2019; Raichle, 2015)) systems. A similar two-state separation has been observed repeatedly in the widefield imaging literature (e.g., (Barson et al., 2020)); recovering the same intrinsic process across methods and species permits contextualization of this observation. Taken together, these results provide converging evidence for an intrinsic arousal cycle as a parsimonious descriptor of brain state and brain-wide spatiotemporal dynamics.

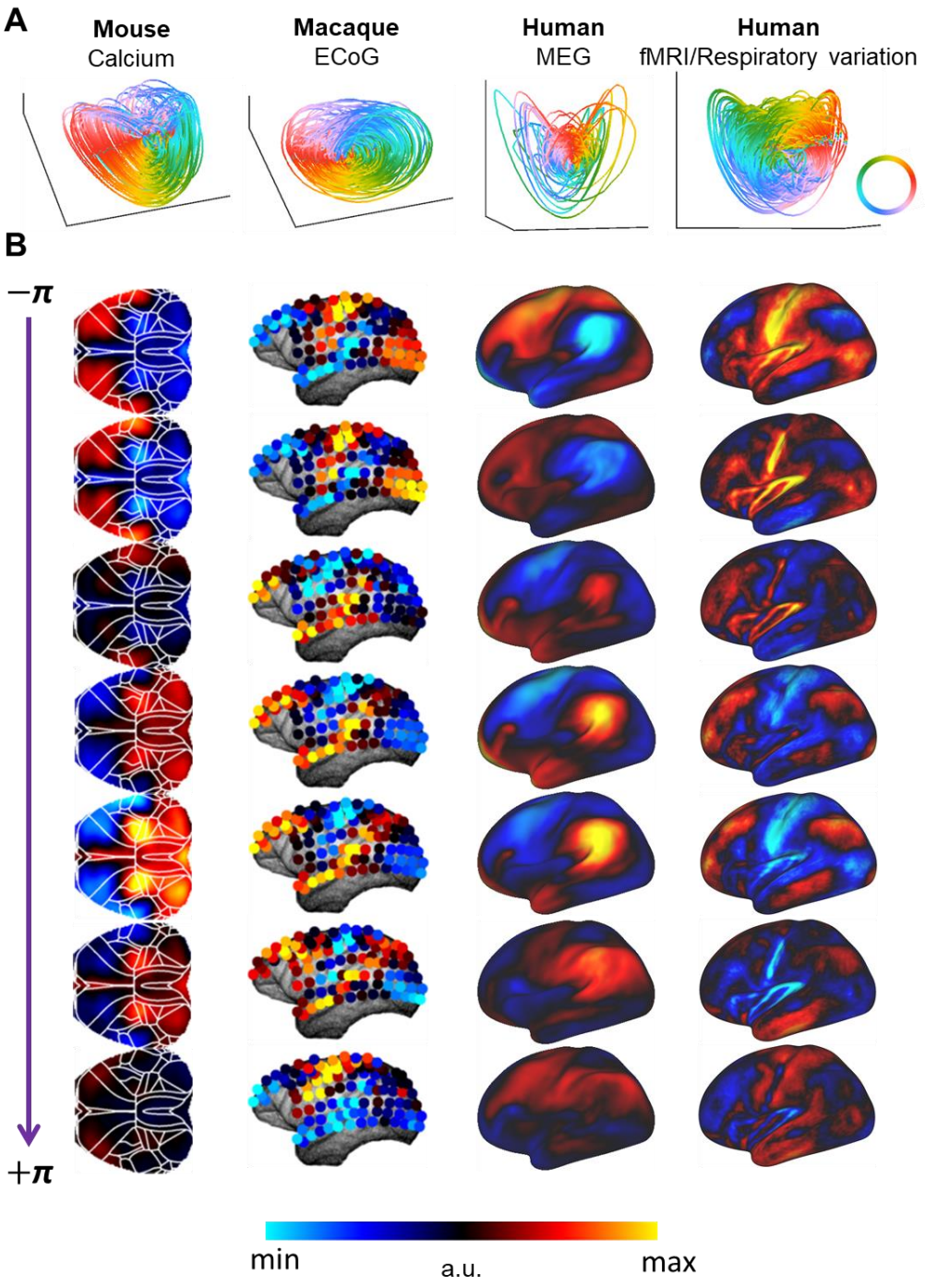

Figure 2. Phase synchronization of brain state dynamics and wave propagation. (A) Delay-embedded attractors obtained for mouse calcium imaging (mean brain time series), macaque ECoG (mean gamma BLP time series), and human MEG (mean gamma BLP time series). Respiratory variation (RV) was used as an arousal index for human fMRI (Raut et al., 2021), as data-driven attractor reconstruction from the global signal failed to yield the attractor structure.

(B) Canonical arousal cycle across brain recording techniques noted in (A). Note that phase offsets across modalities/species are arbitrary; activity sequences were temporally aligned based on visual appearance.

4.3 Methods

Datasets and preprocessing

Dataset 1: Mouse widefield calcium imaging

Mouse model

All procedures described below were approved by the Washington University Animal Studies Committee in compliance with the American Association for Accreditation of Laboratory Animal Care guidelines. Mice were raised in standard cages in a double-barrier mouse facility with a 12 h–12 h light/dark cycle and ad libitum access to food and water. Experiments used n=10 12-week old mice hemizygous for Thy1-jRGECO1a (JAX 030525).

Prior to imaging, a cranial window was secured to the intact skull of each mouse with dental cement (Metabond) under 2% isoflurane anesthesia following scalp retraction according to our previously published protocols (Rosenthal et al., 2020). Data were acquired in 10-minute epochs while the mice were awake. Mice were secured in a black felt hammock with head-fixation, as previously described (Rosenthal et al., 2020).

Widefield imaging was conducted on dual fluorophore optical imaging system; details of this system have been describe in detail elsewhere (Wang et al., under review).

Image processing

Images were spatially normalized, downsampled (to a resolution of 128x128), co-registered, and affine transformed to the Paxinos atlas, as described previously (White et al., 2011). Slow trends in light level (e.g., due to fluctuations in LED illumination) were temporally detrended using a 5^{th} order polynomial fit. The images were spatially smoothed with a Gaussian filter (5x5 pixel kernel with a standard deviation of 1.3 pixels). Changes in 530nm, and 625nm reflectance were interpreted using the modified Beer-Lambert law to calculate changes in hemoglobin concentration as described previously (Wang et al., under review).

Image sequences of fluorescence emission detected by CMOS1 (i.e., uncorrected FAD autofluorescence) and CMOS2 (i.e., uncorrected jRGECO1a) were converted to percent change (dF/F) by dividing each pixel's time trace by its average fluorescence over each imaging run. Absorption of excitation and emission light for each fluorophore due to hemoglobin was corrected as outlined in (Ma et al., 2016).

Pupil size estimates were obtained via DeepLabCut software (Mathis et al., 2018) (Fig 1). Whisker motion was computed via the Lucas-Kanade optical flow method (Lucas & Kanade, 1981) applied to the pupil video frames. Movement magnitudes were averaged across five manually selected data points on the whiskers.

Dataset 2: Neurotycho (ECoG)

Resting-state electrophysiological data were obtained from a publicly available database (neurotycho.org) (Nagasaka et al., 2011). We used ECoG data from two macaque monkeys each chronically implanted with a subdural, 128-channel electrode array spanning the cerebral cortex of the left hemisphere. Details of this recording system (Nagasaka et al., 2011) and this particular dataset (Liu et al., 2015; Yanagawa et al., 2013) are published elsewhere. A total of 8 sessions

were used for Monkey 1 (“Chibi”) and 9 sessions for Monkey 2 (“George”), each lasting 10-20 minutes. Gamma bandlimited power (40-100 Hz) was extracted following a multitaper procedure as described previously (Liu et al., 2015; Raut et al., 2021).

Dataset 3: Human Connectome Project MEG

Resting-state MEG recordings were collected on a whole-head Magnes 3600 scanner (4D Neuroimaging, San Diego, CA, USA) from a randomly chosen subset of 20 subjects from the HCP S1200 release (Larson-Prior et al., 2013). Resting-state data was collected over three consecutive 6-minute long, eyes-open sessions. These data have been preprocessed to exclude faulty channels and artifactual temporal segments, bandpass (1.3-150 Hz) and notch (59-61 Hz, 119-121 Hz) filtering, and ICA-based denoising. Sensor data were subsequently projected to source space. Source reconstruction was performed for ~4,000 cortical vertices per hemisphere (~6 mm resolution). We used the source space BLP outputs from this pipeline – in particular, averaging the mid (50-76 Hz) and high (76-120 Hz) gamma frequency ranges for gamma BLP reported herein.

Dataset 4: Human Connectome Project fMRI and respiratory data

Simultaneously collected resting-state fMRI and physiological data were analyzed from a previously described subset of 190 subjects (Chen et al., 2020) from the WU-UMinn Human Connectome Project (HCP) 1200 Subject Release. Details regarding the HCP dataset are published elsewhere (Smith et al., 2013; Van Essen et al., 2012). Two 15-minute, eyes-open resting-state fMRI sessions (multi-band factor = 8, TR = 0.72 s; 2.0 mm isotropic voxels, one left-to-right and one right-to-left phase encoding direction) were obtained at each of two experimental sessions, for a total of four runs per subject. Physiological data were collected at

400 Hz via a bellow placed around the chest (respiration) and a pulse oximeter placed on the fingertip (pulse). We analyzed all runs from the 190 subjects that included full duration BOLD and physiological time series (22 of 760 possible scans were omitted due to missing/corrupted RV data).

HCP data were preprocessed using the minimal preprocessing pipeline (Glasser et al., 2013) as well ICA-FIX denoising (Salimi-Khorshidi et al., 2014) although this denoising pipeline had minimal influence on the results (cf. Fig. S4 in (Raut et al., 2021)).

All fMRI data were analyzed in CIFTI format, which represents cortical voxels as vertices on a surface mesh while retaining volumetric time series from the subcortex and cerebellum (Marcus et al., 2011). We used the standard HCP "grayordinate" parcellation, comprising 59K cortical vertices and 66K subcortical/cerebellar gray matter voxels (Glasser et al., 2013).

Respiratory variation (RV) was computed as temporal standard deviation of the respiratory trace was computed within 6-second sliding windows centered on each TR (i.e., every 0.72 s) (Chen et al., 2020).

Data analysis

Delay embedding and latent phase assignment

Attractor reconstructions were obtained in eigen-delay coordinates (Broomhead & King, 1986; Brunton et al., 2017) by performing singular value decomposition (SVD) of a Hankel matrix **H** constructed separately for each univariate time series x:

$$\mathbf{H} = \begin{bmatrix} x(t_1) & x(t_2) & \cdots & x(t_p) \\ x(t_2) & x(t_3) & \ldots & x(t_{p+1}) \\ \vdots & \vdots & \ddots & \vdots \\ x(t_q) & x(t_{q+1}) & \cdots & x(t_m) \end{bmatrix} = \mathbf{U\Sigma V}^{\mathrm{T}}. \quad (4.1)$$

The columns of **U** and **V** are arranged hierarchically by their ability to explain variance in the columns and rows of **H**, respectively. Plotting the first three columns of **V** provides the delay-embedded attractor. For mouse pupil, whisking, and calcium dynamics, the first three components explained >80% of the signal variance following lowpass filtering at 0.5 Hz. Similar attractor structure and phase estimates were obtained in the absence of filtering, although only ~40% of the variance in **H** was explained by the first three components.

Instantaneous phase values were obtained by 1) constructing a two-dimensional plane transverse to the flow (embedded in a three-dimensional space), and 2) interpolating from -π to +π between consecutive intersections with this plane.

Phase synchronization was assessed by magnitude of the phase locking value between each pair of latent phase variables θ_x and θ_y:

$$\mathrm{PLV}_{xy} = \frac{1}{T}\left|\sum_{t=1}^{T} \exp\left(i\left(\theta_x - \theta_y\right)\right)\right|. \quad (4.2)$$

Statistical significance of PLVs was assessed by comparision with a null distribution computed by phase randomization of the original time series prior to delay embedding and phase assignment.

Propagation dynamics

For each modalitiy in Fig. 2, movies of a canonical arousal cycle were obtained by 1) concatening brain time series data across individuals, 2) delay embedding the concatenated mean brain signal (or, for fMRI, the RV time series) and assigning a latent phase to each time point, and 3) averaging brain signals within 21 phase bins spanning the interval $(-\pi, \pi]$ according to latent phase values. Propagation displays are shown following subtraction of the global mean time course from the final, group-level result, to aid visualization of spatial specificity.

4.4 Acknowledgements

This chapter is a work in progress that is a collaboration involving quite a few people. Specific contributions include those from Zach Rosenthal (mouse data collection), Ben Miao (DeepLabCut), Victoria Zhang (optical flow analysis), Xiaodan Wang (imaging system), and Naotaka Fujii (monkey data curation), as well as more general involvement and research supervision from Joseph Culver, Adam Bauer, Avi Snyder, Jin-Moo Lee, and Marcus Raichle.

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Chapter 5

Summary and Outlook

5.1 Summary of Findings

The preceding arguments seek to reconceptualize infra-slow intrinsic brain activity as an internal regulatory process for global brain function. This regulation operates on the functional modes of the brain instantiated within its temporal states and spatial networks. Articulation of this perspective was the central aim of Chapter 2.

Chapter 3 saw an empirical investigation of the major hypothesis to emerge from this perspective. Thus, it was predicted that traveling waves propagate along the sensorimotor-association axis of the brain – in both cortical and subcortical structures – in synchrony with arousal fluctuations. In addition to empirically supporting this prediction, we showed how this process can parsimoniously account for a surprising number of prior observations in the neuroimaging literature, including the major spatiotemporal features of resting-state fMRI time series (e.g., large-scale functional connectivity network structure, the principal functional gradient, anti-correlations, quasiperiodic patterns and other accounts of propagating activity, and even the systematic correlates of head motion). Hence, it was proposed that this process provides a heretofore lacking, unifying account of the basic phenomenology studied with resting-state fMRI.

Finally, in Chapter 4, we took a data-driven approach to defining “brain state” and subsequently demonstrated its continuous evolution in synchrony with behavioral and physiological indices of arousal. As predicted in Chapter 2, we showed that this continuous evolution manifests spatially

as the large-scale wave propagation revealed in Chapter 3. Finally, by treating arousal as common "intrinsic coordinate" of global brain dynamics, we were able to provide complementary evidence across diverse systems neuroscience methodologies and multiple species. Taken together, this thesis has provided theoretical and empirical arguments for the existence of an ongoing spatiotemporal regulatory mechanism for global brain function.

5.2 Future Directions

Where does this leave us? Broad consideration of the functionality and evolutionary origins of these waves is provided in Chapter 2. Thus, I will conclude by briefly addressing some of the most pressing questions on my mind as I wrap up this thesis.

Physiological mechanisms

Until now, I have largely avoided discussion of physiological mechanisms supporting arousal dynamics – primarily because of the physiologically integrative nature of this process. Nonetheless, targeted experimental perturbations are likely to provide a powerful approach to shedding light on this topic. As for the generation of infra-slow dynamics, recent evidence points to noradrenergic neurons in the locus coeruleus exhibiting slow fluctuations that suggest a pacemaker-like quality at infra-slow timescales (Totah et al., 2018). Given its influence on arousal throughout the brain and body, targeted manipulation of this nucleus is almost certain to yield insights into the phenomena described in this thesis. Of course, other arousal nuclei (e.g., basal forebrain) are virtually guaranteed to be playing their own role and teasing out their respective contributions may prove to be exceedingly difficult. Finally, the thalamic reticular nucleus is perhaps a less obvious region that may be integral to infra-slow dynamics. In addition to literature describing pacemaker-like infra-slow activity in the thalamus (reviewed in (Palva &

Palva, 2012)), recent evidence has called attention to the capacity of this nucleus to synchronize brain-wide activity in a topographically organized manner (e.g., (Halassa et al., 2014)). It would be fascinating to manipulate any one of these brain regions and observe the effect on the arousal cycle and traveling waves.

State dependence

We have focused here on studying arousal dynamics within the (putative) awake state. The overlap in peak frequency of the wave process described herein (Raut et al., 2021) and in infra-slow physiology described in sleep and anesthesia (Fernandez & Lüthi, 2020; Lecci et al., 2017) strongly implicates a physiological link. On the other hand, there is evidence for changes in the propagation structure of infra-slow brain activity between wake and sleep states (Mitra et al., 2018; Mitra et al., 2015). At present, this reorganization of propagation structure is incompletely understood. I believe there are two possibilities: either the traveling wave process described herein is fundamentally changed during sleep, or propagating activity unique to the sleep state comes to be superimposed upon this basic wave process. Given that functional connectivity structure is only subtly changed between wake and sleep (Mitra et al., 2015), the latter interpretation seems most likely at this stage, given the strong resemblance (and, most likely, significant contribution) of topographically organized traveling waves to large-scale functional connectivity organization. I believe this is one of the most interesting and answerable questions about these dynamics that is addressable in the near future.

Timescales of arousal

Arousal fluctuates over a wide range of timescales. Here we have focused on ongoing fluctuations over tens of seconds. Slower changes include not only diurnal fluctuations, but even

fluctuations in arousal and systemic physiology on a timescale of many minutes. Two recent works have brought these slower changes to the forefront in neuroscience (Cowley et al., 2020; Tingley et al., 2021)). These studies serve as a strong reminder of the (self-reinforcing) experimental bias imposed in neuroscience by specifically examining short timescales in the brain (Marom, 2010). Understanding these slow changes in the present context will be critical moving forward. For example, do these slower fluctuations speak to a nested timescale organization, such that the "arousal cycle" simultaneously plays out on a minutes-long timescale? Or, are these slow changes best represented as a gradual change in magnitude of the infra-slow cycle we have described herein? The two are not mutually exclusive, of course; rather cycles at multiple timescales could be linked through phase-amplitude coupling (Canolty & Knight, 2010). This latter possibility would be favored to the extent that a bona fide rhythm or cycle on the many-minutes long timescale can be substantiated.

Clinical implications

Converging lines of neurological, behavioral, and functional imaging evidence increasingly implicate arousal as a fundamental player in a surprising range of neurodegenerative and psychiatric disorders. A large body of literature has established a strong link between the degeneration of neuromodulator nuclei and neurodegenerative disease (e.g., (Betts et al., 2019; Schmitz et al., 2018) and references therein), paralleling the intimate links between neurodegeneration and sleep and circadian biology (Musiek & Holtzman, 2016). And, while arousal regulation has long been viewed to be deeply intertwined with ADHD, this perspective is now increasingly generalized to mood disorders (e.g., (Hegerl & Hensch, 2014)). These converging lines of evidence complement the present arguments (as well as literature reviewed in Chapter 2) in motivating a shift from understanding arousal as a fundamental but uninteresting

feature of brain activity, to an essential component of brain function, behavior and cognition. I sincerely hope that the basic science covered in this thesis will inform how arousal abnormalities might be addressed in the neurological and psychiatric conditions that continue to prove so difficult to treat or prevent altogether.

5.3 References

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