**Electrophysiological Substates of the Brain in Sleep and Wake**

by

Maxwell Ruckstuhl

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Neuroscience and Scientific Computing)
in the University of Michigan
2026

Doctoral Committee:

Associate Professor Brendon O. Watson, Chair
Associate Professor Omar J. Ahmed
Professor Sara J. Aton
Associate Professor Kamran Diba
Professor Anthony G. Hudetz

Maxwell Ruckstuhl

maxruck@umich.edu

ORCID iD:  0000-0001-9781-5887

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## Dedication

This dissertation is dedicated to my parents, whose endless love and support has made possible my academic career; to my sisters, who have unwaveringly believed in me; and to my 公公, whose championing of scholasticism has defined and guided me in life.

**Acknowledgements**

I would like to acknowledge my classmates, whose camaraderie made this program enjoyable; my labmates, whose friendliness made lab welcoming; and my PI, whose patience and mentorship has enabled my success.

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## Abstract

The brain shifts frequently between distinct regimes of neural activity with associated electrophysiological and behavioral features. These many brain states have different functions and subserve different goals of the animal. No understanding of the brain can be complete without characterization of its states, of how they are affected by disorders of the brain, and of how treatments are modulated by them. We present findings on the relationship between neural activity and substates of REM sleep and on the variance in ketamine's effect in cortex across substates of wake. Specifically, REM exhibits substates distinct in eye movement but continuous in single-neuron and coordinated activity, while the effect of ketamine on both spiking and LFP differs in character during a substate of wake defined by high pEMG. We discuss potential implications for treatment of depression and analysis of multimodal brain data.

# Chapter 1 Introduction

## 1.1 What are brain states?

The brain is not static. Apart even from changes induced by development and by learning, the brain adopts different modes of operation on timescales of minutes and hours. Most prominent and most different from each other are the states of wake and sleep. During wake, an animal is responsive to the environment, eats and drinks, and engages in learning. During sleep, an animal is immobile and unresponsive. For such a state to persist through millions of years of evolution across nearly all animals, it must serve some function vital to the brain. The subjective experience of waking life is itself colored by what might be considered brain states: a bad mood, being stressed or relaxed, daydreaming or paying attention.

These brain states have neural correlates, features of brain activity that, for just over a century now, are accessible to the scientist and allow us to gain insight into the basis of and wide-ranging effects of brain states. At the human level, they affect or even define our lives. At the scientific level, they are a phenomenon that must be investigated to understand the brain in fullness.

Thus brain states are lasting regimes of neural activity with associated behavioral and physiological features. These states are thought to reflect different functions subserving different needs of the animal. For example, sleep facilitates learning, while attention enhances sensory processing. Transitions between states may be driven by sensory input, neuromodulation, or oscillatory mechanisms (Lee & Dan, 2012). Fully explaining specific behavioral patterns and neural phenomena will no doubt require highly specific distinctions between states. Yet much work remains to be done even at the most coarse levels of brain state analysis.

### *1.1.1 Sleep and wake*

The most distinctive brain states are sleep and wake, which are easily distinguished on the basis of behavior. The sleep–wake cycle has a well-defined 24-hour period, with nocturnal animals awake at night and diurnal animals awake during the day. These behavioral differences

coincide with physiological differences in respiration rate, heart rate, and body temperature. What of electrophysiology?

Loomis et al. (1937) was the first report on "cerebral states" during sleep as defined by electroencephalography (EEG). They observed brain waves that we now call alpha, delta, and spindle, the latter 2 of which appeared to be specific to sleep. Furthermore, they found that these oscillations correlate with states of sleep (as defined by responsivity to sensory stimuli). They wrote that "the old idea of a continuous curve of sleep needs modification". Today, electrophysiological features are considered definitional in sleep and wake. Where wake is defined by beta and gamma, sleep is marked by delta, spindle, and theta (Gervasoni et al., 2004).

Thus the best-known brain states of wake and sleep might be defined and subdivided on the bases of behavior, physiology, and electrophysiology.

### *1.1.2 Substates of wake: aWAKE and qWAKE*

Wake is less structured than sleep, but locomotion data suggest a simple division into active wake (aWAKE) and quiet wake (qWAKE). In the active substate, which is accompanied by theta (Rayan et al., 2022) and gamma (Maloney et al., 1997), animals explore, perform tasks, and otherwise attend to the external world. In the quiet substate, animals are sitting or lying down, and responsivity to direct stimulation is greater (Gandolfo et al., 1980). Quiet and active wake differ also in circadian modulation and change with age (Ruigt et al., 1989).

qWAKE is heterogenous; it may encompass resting, grooming, chewing, recall, and planning (Rayan 2022). Similarly, aWAKE contains the diversity of locomotive behaviors that make up most of our conscious experience. aWAKE as defined by locomotion is distinct from but correlated with a high-arousal behavioral state, with both exhibiting desynchronized activity and theta–gamma coupling. However, locomotion is associated with increased spiking in visual cortex, whereas arousal in isolation is associated with suppressed spiking (Vinck et al., 2015).

### *1.1.3 Substates of wake: task and mental states*

Wake can also be broken down on the basis of behavior in a defined context. In humans, you can demand task states like reading (Suhail et al., 2022) and arithmetic (Huang et al., 2024) and recall and rest, and these can be distinguished from each other on the bases of EEG. In one notable study, video game behavioral states were defined to include exploration, close engagement, far engagement, and running away (Zhang et al., 2021). In this study, neural

activity was measured using functional magnetic resonance imaging (fMRI) rather than EEG, and this too proved sufficient to recover the task states. Interestingly, neural activity was different between safe exploration and unsafe exploration as defined by the researchers, demonstrating the existence not just of distinct behavioral states but also of distinct cognitive states.

Cognitive states can be defined to include attention (Napoli et al., 2020; Kaushik et al., 2022; Wan et al., 2021) and fatigue (Banuelos-Lozoya et al., 2021; Zhou et al., 2025), and these of course each contain a range of their defining characteristic. More generally and less concretely, we can posit mental states defined by the subjective experience of being in that state. Anger and sadness and fear (defined by self-report) are mental states just as recall and dreaming are (Oosterwijk et al., 2012). It seems that these mental states are further removed from and less distinguishable on the basis of physiology than, for example, sleep. Nevertheless, emotional states can be inferred from brain activity alone (Kragel et al., 2016). A state of sadness that persists across days and years is a key symptom of depression, which itself has electrophysiological correlates like decreased beta (Shamaeva et al., 2018).

#### *1.1.4 Summary*

Sleep and wake are distinct states of the brain with defining features in terms of behavior and electrophysiology. They are thought to support different functions of import and therefore must be studied to develop a complete understanding of the brain. Within these states are numerous substates that themselves have been characterized and investigated to better understand their diverse roles in supporting brain function. Some map onto the subjective experiences of our lives. Some undoubtedly require considerable further exploration and breakdown. But even our current understanding contributes to the determination of the many critical processes undertaken by the brain. For the interested reader, the next section elaborates on the basis and use of electrophysiology in neuroscience.

### 1.2 Electrophysiology of the brain

#### *1.2.1 Electric fields*

Just as all matter has the property of mass, causing it to exert gravitational force on other matter, matter can have charge, causing it to exert electrical force on other charged matter. A field describes for every location in space the force that would be applied to an object at that

location by present matter. Objects at different distances from this matter would experience different amounts of force and possess different amounts of potential energy. For opposite charges, which attract, this is the amount of energy it would take to move that object to the mass. This is equal to the product of the charge of the object and the potential at that location in the field. An electrode can be used to measure the electric potential at a point in space relative to some reference point.

In a conductive material, charged particles are able to move. Because particles of the same charge repel each other, any movement of charges gets propagated outward in space as a wave. This of course is reflected in changes in the electric field. Thus, in a conductive medium, the recording of potential at a given electrode reflects a weighted average of signal from local sources and from distant ones carried by volume conduction.

### *1.2.2 PSCs and APs*

The brain is made up of a complex network of cells called neurons connected via synapses. The computations achieved through communication across synapses and properties of individual neurons are thought to support such diverse functions as movement, sensation, decision-making, and imagination.

At the synapse, quantized movement of charged particles across the cell membrane, called postsynaptic currents (PSCs), affect the state of the neuron. PSCs that sufficiently coincide cause the postsynaptic neuron to fire an action potential (AP), a phenomenon marked by rapid movement of charged particles and synaptic transmission to all downstream neurons.

### *1.2.3 Spikes*

Single-neuron postsynaptic currents would not be measured until the 1980s with the development of the Nobel-winning patch clamp technique. But as early as 1928, Adrian recorded the much larger action potentials by placing an electrode near a neuron. The movement of charged particles into the neuron is of course reflected in their flow out of the extracellular space, and this rapid change in potential is recorded as a spike.

Spikes last roughly 1 ms, with amplitudes on the order of 100 μV in the extracellular space, and can be detected from neurons within 100 μm of the electrode (Henze et al., 2000). They arise from the dynamics of voltage-gated ion channels, whose kinetics yield well-defined waveforms and refractory periods for each neuron (Hodgkin & Huxley, 1952). Spikes are the

most prominent phenomena exhibited by neurons. As they reflect summed input and define neuronal output, they on individual and circuit bases are thought to perform the computations that underlie all the brain's functions. Among the most fundamental of the brain's functions is perception — gathering information about the environment using senses. Across modalities, spiking has been shown to underlie perception in a causal manner.

A series of investigations going back a century has established that spiking encodes sensory information, meaning information about the environment is reflected in the spiking activity of neurons specific to the different sensory modalities. Adrian and Zotterman (1926) found that as the weight stimulating a muscle increased, the frequency of spikes fired by sensory neurons in that muscle increased correspondingly. Hubel and Wiesel (1959) found that single neurons in primary visual cortex (V1) increased in firing rate only when visual stimuli were located in specific parts of the visual field. Information about taste and odor is represented in the spiking of neurons in the orbitofrontal cortex (Rolls et al., 2009). Neurons in temporal visual cortex primarily respond to and encode faces (Rolls et al., 1997). Most of the information in sensory cortices is encoded in neuronal firing rates (Rolls & Treves, 2011).

In humans, perception can be evaluated by verbal report, so it is a simple matter to induce neuronal activity by electrical stimulation of the olfactory bulb to evoke the hallucinatory perception of an unpleasant odor (Penfield & Jasper, 1954). Stimulation of the orbitofrontal cortex instead evokes a hallucination of a pleasant, fruity smell (Berard et al., 2021). Odors induce spiking in a subset of neurons in the olfactory bulb (or analogous structure). Spatiotemporally patterned optogenetic stimulation of these neurons evokes the percept of a "synthetic odor" that can be used to drive decision-making behavior (Chong et al., 2020). Even early processing from olfactory receptor neurons to postsynaptic projection neurons improves odor discrimination and response reproducibility (Bhandawat, 2007), bringing raw input closer to perception. Downstream of the olfactory bulb, an odor stimulus causes a burst of spiking with information content greater than that leveraged for decision-making (Miura et al., 2012), suggesting a tradeoff between information and reliability. This burst can be locked to the onset of a sniff or even a slow inhalation (Cury & Uchida, 2010). In this downstream region, information about odor concentration is removed such that spiking reflects only the identity of the stimulus (Bolding & Franks, 2018).

As with olfaction, vision exhibits a change with processing from direct reflection of the stimulus in the spiking of highly specific sensory neurons to downstream neurons with larger receptive fields whose spiking better reflects the animal's perception of the stimulus and corresponding behavioral choice (Siegle et al., 2021). Also analogous is the use of optogenetics in V1 to not just influence (Dai et al., 2014), improve (Lee et al., 2012), and impair (Cone et al., 2020) perception but even replicate the effect of a visual stimulus on neuronal spiking and perception (Marshel et al., 2019).

In somatosensory cortex, spiking underlies touch; direct stimulation evokes percepts in nonhuman (Kim et al., 2015) and human primates (Johnson et al., 2013), and optogenetic stimulation and inactivation causally affect the perception of touch in mice (Sachidhanandam et al., 2013). Spiking in only a handful of neurons is sufficient to drive perceptual decision-making (Huber et al., 2008). Together, these findings show that spiking underlies the most basic of the brain's information-gathering functions.

Just as it underlies input, spiking similarly underlies output. Direct stimulation of motor neurons to induce minor changes in their spiking causes changes in the force produced by the postsynaptic muscle fiber. In the context of respiratory motor units, induced changes in spiking affect respiration (Srivastava et al., 2017). The stimulation of single neurons in motor cortex (Brecht et al., 2004) or facial nucleus (Herfst & Brecht, 2008) evokes rhythmic whisking. Optogenetic stimulation of neurons in motor cortex evokes arm movements, with different regions of the brain controlling hand and elbow movements (Ebina et al., 2019).

Spiking also underlies the many less-tangible functions between input and output. For example, spiking in frontal cortex has been shown to underlie working memory in nonhuman (Constantinidis et al., 2018) and human primates (Kaminski et al., 2017) in a manner predictive of behavior (Riley & Constantinidis, 2016) and influenceable by transcranial magnetic stimulation (Barbosa et al., 2020). Spiking underlies even the perception of pain (Xiao et al., 2019), and electrical stimulation of posterior insula has been shown to evoke pain in humans (Mazzola et al., 2012).

Thus spiking is the most critical feature of brain activity for understanding the functions of the brain. While early work primarily focused on the spiking of single neurons, it may be the combination of spiking patterns stable across time that gives rise to distinct brain states. In some neural networks, the pattern of activity has a tendency to change to particular attractor states and

remain in them (Rabinovich et al., 2008). Specific percepts, memories, or brain states might reflect analogous attractors in the brain. The analysis of patterns of activity across populations of neurons rather than within single units increasingly dominates neuroscience as techniques allow us to record from increasingly large populations and theoretical work turns its focus toward population coding.

Assemblies: While the spiking of single neurons can be linked to minor aspects of perception and motor output, assigning single units to specific functions would be inefficient, inflexible, and highly susceptible to noise. It is thought that the brain instead relies on cell assemblies, groups of neurons that are highly interconnected and therefore co-activate. Their interconnectivity might be developed through learning and depend on the information processing required of this functional unit (Huyck & Passmore, 2013). Neurons might be shared among assemblies, allowing them to be recruited for different functions (Sakurai, 1999), and enabling the brain to make use of the far greater number of possible combinations of neurons than the number of single neurons themselves (Barlow, 1996). These were among the properties proposed by Hebb (1949) to mechanistically explain how groups of neurons might be responsible for percepts (Wallace & Kerr, 2010). Since then, advancements in electrophysiology that allow us to record from many neurons at once have enabled empirical testing of his theory (Buzsaki, 2010). Coordinated firing in ensembles of neurons has been observed in cortex and in hippocampus, and assemblies have been linked to functions as diverse as sleep regulation (Krueger et al., 2008), odor detection (Macleod & Laurent, 1996), fear behavior (Dejean et al., 2016), and memory (Grewe et al., 2017).

The coordination of spikes not just locally but across brain regions is a central question in neuroscience. It is thought to help encode sensory stimuli, coordinate movement, and drive changes in the brain. A potential mechanism for spike coordination is neural oscillations.

### *1.2.4 LFP*

PSCs are much smaller than APs — roughly an order of magnitude. They are also slower, lasting milliseconds rather than just one. As a result, their influence on electric potential in extracellular space, both directly via volume conduction and indirectly via change in the electric field, can combine across many neurons when they are spatially and temporally aligned. It has been found that pyramidal neurons in the well-defined laminar structure of neocortex contribute

to distinct oscillations in potential that are measurable in the extracellular space and even outside the brain, at the scalp, where they were first discovered.

In 1924, Berger developed from prior work EEG, a way of recording the electrical activity of the brain from outside the skull (Rossini et al., 2025). Its application to the study of the brain was revolutionary and, at first, met with skepticism. Now it is routinely used for clinical diagnostics, especially in the areas of epilepsy, sleep, and anesthesia.

Berger observed two specific phenomena. Alpha waves, with a frequency of 8–12 Hz in humans, correlate with mental activity, particularly in humans with their eyes closed in a state of relaxed wake (Arjoonsingh et al., 2024). When they open their eyes, alpha decreases in favor of beta waves, with a frequency of 15–30 Hz, especially on paying attention to a sensory stimulus. Since then, other canonical bands have been observed, defined, and investigated: delta, theta, and gamma.

Delta (0.5–4 Hz) is associated with sleep and concentration (Harmony, 2013). Theta (4–8 Hz) relates to learning, memory, and the encoding of sequential information (Roux & Uhlhaas, 2014). Alpha (8–12 Hz) subserves attention by inhibiting irrelevant sensory information (Sadaghiani & Kleinschmidt, 2016). Beta (15–30 Hz) relates to motor control. And gamma (30–100 Hz) has been implicated in feature binding, recall (Herrmann et al., 2004), routing of information (Fernandez-Ruiz et al., 2023), and local network coordination (Kucewicz et al., 2014).

These oscillations are also present inside the brain, and thus extracellular physiology enables simultaneous capture for a given region of both local output (APs) and local input (PSCs), which are closely related, particularly in the gamma band. The local field potential (LFP) reflects PSCs nearby (within a millimeter) and farther away as the geometry of neuronal organization and, in particular, their dendrites allow signals to sum and spread through the brain. LFP is thus an analogue of EEG with greater spatial resolution and fidelity. It offers a view of network input and processing complementary to that provided by spiking. It is inherently a population measure, and meaningful interpretation can be difficult, but elaboration on neural oscillations first described using EEG has proven a fruitful application of LFP. For example, Parkinson's is characterized by abnormally high beta in the basal ganglia (Yin et al., 2021), and its suppression by levodopa (Brown et al., 2001) or direct stimulation (Oswal et al., 2016) reduces motor impairment.

Moreover, neural oscillations are thought to affect spiking. Across frequencies, oscillations affect the propensity of neurons to spike, entraining neurons to local rhythms and thereby synchronizing their activity and giving rise to coordinated population activity (Schaefer et al., 2006). For example, in somatosensory cortex, alpha suppresses irrelevant information, improving perceptual discrimination through its effect on spiking (Haegens et al., 2011). Gamma has been proposed to support attention by synchronizing spiking associated with the attended stimulus (Fries, 2015). Cell assemblies have been shown to coordinate changes in spiking based on their preference for different oscillations, and this preference correlates with neural function and behavior (Canolty et al., 2010).

#### *1.2.5 Summary*

The electrophysiologist is uniquely placed to investigate the coding and computation in the brain that underlies perception, behavior, and brain states. That the primary functional activity of the fundamental units of the brain can be listened in on simultaneous with related population activity seems a happy coincidence and powerful tool for the neuroscientist. Next, we elaborate on the application of these methods to the study of brain states of interest.

### 1.3 Why do we care about brain states?

#### *1.3.1 The animal*

To determine the importance and function of a brain state, one need only prevent it and observe the consequence. In sleep-deprived humans, we observe impairments in learning and memory (Dumitru et al., 2025), attention and decision-making (Lim & Dinges, 2010), reaction time (Ren et al., 2025), and mood regulation (Killgore, 2010). In extreme cases, the ability to distinguish between the external and internal worlds may be diminished such that individuals experience hallucinations. Sleep is known to be important for memory consolidation, lymphatic brain clearing (Xie et al., 2013), and thermoregulation (Rechtschaffen et al., 1989).

#### *1.3.2 The individual*

If brain state mediates the relationship between inputs and their effects, then for any sort of input or behavioral outcome, it is important to consider brain state. Brain state mediates sensory responsivity (McGinley et al., 2015). Food tastes better when we're hungry, and movies are less enjoyable when we're stressed. Brain states color our experience of conscious life. In

terms of behavior, learning is less effective outside the attentive state. Task performance, like driving, is impaired when we're fatigued. These tasks are important in modern life, and understanding this critical variable in their performance is correspondingly important.

### *1.3.3 The scientist*

The goal of the scientist is to explain observable phenomena of some system of interest. What constitutes an explanation is a matter of debate, but one common definition is that an explanation is a conceptual model sufficient to predict observations from that system given some input (Suppes, 1960).

A model is a representation of reality. Models are necessarily simpler than reality (for explanatory ability) and abstracted (for generalizability), which comes at the cost of predictive ability. A maximally accurate model would be a literal recreation of the system. Instead, we accept some loss in predictive ability in exchange for simplicity and practicality. Hence the aphorism "All models are wrong; some are useful". Ideally, a model is only as complex as is necessary to reproduce the phenomena of interest.

The brain is an incredibly complex system in terms of structure and inputs. The diversity of observable outputs can be categorized into behavior and brain activity, which can be measured at the regional, neuronal, and neurochemical levels. To explain the brain is to build conceptual models that help explain these observables. And just as taking into account the state of hunger improves our prediction of burger enjoyment, considering brain state can improve our predictions of behavioral and electrophysiological activity.

### *1.3.4 The clinician*

REM behavioral disorder (RBD) is characterized by a loss of the atonia (muscle paralysis) that normally accompanies rapid eye movement sleep (REM), resulting in behavioral enactment of dreams, such as talking, fighting, or fleeing, sometimes causing injury (Dauvilliers et al., 2018). It is a consequence of neurodegeneration in medulla and is almost always a precursor to a neurodegenerative disorder like Parkinson or dementia with Lewy bodies (Howell & Schenck, 2015) and potentially Alzheimer's and Huntington’s (Zhang et al., 2020). It has a prevalence of roughly 1% among older adults, and this predictably increases with age. Among individuals with narcolepsy, the prevalence of RBD may be as high as 50% (Dauvilliers et al.,

2007). It is still unknown why RBD tends to feature atypically aggressive dreams (Krenzer et al., 2013).

This breakdown of brain state must be studied to develop treatments for its immediate consequences and, ideally, to forestall the subsequent neurodegenerative disorder. Analogous breakdowns can be imagined: non-REM sleep (NREM) without spindles, task states without attention, active wake with atonia. The latter, cataplexy, is thought to result from pathological activation of the same brainstem nuclei that underlie REM atonia (Torontali et al., 2019; Uchida et al., 2021). To what extent do these exist, how might they be treated, and could they serve as advance warning of neurodegeneration.

In the clinical context, we treat the brain using techniques like direct and transcranial brain stimulation and pharmacology. If brain state mediates the effects of these treatments, then understanding brain states may be important for disorders of the brain like Parkinson's, epilepsy, addiction, anxiety, addiction, and chronic pain.

#### *1.3.5 Summary*

Brain states are phenomena that are themselves of interest: Why are certain patterns of neural activity and associated behavior preferred by an animal? What distinct states can be observed or uncovered, and do they differ from each other categorically or along a continuum? Beyond this line of questioning, brain states inform our understanding of every neural phenomenon of interest, as they influence everything from stimulus responsivity to information processing to behavioral goals. The investigation of brain states thus contributes broadly to the brain sciences. Next, we consider specific applications of brain state as a tool for understanding topics of great import.

### 1.4 Depression and ketamine

Depression is a debilitating, unsolved problem in neuroscience and psychiatry. It is characterized by anhedonia, persistent sadness, physical and cognitive fatigue, and disruptions in sleep and appetite that greatly diminish quality of life. Its etiology is complex, encompassing genetic factors (Shadrina et al., 2018), childhood adversity (Kohler et al., 2018), psychological vulnerability (Xu 2023), and stressors (Longoria et al., 2024). One or more of these factors must be worsening, as the prevalence of depression has been steadily increasing for decades (Goodwin

et al., 2022), with estimates as high as 17% for some age groups (Lu et al., 2024). Developing effective treatments for depression thus represents a major goal of these fields.

Established treatments, primarily monoamine reuptake inhibitors, are moderately effective. Roughly 60% of patients respond to these compounds, but 30% exhibit treatment-resistant depression. Uniquely, the NMDA receptor antagonist ketamine achieves a comparable response rate of 50–70% (Alnefeesi et al., 2022; Seshadri et al., 2024), even among patients with treatment-resistant depression. Ketamine was first synthesized in the 1960s as a safer alternative to phencyclidine for use as an anesthetic. In the 1980s and 1990s, mounting evidence suggested a role for glutamate in mood disorders, including depression. This led to the first randomized controlled trial of ketamine for depression in 2000, where it was noted that ketamine is also unique in its time course, taking effect in hours rather than weeks (Krystal et al., 2019). A 2006 study by Zarate et al. found that ketamine is effective even for treatment-resistant depression, and supporting evidence gathered in sequent years led to the FDA approval of ketamine for treatment of depression in 2019. However, its cascade of effects leading to plasticity and its inter-individual variability remain poorly understood. Determining the mechanism of this novel and highly effective NMDAR antagonist is critical as we improve our understanding and treatment of depression and other mood disorders.

### 1.5 Sleep and REM

Depression is inextricable from one of the other great mysteries of neuroscience: sleep. For much of their lives, animals (universally, it seems) exist in an immobile, unresponsive state. This behavior, dangerous for prey and without obvious benefit to predators, occurs daily, suggesting it is vitally important. Various functions have been attributed to sleep with varying degrees of evidential support: memory consolidation, metabolic waste clearance, and maintenance of attention, mood, and immune function. However, we lack an overarching explanation for the necessity of sleep and the concordant degree of evolutionary conservation. Moreover, there remain open questions regarding variance in sleep need across species and individuals, the function of dreaming, and the temporal structure of sleep.

A considerable majority of individuals with depression report either insomnia or hypersomnia, a mere 10% presenting without sleep-related complaint (Nutt et al., 2008; Tsuno et al., 2005). Increasingly, sleep disturbances are being recognized as a core symptom of depression, not a side effect. Thus, to understand one, we must consider the other.

Sleep can be divided into rapid-eye-movement sleep (REM) and non-REM sleep (NREM). REM was discovered in 1953 by Aserinsky and Kleitman when they observed periods of saccadic eye movements 3–5 times a night, increasing in duration from 10 to 50 minutes. During these periods, the brain is highly active, with dominant theta (Fraigne et al., 2023) and gamma (Eban-Rothschild et al., 2018) rhythms. Respiration and heart rate increase as well.

NREM, by contrast, is characterized by delta, K-complexes, spindles (Johnson et al., 2010), and ripples (Meier et al., 2020). Heart rate and respiration are more stable (Wood et al., 2020), and neuronal firing rates are lower and more synchronized (Kajiya et al., 2025).

One hypothesis for the existence of and differences between these states of sleep is that NREM enables cellular maintenance and synaptic plasticity while REM enables activation and selection of networks for processing (Vyazovskiy & Delogu, 2014). In this model, synaptic spines preferentially form during NREM and are pruned during REM. Evidence for this hypothesis remains thin, and the structure of sleep, even at the most macro level, is a topic of ongoing study as we decipher the role of sleep.

### *1.5.1 Substates of REM: pREM and tREM*

While REM was discovered on the basis of rapid eye movements, it is today defined based on a collection of features that includes low-amplitude, low-synchrony EEG, muscle atonia, and activity in REM-generating circuits (Simor et al., 2020). In fact, the bursts of eye movement for which REM is named are more closely associated with the substate of phasic REM (pREM) alongside other muscle twitches and a high arousal threshold. By contrast, tonic REM (tREM) is characterized by more stable heart and respiration rates (Simor et al., 2025), differences in EEG, and a lower arousal threshold (Ermis et al., 2010).

Table 1: Differentiating characteristics of phasic and tonic REM

| | **pREM** | **tREM** |
|---|---|---|
| Eye movement | Bursts | Infrequent |
| Muscle twitches | Frequent | None |
| Heart rate | Irregular | Stable |
| Sensory responsivity | Lower | Higher |
| LFP power | Gamma and delta | Alpha and beta |
| Theta frequency | Higher | Lower |
| Dreams | More vivid and frequent | Less intense |

The eye movements that define pREM are associated with bursts of ponto-geniculo-occipital (PGO) waves that originate in the pons and initiate REM. The corresponding irregular activity in heart rate and respiration are thought to share a cause. These waves end in visual cortex, potentially explaining the visual intensity of REM dreams (Gao et al., 2023). The coupling of this internally generated activity with hippocampal theta (Karashima et al., 2005) and ripples suggests a role in memory consolidation (Ramirez-Villegas et al., 2020). The pontine REM generator, which is located in the ventral part of the oral pontine reticular nucleus and known as the subcoeruleus nucleus, also activates cortex and induces muscle atonia (Fraigne et al., 2015; Reinoso-Suárez et al., 2001).

tREM can be thought of as a period of quiescence between bouts of pREM during which environmental alertness is partially restored (Ermis et al., 2010). It does not have a specific generating circuit; it reflects ongoing background activity that defines and is sustained throughout an episode of REM. Whether tREM plays a distinct role in and of itself or simply supports REM-associated functions by virtue of the fluctuation between substates is undetermined. Sensory stimulation suppresses pREM and favors a transition back to tREM (Stuart & Conduit, 2009), supporting the latter hypothesis. Furthermore, models that define a distinct role for tREM in the integration of memories activated during pREM do not have strong empirical support. Nevertheless, the precise roles of pREM and tREM still require elucidation. In particular, little is known about their temporal relationship and why the brain must cycle between them.

### *1.5.2 Summary*

Among the many areas of study that make up neuroscience, the nature of depression and REM sleep are open questions of great import with known links to brain state. While much has been uncovering regarding these fundamental, closely related phenomena, further research is needed to arrive at a full understanding of their underlying mechanisms and manifestation in electrophysiology.

## 1.6 Brain states in REM and following ketamine

While brain states are broadly applicable as an approach to neuroscience, we are specifically interested in two topics. First, the nature of brain states within REM sleep. Though pREM and tREM have been topics of study for decades in humans and rodents, their

electrophysiological correlates, like spiking in neocortex, remain incompletely understood, and we lack an understanding of how they relate to each other in terms of such features, like neural oscillations. As REM is a substate of sleep rich in brain activity and presumably function, a deeper understanding of its own substates would be valuable in elucidating the role of sleep as a whole and of brain states as supporting mechanism. Based on prior work, we investigated the role of theta in tonic and phasic REM and its association with spiking. This investigation of substates of REM, published in the *Proceedings of the National Association of Scientists*, makes up Chapter 2 of this dissertation.

Second, the relationship between brain states and the effects of antidepressant-dose ketamine. Ketamine response is highly variable both across and within individuals. Changes in neural oscillations and spiking in neocortex are thought to represent early changes induced by this rapid antidepressant, and brain state at the time of treatment is a potential source of variance, consistent with the differences in responsivity between brain states like wake and sleep or pREM and tREM. Uncovering factors that moderate the effect of ketamine would improve treatment of depression specifically as well as more generally any attempt to induce short- or long-term changes in the brain. Thus this is a high-impact area of study for the application of brain state analysis. Our investigation of the moderation of ketamine's electrophysiological effect by substates of wake, currently under review, makes up Chapter 3 of this dissertation.

# Chapter 2 Theta Frequency and Spiking across Substates of REM

Published as Bueno-Junior et al., 2023.

## 2.1 REM

REM makes up half of sleep, alternating with NREM in well-defined cycles. It is defined behaviorally by rapid eye movements produced by bursting of oculomotor muscles. Electrophysiologically, it is reflected in desynchronized LFP and strong hippocampal theta.

REM is regulated by REM-on and REM-off populations as mentioned above. Specifically, REM-on populations are found in sub-laterodorsal tegmental nucleus, ventral medulla, and dorsal paragigantocellular nucleus, and REM-off populations in ventrolateral periaqueductal gray and dorsomedial hypothalamus.

## 2.2 pREM and tREM

Rapid eye movement sleep (REM) is characterized by wake-like brain activity, atonia of postural muscles, and myoclonic events (Blumberg et al., 2020; Chase, 2013; Luppi & Fort, 2019). REM is believed to have a substructure of "phasic" and "tonic" periods with high and low incidence of rapid movements, respectively (Simor et al., 2020). In humans, phasic REM is less sensitive to sensory stimuli, despite being motorically active, whereas tonic REM is more reactive to stimuli, despite being quiescent (Ermis et al., 2010; Koroma et al., 2020; Sallinen et al., 1996; Takahara et al., 2002; Wehrle et al., 2007; Simor et al., 2018; Simor et al., 2019).

Phasic and tonic REM also seem present in rodents, with studies showing differences in oromandibular motricity (Brooks et al., 2008; Burgess et al., 2008; Morrison et al., 2003; Morrison et al., 2003) and hippocampal activity (Mizuseki et al., 2011; Montgomery et al., 2008). Although these studies have broad implications for sleep health and memory consolidation, they do not provide detail in distinguishing REM microstates. A REM-focused study (Brankack et al., 2012) contributed more directly to that distinction in mice, finding that brain oscillations in the theta band (5 to 10 Hz) peak at higher and lower frequencies in phasic versus tonic REM, respectively, reinforcing the neurophysiologic heterogeneity within REM.

## 2.3 Experimental goals and design

However, the methods for distinguishing REM microstates are inconsistent in both humans and mice. There is no consensus on how to subdivide REM, both in terms of time binning and scoring criteria (Koroma et al., 2020; Burgess et al., 2008; Mizuseki et al., 2011; De Carli et al., 2016; Tamaki & Sasaki, 2019; Simor et al., 2016). In addition, even if we had standardized methods to study phasic and tonic REM, simply comparing these microstates cannot elucidate the periodicity with which they alternate or the extent to which they are dissociable. Therefore, we still lack a fundamental understanding of REM temporal structure.

Here, we address this gap in a comprehensive manner, at levels ranging from motor to brain activity in both mice and humans. We asked: do REM microstates alternate rhythmically? Are microstate transitions unambiguous? Are there intra-REM fluctuations in brain and body activity? Are these fluctuations correlated?

Basically, we find that REM demonstrates a combination of brain and body signals fluctuating on a timescale of minutes, with some signals suggesting phasic/tonic-like alternation (e.g., oculomotor activity) and others implying nondiscrete continuous variation (e.g., theta frequency in mice, respiration rate in humans).

## 2.4 Methods

### *2.4.1 Subjects*

We used six adult male mice under standard housing conditions, in accordance with bioethical guidelines from the NIH (Institutional Animal Care and Use Committee protocol PRO00009818, University of Michigan Medical School). Deidentified PSG data from nine healthy adult humans were analyzed under the Veterans Affairs Portland Health Care System (VAPORHCS) Institutional Review Board approval (Medical Institutional Review Board #4108) in accordance with the Belmont Report.

### *2.4.2 Surgeries*

Each mouse underwent two surgeries, seven days apart: 1) intrinsic optical imaging of S1 barrel cortex followed by partial construction of a chronic electrophysiology head cap and 2) imaging-guided silicon probe implantation followed by completion of the head cap.

We used intrinsic imaging with high-power red illumination (630 nm) during whisker stimulation (10-Hz piezoelectric) to identify whisker-related cortical barrel fields based on

previous studies (Aronoff & Petersen, 2007; Knutsen et al., 2016). After imaging, skull microscrews, ground pin, and a 3D-printed head fixation ring (Fig. 1A) (Osborne & Dudman, 2014) were cemented together around the cranial window to enable later cranial implantation, after a 1-wk postsurgical recovery period. We then implanted a one-shank silicon probe (64 electrodes) into the somatosensory area defined as described above. Implantation was made during recording, so that channels could be visualized in real time. We then finished constructing the headcap cement around the probe and its connector.

The implant was validated functionally by testing whisker-barrel somatotopy and by analyzing a depth profile of oscillatory band power, suggestive of neocortical-hippocampal probe placement. After experiments, brains were fixed and sectioned for histological verification (Paxinos & Franklin, 2019) using triple staining: NeuN, Netrin-G1a, and DAPI.

### *2.4.3 Electrophysiology*

Brain activity was amplified (1,000×) and digitized (20 kHz) by a 64-channel headstage and transmitted into a multichannel interface (Intan). The wide-band signal was preprocessed as LFP (450-Hz low-pass, 1.25 kHz sampling), pEMG from intracranial signals (Schomburg, 2014), and spiking activity (500-Hz high-pass, 20-kHz sampling). Home-cage sleep sessions consisted of allowing the mice to behave freely while plugged into the recording cable (Fig. 1A). Head-fixed sleep was recorded from an electrophysiology, videography, and infrared illumination setup centralized by a pair of 3D-printed head-fixation forks (Fig. 1 A and B) (Osborne & Dudman, 2014). Both setups were Faraday protected using a metal mesh connected to the ground.

### *2.4.4 Sleep scoring*

Sleep scoring was made in 1-s bins based on published procedures (Grosmark et al., 2012; Watson et al., 2016). Three variables were used for scoring: power spectral slope (PSS), theta ratio, and normalized pEMG. Bins were then sorted into NREM (low PSS), REM (high theta ratio, low pEMG), and qWAKE (all other times). qWAKE, NREM, and REM epochs were curated using an interactive spectrogram accompanying theta ratio and pEMG curves (Fig. 1C). REM episodes were extended 30 to 60 s in both directions, creating margins for later trimming at higher temporal resolution (125 Hz sampling; Fig. 1D). For each REM episode, we defined a

paired qWAKE epoch with the same duration so that REM and qWAKE could be compared in an own-control design (Figs. 2 and 3).

### *2.4.5 Videography*

The left eye was filmed using infrared reflectance, i.e., without the trans-skull back illumination method of previous studies (Yüzgeç et al., 2018; Tsunematsu et al., 2020; Sattler & Wehr, 2021). Whiskers were filmed against a white background. Video timestamps were streamed into the multichannel electrophysiology interface at 20-kHz sampling. Eye and whiskers were filmed continuously to capture the spontaneously occurring REM episodes. We then extracted REM- or qWAKE-containing video segments based on the electrophysiological sleep scoring. To extract video segments, we delimited the camera timestamps within each electrophysiological epoch and indexed the corresponding frames in the original video file.

Facial movements were tracked using DeepLabCut (DLC) (Nath et al., 2019). For network training, we provided DLC with frames representing a diversity of video scenarios. Once representative frames were selected, eyelids and pupil were tracked in the form of moving octagons. Whiskers, as well as nose and mystacial pad, were tracked as moving lines (Fig. 2A). DLC data were then submitted to custom analysis (see below). Problematic videos were excluded. DLC data were then measured as follows. Eyelid opening: vertical distance between upper and lower eyelids followed by moving average. Pupil diameter: horizontal distance between the anterior-most and posterior-most pupil vertices. Saccading: speed of the dorsal-most pupil vertex, calculated as the shift between adjacent frames divided by the time between frames. Blinking: raw eyelid opening curve minus its moving average. Whisking: same speed calculations used for saccading but from the multiple vertices on the whiskers.

Saccading, blinking, and whisking curves suggested alternation between movement bursts and quiescence (Fig. 2B). We captured this alternation using peak envelopes (2-s window), which were then examined for their distributions across normalized scales (Fig. 2C). Normalization was achieved by jointly rescaling duration-matched REM-qWAKE epochs from 0 to 1.

### *2.4.6 Theta activity*

For each REM and qWAKE epoch, we generated a wavelet theta-band spectrogram (5 to 10 Hz). REM-qWAKE spectrogram pairs were jointly Z scored along the frequency dimension

(Fig. 3C). Wavelet spectrograms yielded two separate measures of theta activity: frequency and power. They were respectively calculated using maximum-energy time-frequency ridges and frequency bin averaging. Specifically, 10 ridges were extracted per spectrogram (Fig. 3D). This allowed us to compare REM and qWAKE in terms of ridge contiguity. To translate this contiguity into a single curve, ridges were divided by their mean variance and averaged (Fig. 3 E, Top and Center). Resulting curves were negatively weighted by ridge variance. In turn, theta power fluctuations were obtained by vertically averaging spectrograms. Ridge and power curves were detrended one epoch at a time and Z scored within REM-qWAKE pairs, generating stationary curves (Fig. 3E).

Theta frequency and theta power fluctuations were observed to occur in cycles of several seconds and therefore were examined for infraslow periodicity using Welch's PSD (3-min Hamming window, 50% overlap; 0 to 0.15-Hz band). The same data were examined for distribution bimodality. These analyses were all made in epochs longer than 60 s and resulted in Fig. 3 F and G.

### *2.4.7 Combined video and electrophysiology*

We examined the timing of facial movements in relation to infraslow cycles. First, video data were upsampled to match the electrophysiology sampling rate (125 Hz). Spike-like facial movements were then thresholded into timestamps (Fig. 4D) (Lerma & García-Austt, 1985). Next, infraslow fluctuations were Hilbert-transformed into phase angles, which were indexed by movement timestamps and analyzed as polar histograms (Fig. 4 E and F).

### *2.4.8 Neuronal activity*

Infraslow fluctuations were Hilbert-transformed and subdivided into 45° steps, creating eight subepochs per infraslow cycle. Specifically, each phase value of the transforms was rounded to 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°, or 360°, whichever was closest (Fig. 5A). Values rounded to 360° were assigned to 0°, resulting in eight infraslow phases (Fig. 5B).

Neuronal spikes were sorted from wideband data using Kilosort2 (Stringer et al., 2019). Parameters: minimum firing rate per channel = 0.1 Hz, threshold = [10 4], lambda = 10, area under curve = 0.9. This was followed by manual curation of neuronal units using Phy. Spiking was quantified across mice in the form of phase histograms combining all units followed by Rayleigh tests (Fig. 5F). Additional distinction was made between putative excitatory and

inhibitory neurons based on firing rates and spike widths (putative inhibitory: faster firing, narrower spikes) as described in previous studies (Watson et al., 2016; Stark et al., 2013).

### *2.4.9 Assembly analysis*

We also investigated whether neuronal assembly activity changes with REM infraslow cycles (Fig. 6). Assembly activity was detected using a published method (Lopes-dos-Santos et al., 2013). For assembly detection, we converted REM epochs into spike count matrices with 100-ms bins and Z scored these matrices across time. We then examined neuronal units in a pairwise manner. For each pair of units, (1) the linear correlation was used to populate a correlation matrix for each session and (2) the principal components were extracted. For pairs whose activity is uncorrelated, the variance along each principal component has an upper bound defined by the Marčenko–Pastur distribution. Variances exceeding this bound were taken to indicate principal components that violated this null hypothesis of independent activity and were therefore statistically significant. This yielded 90 assemblies in REM across mice. The standardized spike matrix was projected onto the subspace defined by the significant principal components to reduce its dimensionality. Then, independent components were extracted via fast ICA. The independent components attribute large weights to select units, defining that assembly pattern.

Following assembly detection, assembly activity was calculated as the weighted sum in each 100-ms bin of the spike matrix. This temporal resolution allowed us to sub-epoch assembly activity into the eight coarse infraslow phases, as illustrated in Figure 6A. The mean assembly activity in each infraslow phase was then plotted to form violin distributions (Fig. 6B-C). Each distribution yielded a mean coactivation strength value. These values were observed to fluctuate across infraslow phases, and thus we correlated them against sinusoidal fits. Each sinusoidal fit was determined by setting the period equal to that of the infraslow oscillation (nine phases, corresponding to the full 180°–180° cycle), vertical shift equal to the mid-range of the fluctuation, and amplitude equal to half the range. The phase shift was varied from 0 to $2\pi$ in 100 increments, and the value that yielded the greatest correlation between the sinusoid and the fluctuation was used.

### *2.4.10 Statistical analysis*

The distributions of enveloped eye and facial movements as well as physiological fluctuations were examined for bimodality using Hartigan's test. To compare infraslow PSD curves from REM and qWAKE, we used two-way ANOVA (frequency bins as repeated measures) followed by Tukey's post hoc tests. Circular statistics consisted of Rayleigh tests with Bonferroni correction. Comparisons between infraslow categories 0° and 180° were also quantified using two-way ANOVA (with depths as repeated measures) followed by Tukey's post hoc tests.

## 2.5 Results

### *2.5.1 Sleep recording in mice*

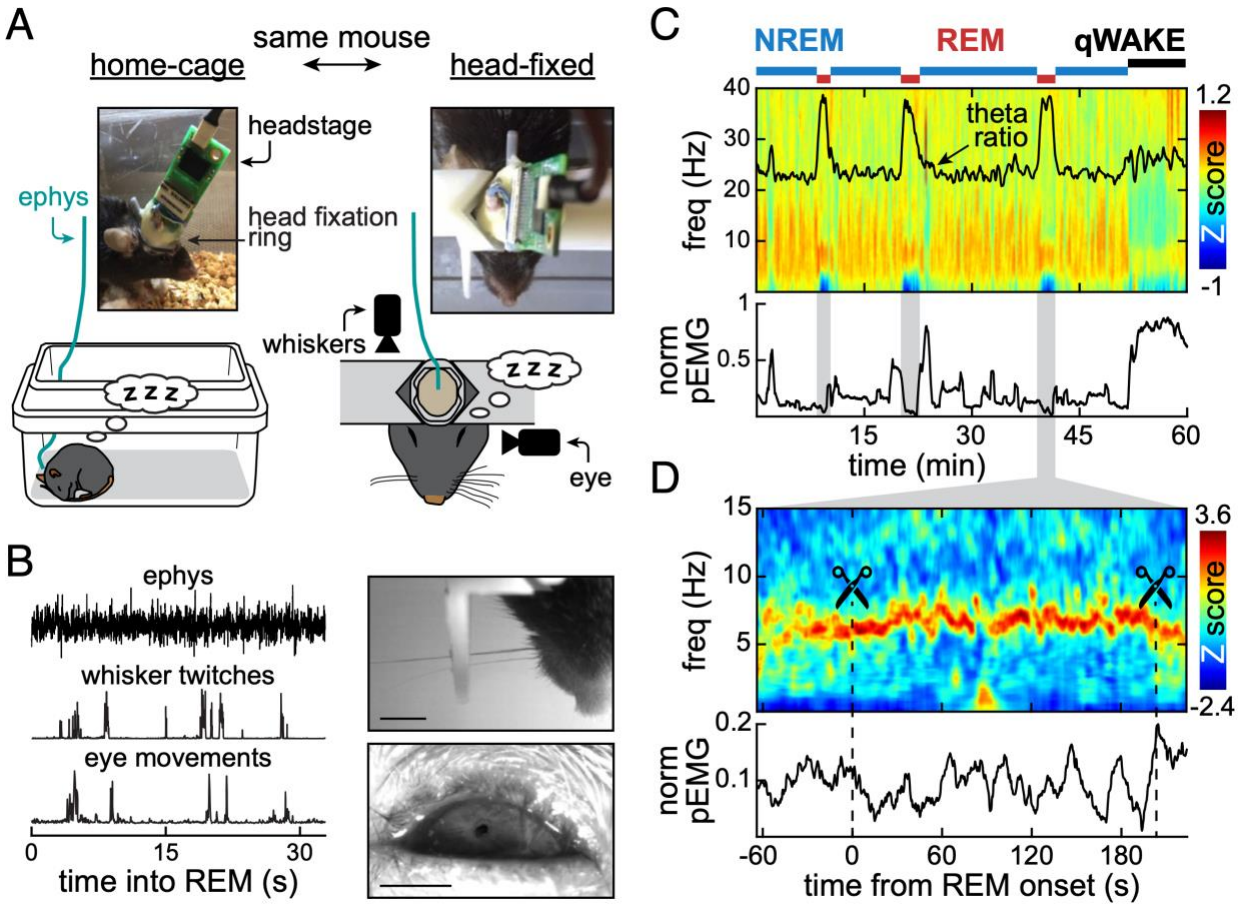


Figure 1: Flexible freely moving and head-fixed sleep recording with REM epoching in mice. (A) Mice were prepared for chronic electrophysiology by implanting a silicon probe (one shank, 64 channels) and a 3D-printed head-fixation ring so that mice could be transferred between home-cage and head fixation setups, the latter including cameras for eye and whiskers. Implants were made in barrel cortex and hippocampus. (B) Left: alignment of LFP and rapid movements. Top Right: untrimmed whiskers with somatotopic correspondence to the implanted area. Scale: 3 mm. Bottom Right: head-fixed eye imaging using infrared reflectance thanks to the incomplete eyelid closure we typically observed during sleep, as in previous studies (Yüzgeç et al., 2018; Tsunematsu et al., 2020; Sattler & Wehr, 2021). Scale: 1 mm. (C) Sleep scoring in 1-s bins (Grosmark et al., 2012; Watson et al., 2016;

Schomburg, 2014). REM epochs were extended to include 30- to 60-s margins. (D) REM margin trimming at higher temporal resolution, emphasizing intra-REM fluctuations. Sleep and REM occurred in both freely moving and head-fixed preparations

We developed a dual-mode recording system, so that the same mice (n = 6) could be transferred between freely moving and head-fixed setups (Fig. 1 A and B). Head fixation allowed us to quantify eye and whisker movements during REM in conjunction with brain electrophysiology, similar to a previous study (Yüzgeç et al., 2018). Additionally, electrophysiologic recordings in both head-fixed and freely moving mice allowed us to cross-validate REM characteristics between preparations. Using local field potentials (LFP) and LFP-derived electromyogram (here called pseudo-electromyogram, or pEMG), we produced spectrograms with 1-s bins (Fig. 1C) (Grosmark et al., 2012; Watson et al., 2016; Schomburg, 2014), from which we identified REM epochs. REM epochs were then reanalyzed as higher resolution wavelet spectrograms (125 Hz), allowing us to precisely trim the margins of each REM episode (Fig. 1D). REM epoch trimming was important to rule out state transitions, thus emphasizing intra-REM fluctuations (Fig. 1D). Electrophysiologic recordings were made from the barrel cortex and hippocampus using 64-channel linear probes, with somatotopic whisker-barrel correspondence.

We also obtained wake epochs for comparisons with REM. These epochs were mainly characterized by intermediate theta ratio relative to REM and non-REM sleep (Fig. 1C). This study did not involve theta-potentiating interventions such as behavioral tasks or stimuli, so here we conservatively refer to our wake epochs as quiet WAKE (qWAKE). These qWAKE comparators provide context for the mouse analyses in Figs. 2–4, aiming at a transparent explanation of our algorithms and their outcomes.

### *2.5.2 Rapid movements suggest bimodal temporal structure in mouse REM*

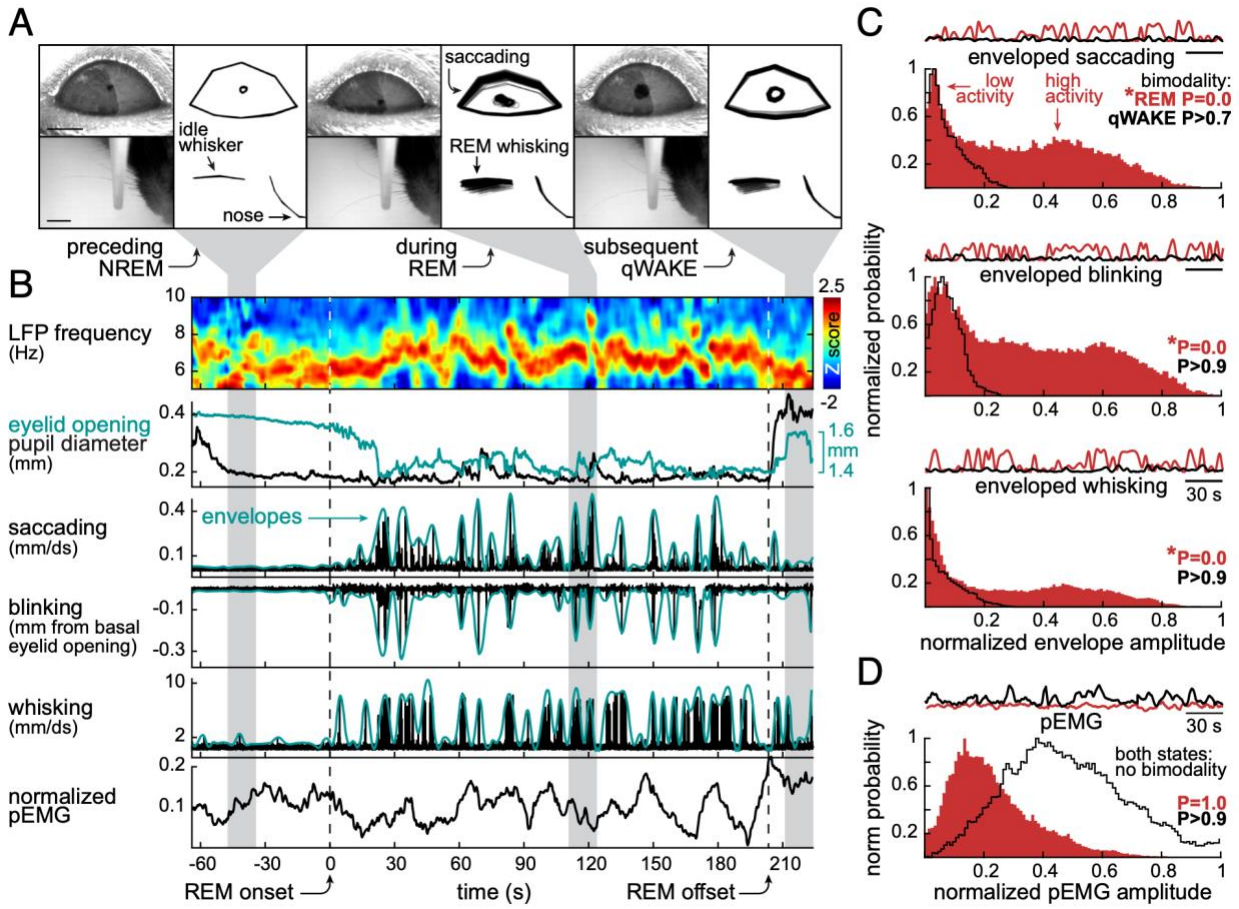


Figure 2: Rapid movements suggest bimodal temporal structure in mouse REM. (A) Facial movements were tracked using DeepLabCut (Nath et al., 2019). Scale bars: 1 mm (eye/pupil) and 3 mm (whisker). (B) Time-locked electrophysiology and videography. Bursts of saccading, blinking, and whisking events were captured using peak envelopes. (C) Distributions of envelopes. REM-qWAKE epoch pairs were jointly normalized, as represented by the curves at the top of each subplot. Data were examined for bimodality (Hartigan's test; see P values). All distributions were bimodal in REM, suggesting alternation between REM substates. (D) Similar analysis but from pEMG, which was higher in qWAKE than REM due to the postural atonia in REM. No bimodality was found in pEMG.

Fig. 2A illustrates eye and whisker tracking using DeepLabCut (Nath et al., 2019). Notable is the incidence of movements in REM and qWAKE but not in non-REM sleep (NREM). Additionally, partial eyelid opening and smaller pupil diameter were observed during sleep, replicating prior studies (Yüzgeç et al., 2018; Tsunematsu et al., 2020; Sattler & Wehr, 2021).

Fig. 2B illustrates the alignment of electrophysiologic spectrograms (theta band) and pEMG with video-derived measures. Here, we focused on saccading, blinking, and whisking. These exhibited spike-like bursts, as in previous studies (Massot et al., 2019; Meng et al., 2021;

Sánchez-López & Escudero, 2011; Sánchez-López & Escudero, 2015). We captured these bursts using peak envelopes (Fig. 2B).

Enveloped facial movements were examined for bimodality of distribution, with the hypothesis that periods with high and low motor activity would form two modes suggestive of phasic/tonic-like REM microstates. qWAKE movements were used as controls. Envelopes from REM and qWAKE epochs were thus normalized together, resulting in the common X-axes of Fig. 2C. Joint REM-qWAKE normalization was also important to homogenize video-based measures across recordings. All facial movement measures were bimodal in REM but not qWAKE, suggesting microstates (Fig. 2C). We also analyzed pEMG (Fig. 2D), and no significant bimodality was found. pEMG was also lower in REM, consistent with REM atonia (Chase, 2013; Burgess et al., 2008).

Thus, enveloped facial movements in mouse REM formed bimodal distributions. This supports the existence of two REM microstates, at least by facial movement metrics.

### *2.5.3 Theta frequency fluctuates continuously at an infraslow frequency during mouse REM*

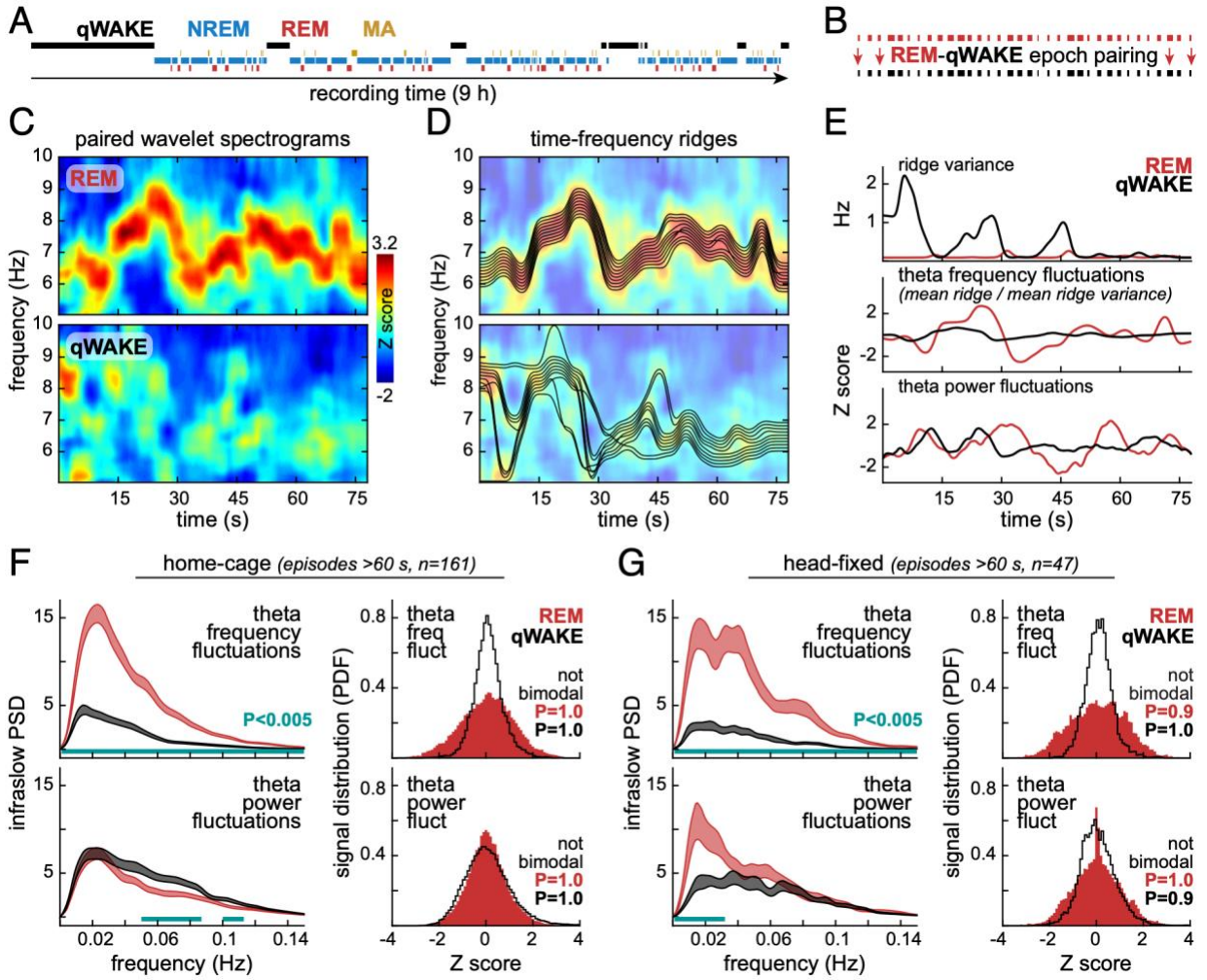


Figure 3: Theta frequency fluctuates continuously at an infraslow frequency during mouse REM. (A) Hypnogram from a home-cage session. MA: microarousals. (B) For each REM epoch, we extracted a duration-matched qWAKE epoch from the same hypnogram. (C) Theta-band spectrograms from a REM-qWAKE pair. Theta activity was more organized in REM. (D) Same pair of spectrograms in (C) overlaid with time-frequency ridges. REM ridges were mostly adjacent to each other, unlike qWAKE ridges. (E) Separate examination of theta frequency and theta power. Top: variance from the ridges in (D). Center: ridges were averaged, divided by their variances, and Z scored within each REM-qWAKE pair. Bottom: theta power from the same spectrograms. The resulting fluctuations showed waves lasting several seconds, suggesting infraslow rhythms. (F) PSD and distribution of infraslow fluctuations. Data from all home-cage sessions are shown (312 REM-qWAKE pairs, six mice). Infraslow PSD was stronger in REM theta frequency fluctuations. We found no evidence of phasic/tonic-like bimodality. (G) As in (F), but from head-fixed data (76 REM-qWAKE pairs, six mice).

However, Fig. 3 shows that the frequency of theta-band LFP oscillations fluctuated continuously without discrete microstates. Interestingly, we found this fluctuation to occur in approximately 1-min cycles.

As depicted in Fig. 3 A and B, each REM epoch was paired with a duration-matched qWAKE epoch from the same recording. Fig. 3C contains a representative REM-qWAKE pair, shown as theta-band spectrograms from hippocampal LFP. REM showed stronger frequency-

varying patterns (Fig. 3C), which were quantified using a time-frequency ridge algorithm. As shown in Fig. 3D, ridges were more contiguous in REM, leading to lower ridge variance in REM (Fig. 3 E, Top). To quantify the consistency of theta frequency—not theta power—in REM versus qWAKE, multiple ridges were detected per spectrogram, the strongest first. Ridges were then averaged and divided by their variance before being detrended and Z scored into minute-scale fluctuations (Fig. 3 E, Center). We then separately measured theta power. Spectrograms were averaged vertically resulting in band power curves, which were also detrended and Z scored. We again observed minute-scale fluctuations (Fig. 3 E, Bottom).

The epochs in Fig. 3E suggested predominant rhythms around 0.1 Hz, i.e., infraslow band (Lecci et al., 2017; Mitra et al., 2018; Osorio-Forero et al., 2021; Watson, 2018). These rhythms seemed stronger in REM theta frequency. To quantify this, we selected REM-qWAKE epochs longer than 1 min and performed a spectral analysis using a minute-scale sliding window. We then constructed power spectral density (PSD) plots (Fig. 3 F and G). REM indeed showed stronger infraslow PSD of theta frequency fluctuations in both home-cage ($F_{1,320} = 255.18$, $P = 1.2*10^{-42}$) and head-fixed data ($F_{1,92} = 158.73$, $P = 9.69*10^{-22}$). The difference in the infraslow PSD of theta power fluctuations was less significant between REM and qWAKE (home-cage: $F_{1,320} = 23.86$, $P = 1.64*10^{-6}$; head-fixed: $F_{1,92} = 6.09$, $P = 0.015$). We then interrogated whether theta activity varies continuously or in a bimodal manner. Evidence of bimodality would match our previous observations on facial movements (Fig. 2C) and corroborate phasic and tonic microstates in REM. However, we found no bimodality (Fig. 3 F and G).

Therefore, theta frequency variations during REM may be a manifestation of infraslow rhythms, which we believe to entail fluctuations, rather than bimodal flipping. This stands in contrast to the binary facial movement data, which we address below.

#### *2.5.4 REM facial movements in mice preferentially accompany theta frequency fluctuations*

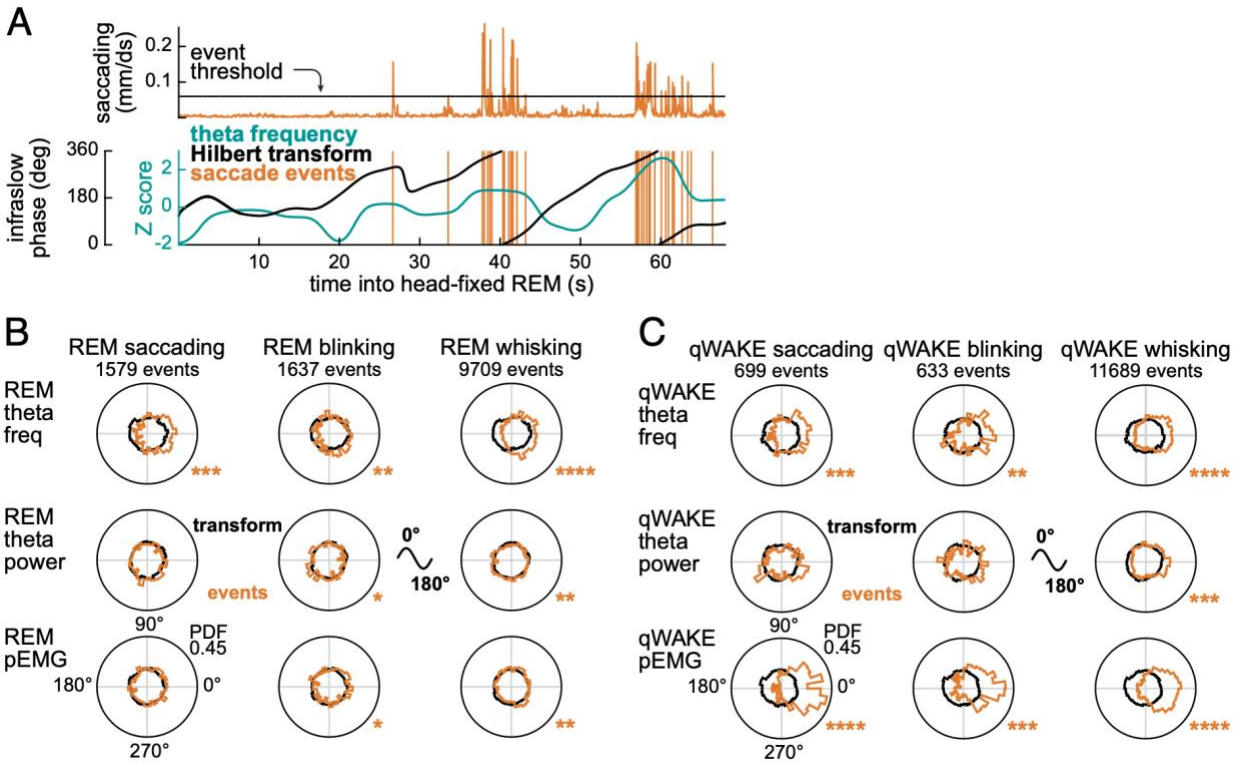


Figure 4: REM facial movements in mice preferentially accompany theta frequency fluctuations. (A) Facial movements were thresholded into timestamps and examined for phase relationships with Hilbert-transformed infraslow fluctuations. (B) Polar histograms from the head-fixed dataset showing phase relationships between REM facial movements (columns) and infraslow signals (rows). Rayleigh tests: *P < 0.0028, **P < 10−8, ***P < 10−25, ****P < 10−66. REM facial movements showed preference for the peaks of theta frequency cycles, i.e., faster theta. (C) In qWAKE, facial movements showed preference for the peaks of both theta frequency and pEMG cycles.

In Fig. 4, we examined facial movements for phase relationships with infraslow fluctuations. First, facial movements were thresholded into timestamps at the electrophysiology sampling rate (125 Hz; Fig. 4 A, Top), similar to a previous study (Lerma & García-Austt, 1985). Based on such timestamps, we extracted phases from Hilbert-transformed fluctuations (Fig. 4 A, Bottom). Fig. 4 B and C shows that REM facial movements showed strongest phase modulation by theta frequency (Fig. 4B). The same was found in qWAKE, which additionally showed relationships to pEMG phase (Fig. 4C). Theta power distributions were more uniform. All phase relationships were aligned with the peaks of infraslow cycles (zero degrees).

Thus, facial movements were more likely to occur in periods of faster theta frequency (both REM and qWAKE) and higher pEMG (qWAKE only). This reconciles our results of bimodally distributed facial movements (Fig. 2) and unimodally distributed theta frequency (Fig. 3).

### *2.5.5 Spiking accompanies the infraslow structure of mouse REM*

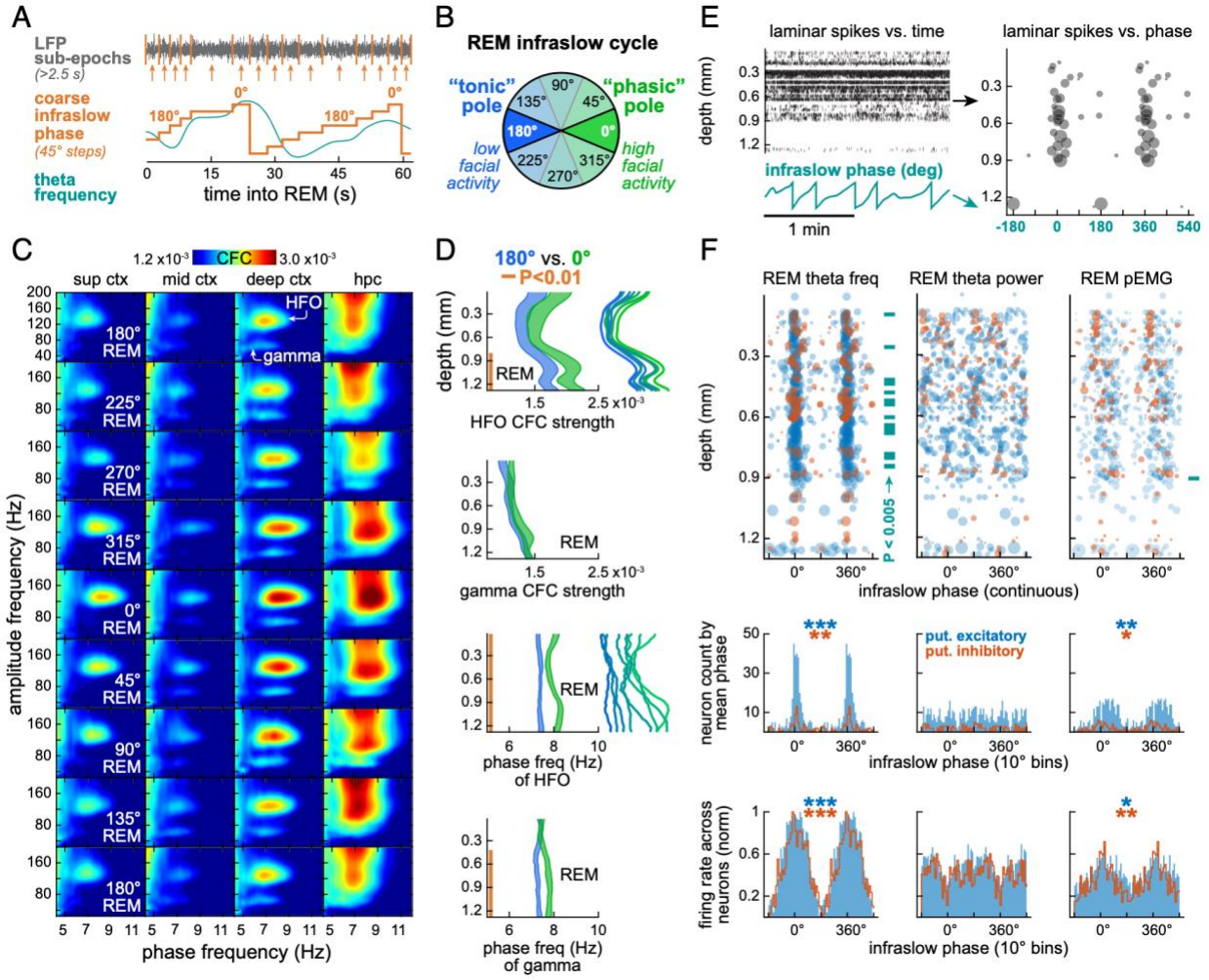


Figure 5: Laminar LFP and spiking accompany the infraslow fluctuation of theta frequency in mouse REM. (A) Infraslow phases from theta frequency fluctuations were coarsened into 45° steps. These were used to subdivide the LFP for the analysis in (B, C, and D). (B) Interpretation of extreme infraslow phases 0° and 180° as the "phasic" and "tonic" poles of REM, respectively, based on Fig. 4. (C) Phase-amplitude CFC between theta and faster oscillations (gamma and HFO) (Brankačk et al., 2012; Scheffer-Teixeira & Tort, 2017). This qualitative analysis was made at four representative depths. (D) Full laminar profiles of CFC measures comparing 0° and 180°. Shaded curves show the variation from all home cage sessions. Insets illustrate the continuity between 0° and 180°. (E) Graphical explanation on the analysis in (F). Laminar spikes were examined for phase relationships with infraslow fluctuations. (F) REM theta frequency showed the strongest phase relationships with laminar spiking. P values on the right of each scatter plot illustrate depth variations. Neuron count histograms (10° bins) suggest discrete transients around the 0° mode. However, firing rate histograms (10° bins) show no such transients, suggesting underlying smooth fluctuations in firing rates. Asterisks indicate Rayleigh tests (*P < 10−2, **P < 10−7, ***P < 10−21).

Spiking is known to vary across brain states (Watson et al., 2016). Thus, we investigated if spiking also varies within the REM structure (Fig. 5 E and F).

This analysis involved phase relationships with three physiologic fluctuations in REM (theta frequency, theta power, and pEMG). Specifically, spiking across depths was used to index

into the Hilbert transform from a given infraslow fluctuation (Fig. 5 E, Left), resulting in one circular distribution per neuronal unit. We then calculated the mean phase and mean resultant length (MRL) per unit, resulting in depth versus phase scatter plots (Fig. 5 E, Right), with MRL being represented by circle diameters, for illustration. Fig. 5F shows similar scatter plots from all mice, along with the strength of phase preference per depth (see Rayleigh tests on the right of each scatter plot), suggesting some laminar heterogeneity. We then quantified these data using two types of histograms: neuron counts and multiunit firing rates, both in 10° bins of infraslow phases. Neuronal units were additionally sorted into two cell classes—putative excitatory and inhibitory—based on waveform widths and intrinsic firing rates (Watson et al., 2016). We found that the strongest circular modes were related to REM theta frequency (Fig. 5F), regardless of cell class. The neuron count histograms suggest a sharp mode around 0°. In contrast, the firing rate histograms show rather smooth distributions, indicating that continuous firing rate fluctuations underlie the scatter plot and neuron count patterns.

Thus, laminar spiking was modulated by REM theta frequency, with firing rates being commensurate with theta frequency. Overall, our mouse data demonstrated that the infraslow structure of REM affected a range of brain and body signals, from facial motricity and field oscillations to oscillatory coupling and neuronal activity.

### *2.5.6 Coordinated spiking accompanies the infraslow structure of mouse REM*

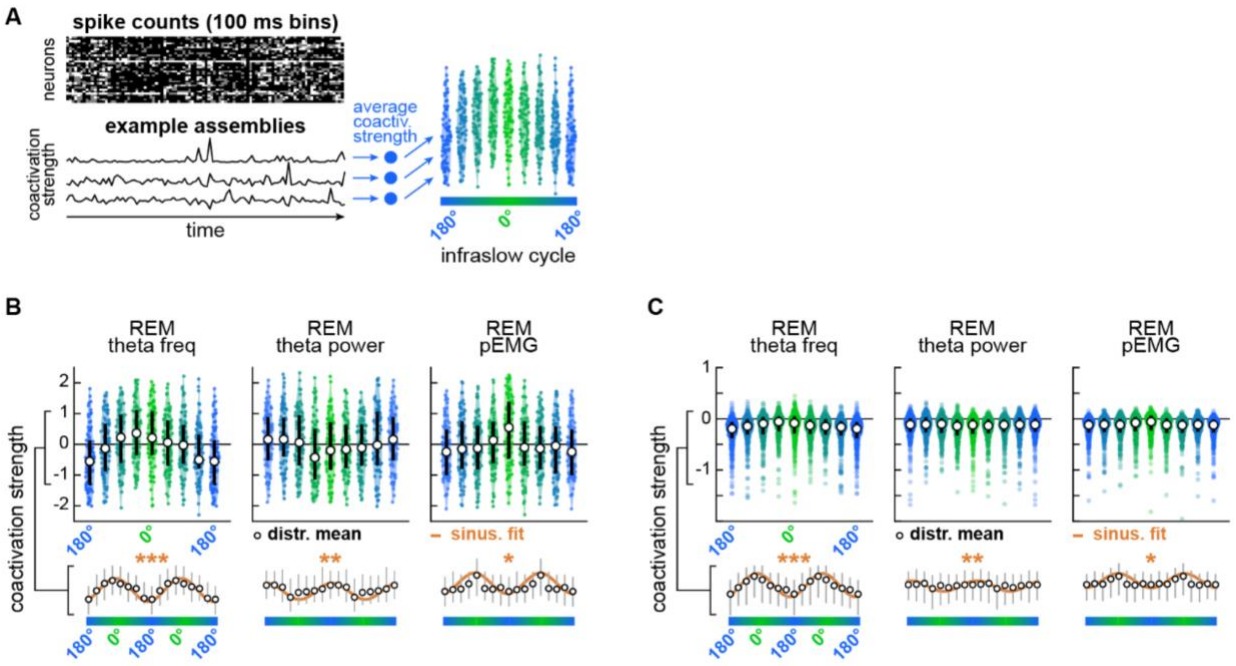


Figure 6: Assembly analysis corroborates REM theta frequency as an important driver of spiking in mouse REM. (A) Spikes count matrices from REM were used for cell assembly detection, using a Hebbian-inspired ICA-based method from a previous study (Lopes-dos-Santos et al., 2013). Assembly curves were sub-epoched into coarse infraslow phases, averaged into coactivation strength values and analyzed in (B). (B) REM theta frequency fluctuations were associated with sinusoid-like fluctuations in assembly activity, confirmed by Pearson's correlations between sinusoidal fits and mean coactivation strengths (*P < 10-3, **P < 10-5, ***P < 10-7). This is consistent with the firing rate data in Figure 5F, suggesting relationships between firing rates and co-activation strengths (which we did not explore further). (C) Alternative assembly analysis. Cell assemblies from the same published method were detected within each infraslow phase, rather than within all of REM. This yielded a corresponding increase in the number of assemblies detected per session, roughly eightfold. So that coactivation strengths could be compared across assemblies detected in different infraslow phases, strength values in each phase were normalized as a log fold change relative to the value in the phase in which that assembly was detected. Results were similar to (A): the fluctuation in coactivation strength across infraslow phases was most sinusoidal relative to the fluctuation of REM theta frequency.

REM theta frequency fluctuations were associated with sinusoid-like fluctuations in assembly activity, confirmed by Pearson's correlations between sinusoidal fits and mean coactivation strengths (*P < 10-3, **P < 10-5, ***P < 10-7). This is consistent with the firing rate data in Figure 5F, suggesting relationships between firing rates and co-activation strengths (which we did not explore further).

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### 2.6 Conclusion

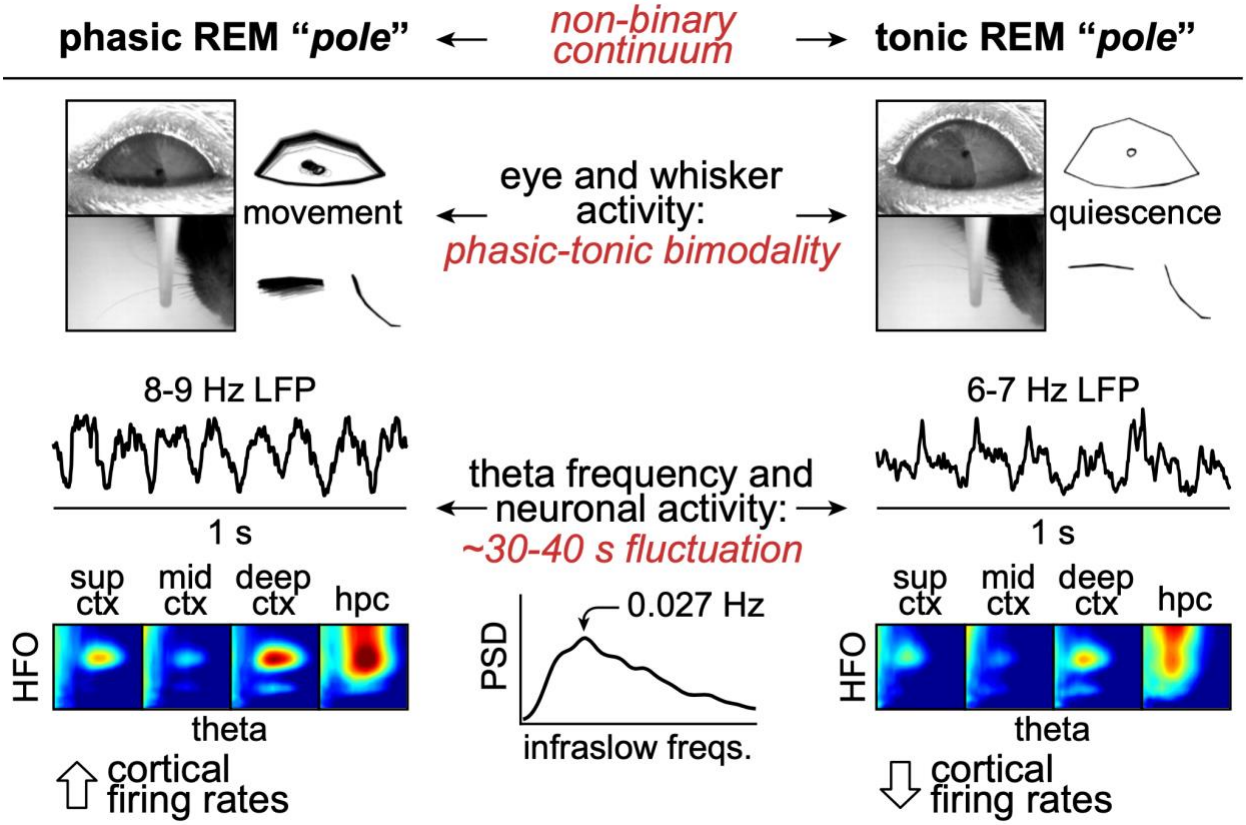


Figure 7: Summary of findings: evidence of a minute-scale continuum between phasic and tonic poles within REM sleep. REM showed phasic/tonic-like bimodality in eye and whisker activity accompanying continuous fluctuations in theta frequency, theta-HFO CFC, and firing rates in hippocampus and neocortex. These fluctuations occurred in cycles of approximately 30 to 40 s.

Our study advances the understanding of REM structure by clarifying that brain and body signals within REM are heterogeneous in terms of temporal statistics, with some signals indicating discrete phasic/tonic microstates (facial and oculomotor activity) and others showing nondiscrete continuous variation (theta frequency). Despite this paradox, we find that these two types of signals co-occur on an infraslow timescale (<0.1 Hz) and are correlated. This suggests that approaching REM at this time scale will be more efficient at characterizing REM signals—be they binary or not—than dismantling intra-REM rhythms into phasic and tonic subepochs. Opportunities for basic or clinical research may arise by leveraging the periodicity of REM

structure, whose alterations may be linked with brain disorders. See Fig. 7 for a summary of our results.

## 2.7 Discussion

### *2.7.1 Theoretical context*

Human REM is traditionally subdivided into phasic (high motor activity) or tonic (low or absent motor activity) periods, which can be compared in terms of dreaming, arousability, and brain activity patterns (Ermis et al., 2010; Koroma et al., 2020; Sallinen et al., 1996; Takahara et al., 2002; Wehrle et al., 2007; Simor et al., 2018; Simor et al., 2019). This phasic/tonic dichotomy is built upon research in laboratory animals, whose phasic REM periods can be additionally distinguished by the presence of pontine waves (P-waves). P-waves are discrete waveform patterns that originate in the brainstem and may serve as pacemakers in several brain states (Tsunematsu et al., 2023; Gott et al., 2017). REM sleep is the state that is more typically associated with P-waves (Gott et al., 2017), partly because of the relationship between P-waves and another marker of nonhuman REM: theta oscillations. Through ascending neuromodulatory projections, including cholinergic ones (Datta et al., 1998), bursts of P-waves are known to accelerate theta in the septal-hippocampal rhythmogenic system (Karashima et al., 2001; Karashima et al., 2004; Karashima et al., 2005; Karashima et al., 2010; Buzsáki, 2002; Ramirez-Villegas et al., 2021; Steriade et al., 1990). P-waves in nonhuman REM are also known to co-occur with oculomotor activity (Steriade et al., 1990), inhibition of diaphragmatic activity (Dunin-Barkowski & Orem, 1998), and heart rate surges (Rowe et al., 1999). Thus, given the diversity of processes affected by P-waves, we can suggest that variations in P-wave rates may modulate the larger brain–body fluctuations we report in mice and humans, at least partially.

### *2.7.2 Practical implications for the study of REM temporal structure*

As contextualized above, most of our mechanistic knowledge of REM structure relies on P-wave data from laboratory animals, as we cannot easily record P-waves in humans (Gott et al., 2017). That knowledge includes relationships between P-waves and deeper processes we can manipulate in the laboratory, such as learning and synaptic plasticity (Mavanji & Datta, 2003; Mavanji et al., 2004; Datta et al., 2004). However, even in the laboratory, it is often more feasible to define phasic/tonic REM using more accessible signals, such as hippocampal and neocortical theta in rodents. This was the case in previous studies that used rodent theta

oscillations, not P-waves, to discretize REM (Mizuseki et al., 2011; Montgomery et al., 2008; Brankačk et al., 2012). In fact, theta oscillations have their own downstream roles in learning, plasticity, and a myriad of other forebrain processes (Buzsáki, 2002; Puentes-Mestril et al., 2019; Karakaş, 2020), so using theta oscillations to study REM structure makes sense both methodologically and biologically. This is also the case in the mouse portion of our study, which is also based on theta oscillations. However, here we avoided the bias of binary REM categorization. Instead, we analyzed REM theta in a data-driven manner, accompanied by facial videograp 2012hy, which is a relatively recent development in rodent sleep research (e.g., Yüzgeç et al., 2018; Tsunematsu et al., 2020; Sattler & Wehr, 2021). This resulted in the finding that theta frequency varies unimodally at infraslow frequencies, which in turn correlates with the bimodal incidence of eye and facial movements. This builds upon older studies that also recognized theta frequency variations in other mammalian models but did not quantify the periodicity of such variations or their correlations with myoclonic activity (Leung, 1984; Sakai et al., 1973; Sano et al., 1973).

We then studied human REM and found a similar infraslow structure involving oculomotor activity and underlying physiological signals. In our human data, however, the physiological signal best aligned with oculomotor activity was respiration rate. Interestingly, respiration rate was previously reported to correlate with theta frequency in mouse REM (Tort et al., 2021). This, along with our findings, has at least three implications. First, this infraslow REM structure may modulate—or be modulated by—several physiological fluctuations across brain and body, possibly orchestrated by common rhythm generators (for example, P-waves). Second, respiration rate combined with oculomotor activity could be a practical unifying measure of REM structure in humans and laboratory animals, as opposed to signals that are more accessible only in the laboratory, such as theta oscillations and P-waves. Third, binary classification of REM subepochs based on presence/absence of transient signals (e.g., P-waves or rapid movements) may force the discretization of continuous processes elsewhere in the brain and body. For example, several higher order processes are known to depend on REM, including sleep homeostasis, synaptic plasticity, and the stages of memory consolidation (Montgomery et al., 2008; Watson et al., 2016). Can we discretize such processes into phasic and tonic periods without distortions?

Thus, the phasic/tonic REM dichotomy may be distracting us from broader questions. For example, according to our human data, signals from brain and body fluctuate in different infraslow phases relative to each other: Are these phase shifts predictable and quantifiable? Are REM infraslow fluctuations stereotypically driven by brainstem pacemakers or by feedback loops involving respiration rate? Periodicity analyses or more granular (i.e., nonbinary) REM discretization methods such as the one proposed here may help us investigate these questions.

### *2.7.3 REM structure as a manifestation of infraslow rhythms*

Infraslow rhythms are biological fluctuations with frequencies between 0.01 and 0.1 Hz. These fluctuations are intrinsic to several phenomena, including heart rate, EEG power, and functional imaging signals (Lecci et al., 2017; Picchioni et al., 2011). Infraslow rhythms are of increasing interest among neurophysiologists studying both sleep and waking behavior (Watson, 2018). In fact, both resting-state networks and cognitive performance in humans are modulated at the infraslow timescale (Biswal et al., 1995; Fox & Raichle, 2007; Monto et al., 2008; Gutierrez-Barragan et al., 2019; Sihn & Kim, 2022). Additionally, markers of NREM sleep (including thalamic noradrenaline and sleep spindles), as well as oscillatory sequences during WAKE in medial entorhinal cortex (involved in episodic memory formation), are all coordinated at infraslow periodicity (Lecci et al., 2017; Osorio-Forero et al., 2021; Cogno et al., 2022). Here, we incorporate REM sleep into that context. Two previous studies had actually noted minute-scale periods in human REM: one EOG study reporting that the density of rapid eye movements fluctuates at about 2-min intervals (Ktonas et al., 2003), and a functional imaging study describing infraslow fluctuations in resting state network signals during REM (Chow et al., 2013). Our work, however, explicitly demonstrates the infraslow periodicity in REM through interspecies comparisons and the use of several controls, including phase relationships between physiological signals and rapid movements.

Since we implanted linear probes across neocortical layers and the hippocampus in mice, we were also able to map electrophysiological measures onto both a spatial (laminar depths) and temporal continuum (REM infraslow subepochs). We found that theta-HFO coupling is optimal at a particular location (deeper channels in the neocortical-hippocampal profile) and timeframe (phasic REM pole). This links two previous studies that separately analyzed the dependency of phase-amplitude coupling on the anatomical depth (Scheffer-Teixeira & Tort, 2017) or binarily classified REM microstates (Brankačk et al., 2012). In addition, we observed that the infraslow

structure of REM affects laminar firing rates, which were higher around the phasic REM pole. This is possibly consistent with the notion that phasic REM promotes coordination of neural activity (Montgomery et al., 2008). All these processes can now be examined under the infraslow time metric, which will potentially optimize the prediction of network function variations within REM, as well as their emergent properties, such as the stages of memory consolidation. Future studies could also formally examine the laminar anatomy of intra-REM fluctuations by assigning neuronal units to physiological layers, as done previously (Senzai et al., 2019). In addition, future studies could explore variations in the infraslow period, both across the duration of a single REM episode and across multiple REM episodes, potentially revealing the functional roles of these fluctuations in more detail.

### *2.7.4 Involvement of within-REM rhythms in development and sleep health*

What other benefits might intra-REM rhythms serve? One conception of REM comes from studies on its muscular twitches, which emerge developmentally as one of the first coordinators of neural activity in the young brain. REM twitches are hypothesized to enable sensorimotor feedback in infancy, thus promoting activity-dependent circuit sculpting in preparation for further plasticity later in life (Blumberg et al., 2013; Dooley et al., 2020; Sokoloff et al., 2020; Tiriac et al., 2012). Thus, early-life intra-REM rhythms may allow network tuning to internally versus externally driven activity in a cyclical manner, and the persistence of such cycling in adult REM may be important for circuit adjustments.

Healthy phasic-tonic cycling may also play roles for REM-related processes such as homeostatic effects on neuronal spiking (Grosmark et al., 2012; Watson et al., 2016), dreaming (Siclari et al., 2017), and consolidation of emotional memories (Vandekerckhove & Wang, 2018). In particular, overconsolidation of emotional memories, as in posttraumatic stress disorder, as well as major depression, have been proposed to involve alterations in REM sleep (Murkar & Koninck, 2018; Riemann et al., 2020). Furthermore, dysfunctional phasic and tonic muscle activity in REM sleep behavior disorder (RBD) predicts neurodegenerative disorders, such as Parkinson's disease (McCarter et al., 2014; Schenck et al., 1996; Louis et al., 2017). Also interestingly, abnormal separation between phasic and tonic REM, possibly indicative of dysfunctional intra-REM cycling, was found to predict the conversion to neurodegenerative disease from RBD (Nepozitek et al., 2019). Therefore, additional analytical methods to

characterize human REM, such as the ones proposed here, combined with accessible measures, such as respiration rate, may provide greater diagnostic information.

### *2.7.5 REM and depression*

Abnormalities in REM are a biomarker of depression. Individuals with depression enter REM more quickly (Kupfer & Foster, 1972) and exhibit extended periods of REM (Steiger & Pawlowski, 2019). REM abnormalities are a risk factor for depression (Palagini et al., 2013), and antidepressants suppress REM in a manner predictive of treatment response (Berger & Riemann, 1993), including to novel antidepressants like ketamine (Kheirkhah et al., 2025). This study of the structure of REM may thus improve depression detection and treatment.

## 2.8 Authors and Contributions

The paper that constitutes Chapter 2 was composed by Dr. Lezio S. Bueno, Jr, who also carried out the data collection and analysis of video and LFP data. MSR completed the spike sorting, analysis of spiking data, and analysis of assembly activity. All other writing in this work was composed by MSR. The manuscript that constitutes Chapter 3 was composed by MSR, who was also responsible for the normalization, statistical approach, and analysis of both LFP and spiking data. The data were collected by Dr. Brendon O. Watson.

## Chapter 3 The Effect of Ketamine on Gamma Power and Spiking across Substates of Wake

Manuscript currently under review

### 3.1 Depression

Depression is a debilitating psychiatric condition characterized by anhedonia, persistent sadness, physical and cognitive fatigue, and disruptions in sleep and appetite. It has an estimated prevalence of 8% among adolescents (Shorey et al., 2022) and 30% among older adults (Zenebe et al., 2021; Hue et al., 2022; Cai et al., 2023), with recent upward trends across the world (Moreno-Agostino et al., 2021). In terms of disability-adjusted life years, it has an estimated human cost of 350 years in males and 560 years in females (Li et al., 2022), making it the second-most burdensome mental health disorder after addiction. Addressing depression is thus a major priority in mental healthcare. However, roughly 30% of cases of depression prove resistant to conventional treatment (Voineskos et al., 2020; McIntyre et al., 2023). Moreover, these cases of treatment-resistant depression represent half of the total burden of depression in the United States, taking into account loss of productivity and direct health care costs (Zhdanava et al., 2021). There is an unmet need for improved treatments for depression, and creating deeper understanding of the mechanisms of novel treatments can lead us to more effective, consistent treatment options.

### 3.2 Ketamine as an antidepressant

Ketamine has a response rate of 60%, even in patients with treatment-resistant depression (Schwartz et al., 2016). Unexpectedly, ketamine exhibits not only a long-term effect but also an immediate one, with patients reporting improvements in mood and decreases in suicidal ideation within hours and lasting days (Marcantoni et al., 2020; Coyle & Laws, 2015). While ketamine's promise is now widely appreciated and under active refinement, we are limited by our lack of understanding of its underlying mechanism.

The multi-day effect of ketamine appears to be dependent on its immediate effect, which lasts on the order of hours (Moda-Sava et al., 2019). The immediate antidepressant effect of

ketamine is correlated with alterations in firing rate and neural oscillations in the PFC and in other brain regions that are mediated by glutamatergic activity (Zanos et al., 2016; Fuchikami et al., 2015; Hare et al., 2019; Cichon et al., 2023; Hare et al., 2020; Yang et al., 2018). This is also linked to glutamatergic activity increases in the PFC of patients (Abdallah et al., 2018). It is known that this immediate-term response to ketamine is not dependent on synaptic changes while the effect beyond 24 hours appears to be driven by plasticity in PFC (Moda-Sava et al., 2019), presumably due to Hebbian changes in response to the activity burst from the early-stage response (Zanos & Gould, 2018). Furthermore, despite the fact that immediate-term effects take hours to translate into synaptic changes, anti-depressant effects in humans and antidepressant-like behavioral effects in rodents span both the immediate and 24-hour+ timescales. This implies that the immediate-term effects of ketamine are antidepressant by themselves, and the synaptic effects may simply consolidate these changes in the subsequent days.

The immediate-term effects of ketamine are therefore of great interest since they are measurable, acute, and sufficient to lessen depression. Thus, understanding immediate ketamine effects represents a major goal in affective neuroscience since it can reveal network-electrophysiologic signatures of improved mood.

### 3.3 Ketamine and electrophysiology

A cross-species immediate-term signature of antidepressant-dose ketamine is an increase in gamma-band oscillations in electroencephalographic voltage recordings (in human) or LFP (in rodents) (Pinault, 2008; Amat-Foraster et al., 2018; Lazarewicz et al., 2010; Furth et al., 2017). This increase is thought to reflect changes in the coordinated spiking of cortical pyramidal neurons, since that is the means by which cortical gamma oscillations are induced (Keeley et al., 2019; Adesnik & Scanziani, 2010; Lu et al., 2015). Therefore, gamma oscillations after ketamine dosing are consistent with induction of ketamine-like effects after either optogenetic activation of pyramidal neurons (Fuchikami et al., 2015; Hare et al., 2019), or blockade of ketamine effects by AMPA blockade (Moda-Sava et al., 2019). This broad-scale prefrontal activation may then both create the short-term changes in mood and behavior and, through plasticity defined by basic fire-together-wire-together Hebbian mechanisms, drive the long-term changes in connectivity that define remission.

## 3.4 Experimental goals and design

We lack, however, a characterization of activity changes post-ketamine at the level of individual neurons in neocortex. This is because many studies do not use high-resolution single-neuron spiking recordings.

Understanding how short-term activity changes in individual neurons correlates with short-term behavioral/antidepressants may open a direct door to targeting neuronal activity to modulate depression at any timescale. More specific pharmaceuticals or direct circuit manipulation methods may be revealed by such investigations.

Our approach is to measure the effect of antidepressant-dose ketamine on oscillatory and single-unit activity using silicon probes to record in prefrontal cortex while animals are in baseline condition followed by treatment with ketamine or saline control.

## 3.5 Methods

### *3.5.1 Animals and treatment*

All experimental protocols were approved by the Institutional Animal Care and Use Committees of New York University and Weill Cornell Medical College. Recordings took place 2013–2016. A total of 4 Long-Evans rats were used, all male and weighing 250–400 g at the time of surgery. All animals were implanted in prefrontal neocortex, either medial PFC (mPFC) or anterior cingulate cortex (ACC). Probes were from NeuroNexus and had 5–8 shanks each with a total of 64 channels, mounted on drives (Vandecasteele et al., 2012). mPFC coordinates were: bregma AP +1.5 mm, ML 0.5 mm, and DV 2.5 mm. ACC coordinates were identical save for DV 1.0 mm. Screw-based driving was performed if unit yields were low. No driving was performed within 16 hours of a recording.

Animals were injected intraperitoneally with either 10 mg/kg ketamine in ~0.5 mL saline (based on weight and concentration of diluted solution) or, as control, an equivalent volume of either saline or MK801, an NMDAR antagonist that does not reproduce the sustained antidepressant effect of ketamine.

### *3.5.2 Electrophysiology*

Recordings were performed at 20 kHz with either Amplipex or Intan RHD2000 and Intan headages. Recordings began at approximately 10:00 and lasted at least 30 hours in the homecage of the rat, with the rat unperturbed except for an injection of ketamine or saline control. All rats

had been previously handled and had a day of homecage recordings prior to the experiment recordings so that they would be accustomed to the homecage while plugged in.

The first 6+ hours of each recording were pre-injection control periods, then either ketamine or saline control was administered. Then a post-injection 24 hours of recording were performed, lasting until 16:00 the day after recording start. Recordings were manually started and stopped approximately every 2 hours and were concatenated for spike sorting and sleep scoring. These intermissions were primarily <10 seconds in duration, the exception being <5-minute breaks for injection of ketamine or control as the animal had to be removed from the homecage recording setup. Timestamps were recorded for every intermission and injection.

### *3.5.3 Data preprocessing*

Using MATLAB scripts, all 20-kHz files were processed in three streams. First, they were low-pass filtered and down-sampled to 1250 Hz for LFP and sleep state analysis. 60-Hz noise and harmonics of it were excised where prominent.

Second, a measure of EMG was derived from LFP by calculating Pearson correlation across shanks in the 300–600-Hz band in 0.5-s bins. This correlation has been validated as a measure of EMG (Watson et al., 2016). LFP and this LFP-derived pseudo-EMG (pEMG) were used to sleep-score 1-second bins of each recording into wake, non-REM, or REM: First, non-REM was distinguished based on low power spectral slope (relatively high delta and low gamma). Then, REM was parsed from wake based high theta/delta ratio (specific to REM and wake) coincident with low pEMG (during wake, high theta/delta usually happens during movement). State scoring was initially performed with SleepScoreMaster.m (https://github.com/buzsakilab/buzcode/tree/master/detectors/detectStates/SleepScoreMaster) and manually curated with TheStateEditor GUI (https://github.com/buzsakilab/buzcode/tree/master/GUITools/TheStateEditor).

The third stream used the wide-band data for spike sorting. Data were fed into KlustaKwik (Kadir et al., 2014) for automated initial clustering. Adjustments to RAM were made to allow the 30-hour recordings to be processed. Klusters (Hazan et al., 2006) was then used for manual curation of the automated sorting output.

Spikes and LFP were then imported into Buzcode format using the buzcode toolbox (https://github.com/buzsakilab/buzcode/tree/master/preprocessing/amplipexToolbox) for further processing. At this stage, the brief intermissions in each concatenated recording were padded

with null values using the recorded timestamps. Additionally, brief (<10-s) periods of high-power noise (for example, due to the animal bumping its head against a wall) were replaced with null values.

### *3.5.4 LFP analysis*

Bands of interest were defined based on literature as delta (0.5–4 Hz), theta (4–10 Hz), spindle (10–15 Hz), slow gamma (30–50 Hz), medium gamma (50–90 Hz), and fast gamma (90–140 Hz). For each band, mean power across time was calculated in 1-second bins. Then, for each bin, power relative to the baseline period was quantified as the logarithm of fold change (logFC) where fold change is mean power during that bin divided by mean power during the 6-hour baseline period. This normalization corrects for differences in LFP recording fidelity across animals and across recording days by using fold change, and it gives equal weight to increases and decreases in power by then taking the logarithm.

To quantify the effect of a treatment, we consider all bins of logFC data during the 1-hour response period. The distribution of these 3600 values can be compared between each animal's ketamine treatment and its control treatment(s). However, because there are so many data, all comparisons yield significant differences in median, even under the extended nonparametric Kruskal–Wallis test with post-hoc Dunnett's tests.

As there is no well-defined clinical or physiological threshold against which we might compare the size of an effect of treatment on fold change in band power to evaluate its relevance in this context, we instead follow up with a stringent but highly interpretable criterion for significance by performing a simple paired t-test between medians. Information about the distribution of change in power is omitted, but each comparison across experimental conditions is straightforward and within-animal. The pairwise comparisons included in the LFP analysis are ketamine versus saline in all 4 animals as well as ketamine versus MK801 in 2 of those animals.

The length of the response period was standardized to 1 hour across animals despite some variance in the duration of the response. The length chosen was based on prior literature and validated in preliminary analysis of these data. The set response period improves interpretability and eliminates subjectivity in judging the response of each animal. Responses varied in duration even within animals across LFP and spiking, and so a response period defined strictly rather than on a per-animal basis ensures that experimenter choice of cutoff does not artificially increase power by isolating the period of maximal response. However, as with the choice of statistical

test, this approach sacrifices some statistical power and our reported findings are thus conservative.

### *3.5.5 pEMG-based state scoring*

The distribution of pEMG in 1-second bins of wake across all recordings was trimodal, a pattern that held within individual recordings, with only slight (±0.1) tuning of the pEMG thresholds required to cleanly divide all bins of wake in each recording into one of 3 pEMG states. LFP and spiking data were combined across all recordings to characterize each state, with differences determined by Kruskal–Wallis.

### *3.5.6 Spiking analysis*

For each unit in each recording, cell type was determined based on spike waveform (Watson et al., 2016). As putative inhibitory units were uncommon in some recordings and dominated averaged measured due to high firing rate (FR), they were excluded from analysis.

Mean firing rate was calculated in 1-second bins across all putative excitatory units in a recording. As with LFP, each FR value was normalized to mean FR during the baseline period by taking the logarithm of the fold change. To test for differences between the control and ketamine treatments, we again used the very sensitive Kruskal–Wallis test followed by a very strict t-test. In the spiking analyses, we used only the saline and ketamine conditions as the MK801 recordings yielded few units. Thus each animal is reflected in a single comparison.

In addition to analyzing groups of units, we classified each unit as increasing, decreasing, or unchanging in FR following treatment by comparing the distributions during the baseline and response periods with the Kruskal–Wallis test. We then compared the distribution of units across these 3 categories between the control and experimental conditions using a chi-squared test. When nonuniformity was detected, post-hoc Fisher's exact tests were used to determine which pairwise comparisons were significant after adjusting for multiple comparisons using the Holm–Bonferroni method.

Within the ketamine-responsive classes, the distribution of logFC in FRs was compared between the control and experimental conditions with a rank-sum test for a difference in medians.

## 3.6 Results

### *3.6.1 Data collection*

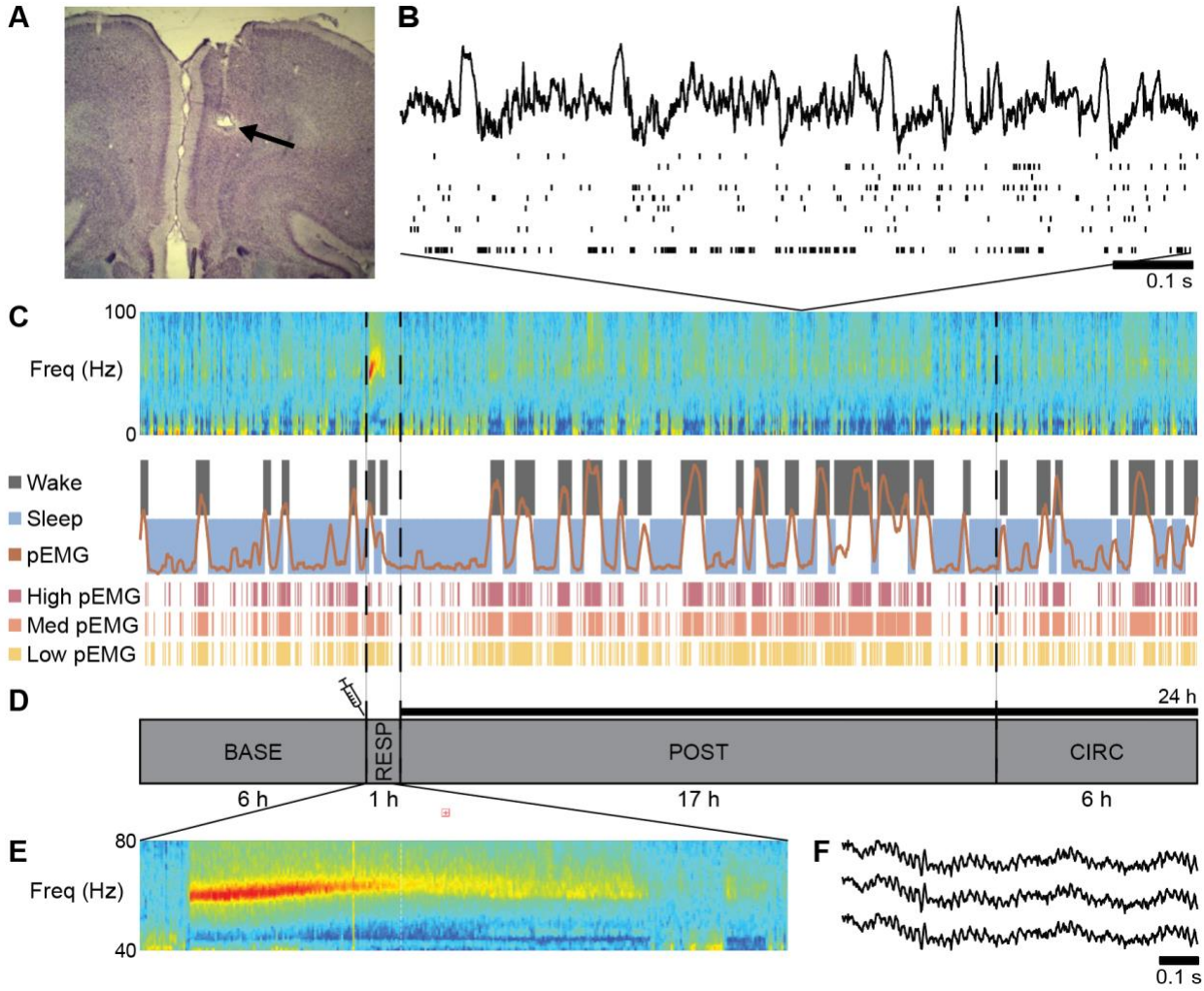


Figure 8: Experimental design, data collection, and preprocessing. (A) Example probe implantation histology shown with Nissl staining. (B) Electrophysiology example: LFP (top) and spiking activity from 10 sample units (bottom). (C) Spectrogram, hypnogram, and pEMG over 30 hours. Power was calculated using multi-taper fast Fourier transform at a frequency resolution of 0.1 Hz and temporal resolution of 1 s. Sleep scoring was achieved using semi-automated detection based on power spectral slope and pEMG. Note both a simple wake–sleep dichotomy (upper hypnogram) used in the first half of this manuscript as well as sub-division of wake into 3 states (bottom hypnogram, higher temporal resolution) used in later analyses. (D) Experimental timeline for each 30-hour continuous recording. Following a 6-hour baseline period, animals were injected with ketamine or saline control, initiating an empirically defined 1-hour response period. (E) Detailed view of the ketamine response. Ketamine administration is followed immediately by a transient increase in power in high frequency spectral power. (F) Post-ketamine LFP trace showing prominent gamma oscillations.

To record electrophysiological data, 4 Long–Evans rats were implanted with 64-channel silicon probes in PFC (Figure 8A). 20-kHz recordings were high-pass-filtered to yield LFP and spike-sorted to disambiguate spiking from each unit (Figure 8B). Each 30-hour recording was

sleep-scored on the basis of delta, theta, and pEMG, and wake was further subdivided based on pEMG (Figure 8C).

Each recording began with a 6-hour baseline period in the homecage before treatment. After administration of ketamine or saline, recordings continued for 24 hours. Preliminary spectral analysis reveals a large signal in the gamma band immediately following treatment with ketamine (Figure 8E) and lasting ~1 hour. Concomitant gamma oscillations are visible in the LFP (Figure 8F).

### *3.6.2 LFP*

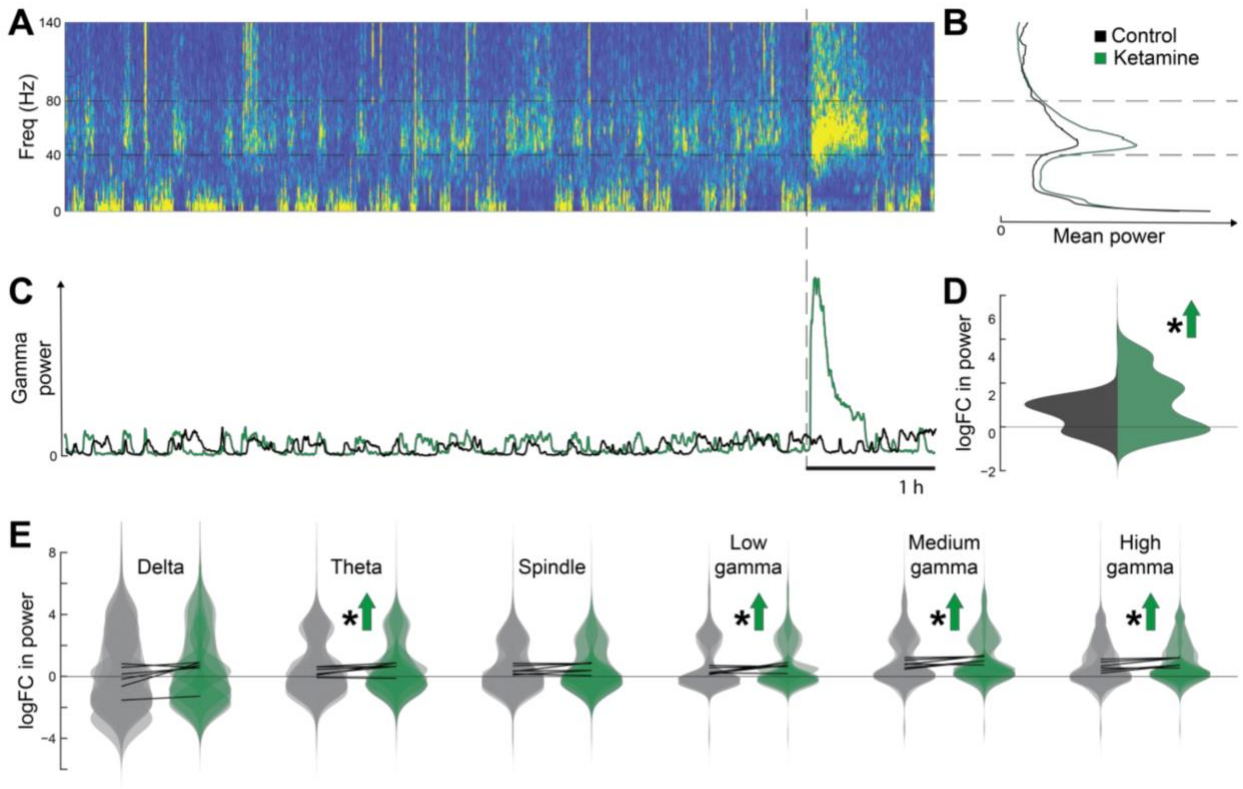


Figure 9: Ketamine induces an immediate increase in gamma and theta power. (A) A representative spectrogram of the baseline and response periods with the injection time indicated by a vertical line. Reveals a response characterized by power in the 40–80-Hz band. (B) Mean power spectral density of example recording and its paired control. The ketamine recording exhibits a high peak in the range of interest. (C) Gamma-band power over time. Compared to control, ketamine induces a transient increase in gamma band power in the response period after injection. (D) LogFC in gamma power. Relative to their respective baselines, gamma power during the response period is elevated in the ketamine recording compared to the control recording. (E) Ketamine-induced changes in power in various frequency bands. Across three divisions of gamma as well as theta, ketamine but not control induces an increase in power (n = 6 comparisons). Differences between control and ketamine are indicated with * ($p<.05$).

To quantify LFP responses to ketamine, we first performed multi-taper Fourier analysis at a temporal resolution of 1 second to create spectrograms (Figure 9A). We then performed

preliminary quantification of changes in gamma power in a range (40–80 Hz) defined by visual inspection of the difference in spectral profiles between ketamine and control recordings in the same animal (Figure 9B). These means were normalized to total spectral power to enable meaningful comparison across recordings. In terms of timing, we observed a notable difference in gamma power specifically following administration of ketamine and not following saline (Figure 9C).

To correct for differences in recording fidelity, enable comparison across animals, and remain unbiased with respect to increases and decreases, we quantified change in each metric from baseline to response as logFC. We then compared logFC in power in the frequency band of interest between ketamine and saline. The distributions of logFC in gamma power reveal an increase specific to this animal's ketamine session (Figure 9D, $p<.05$).

We then analyzed multiple frequency bands across all animals. Based on prior literature, we defined additional bands as follows: delta: 0.5–4 Hz, theta: 7–10 Hz, spindle: 10–20 Hz, low gamma: 30–50 Hz, medium gamma: 50–90 Hz, high gamma: 90–140 Hz. Due to the number of data points, all comparisons between control and ketamine distributions of logFC in power are significant. Collapsing within each recording to medians only, we find that ketamine induces an increase in median power in all sub-bands of gamma ($p=.03$) as well as theta ($p=.02$) (Figure 9E).

### *3.6.3 Spiking*

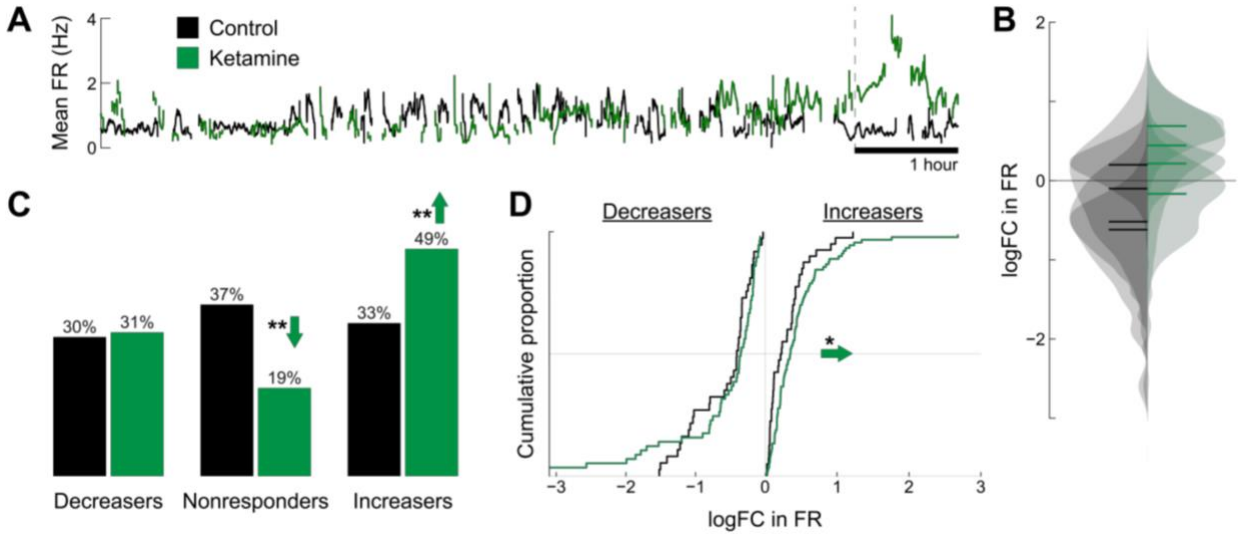


Figure 10: Ketamine induces an immediate increase in excitatory unit spike rates in a responsive subset of units. (A) Mean firing rate across baseline and response period. FR rises after ketamine injection but not control. (B) Across animals, the logFC in FR averages zero following saline and is usually positive following ketamine (n = 4

comparisons). (C) The proportion of units significantly increasing or decreasing in FR during the response period varies between saline and ketamine. While the proportion of units the decrease in response to treatment is consistent between the conditions, compared to control, ketamine results in a smaller proportion of nonresponding units and a greater proportion of units that increase in FR. (D) Quantification of the change in FR among responsive units reveals that the increasers are greater not only in proportion but also in FR increase. Horizontal line crosses median of each distribution. Differences between control and ketamine are indicated with * ($p<.05$) or ** ($p<.005$).

Following analysis of circuit-level electrophysiology, we examined changes in neuronal spike rates in response to ketamine. In a representative recording, mean FR increases following ketamine but not saline (Figure 10A). Normalization of changes in FR by logFC reveals that across all paired recordings, ketamine induces a greater increase in FR. However, a stricter test using only medians reveals a trend that does not reach significance (Figure 10B).

To more deeply investigate the responses of single units, the distribution of FRs of each unit was compared between the baseline and response periods using a non-parametric test appropriate to most units' non-normal FR distribution. Units whose FRs were significantly different following treatment were further classified as increasers or decreasers based on the direction of change in FR.

An omnibus chi-squared test reveals that the distribution of units across the categories of increasers, decreasers, and nonresponders differs between control recordings and ketamine recordings. Follow-up pairwise comparisons confirm that relative to the control condition, the proportion of nonresponders is smaller and the proportion of in-creasers larger under the ketamine condition (Figure 10C, $p=.0003$).

To quantify the behavior of these classes of units, we examined logFC in FR of all increasers and all decreasers. Rank-sum tests reveal that the increasers demonstrate a significantly greater change in FR following ketamine than increasers following saline (Figure 10D, $p=.02$). Thus, increasers increase in FR more after ketamine than after saline.

### *3.6.4 pEMG states and LFP*

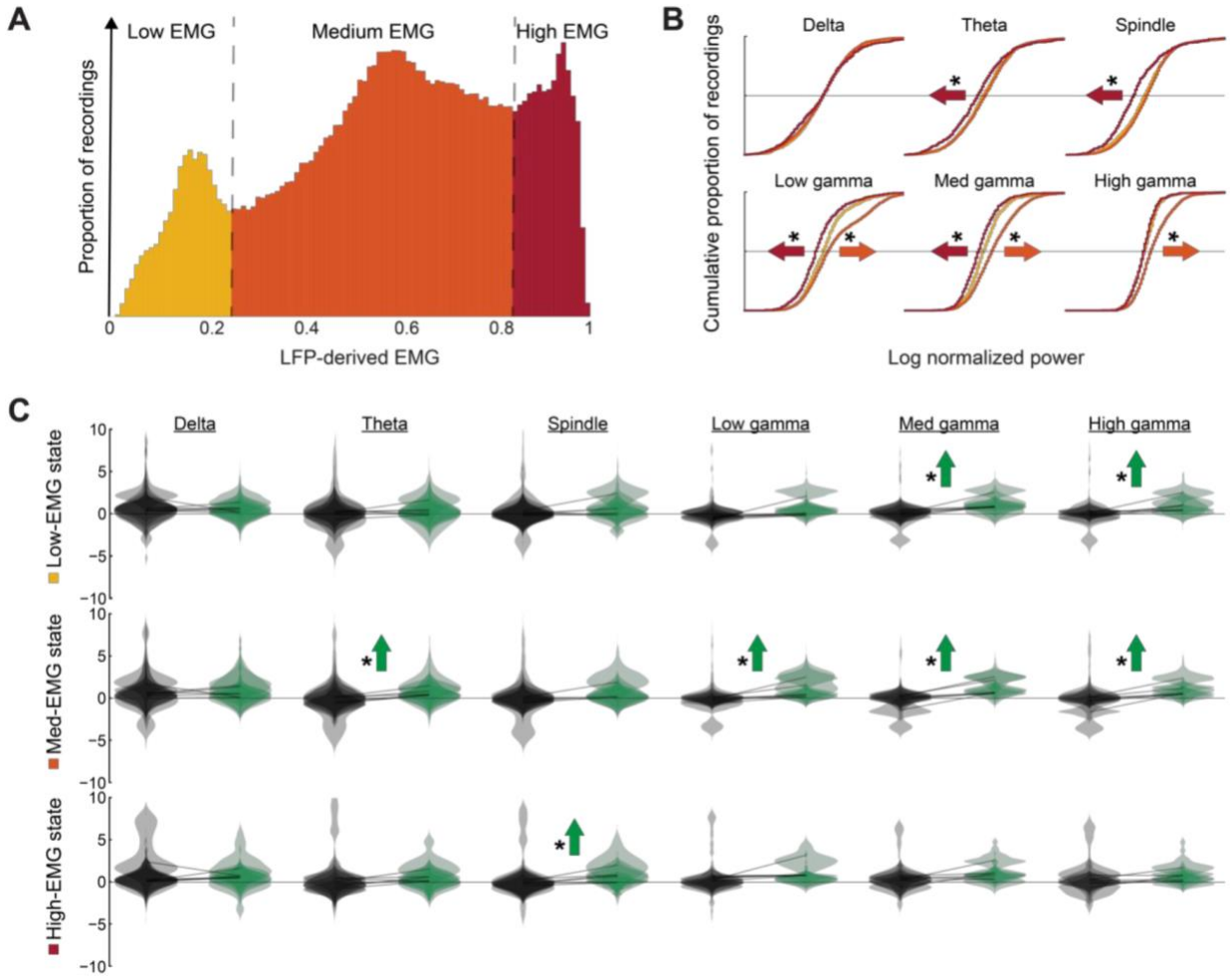


Figure 11: The effect of ketamine on LFP varies across distinct wake sub-states. (A) Distribution of pEMG from all sessions. A trimodal distribution is observed in individual recordings and their sums, shown here, with troughs consistent across conditions. (B) Cumulative distributions of power in each LFP bands in each pEMG state. The high-EMG state is characterized by lower power in the theta through medium gamma range. The medium-EMG state is characterized by greater power in all gamma bands. (C) Mean response (logFC) in power is greater in the ketamine condition in canonical bands that vary across pEMG states. Note that theta power increase is isolated to the medium-EMG state, while the high-EMG state shows a paradoxical increase in spindle-band power only (n = 6 comparisons). Differences between control and ketamine are indicated with * ($p<.05$).

All multi-animal analyses presented thus far were analyzed across all wake periods without subdivision of the behaviorally diverse wake state. Indeed, substates also exist within wake, affecting electrophysiologic activity. To account for differences driven by changes in brain state and thereby attain better specificity, we separated all time-series data on the basis of pEMG, a measure of EMG signal calculated from correlations across channels in a high-frequency band (300–600 Hz). This has been shown to correlate strongly with nuchal EMG.

The distribution of pEMG amplitude across all wake reveals a novel, well-defined trimodal distribution irrespective of experimental condition or animal. Using the dips between

these 3 modes as thresholds, every one-second bin of wake was classified as belonging to the low-, medium-, or high-pEMG state.

We find that while spiking is similar across states, LFP varies across state, including in gamma bands of interest (Figure 11B). Thus, to make like-to-like comparisons in each frequency band, we first separated data by pEMG state. This also improved the normalization of power in each band by using only bins of a given state to calculate logFC in mean power. In Figure 11C, the distributions of logFC in LFP power for each animal's control and ketamine recordings are displayed along with line segments indicating changes in median logFC between the control and ketamine conditions. We find increases in theta (p=.02) specific to the medium-pEMG state, increases in gamma (p=.02) specific to the low- and medium-pEMG states, and an increase in spindle-band power (p=.04) specific to the high-pEMG state.

### *3.6.5 pEMG states and spiking*

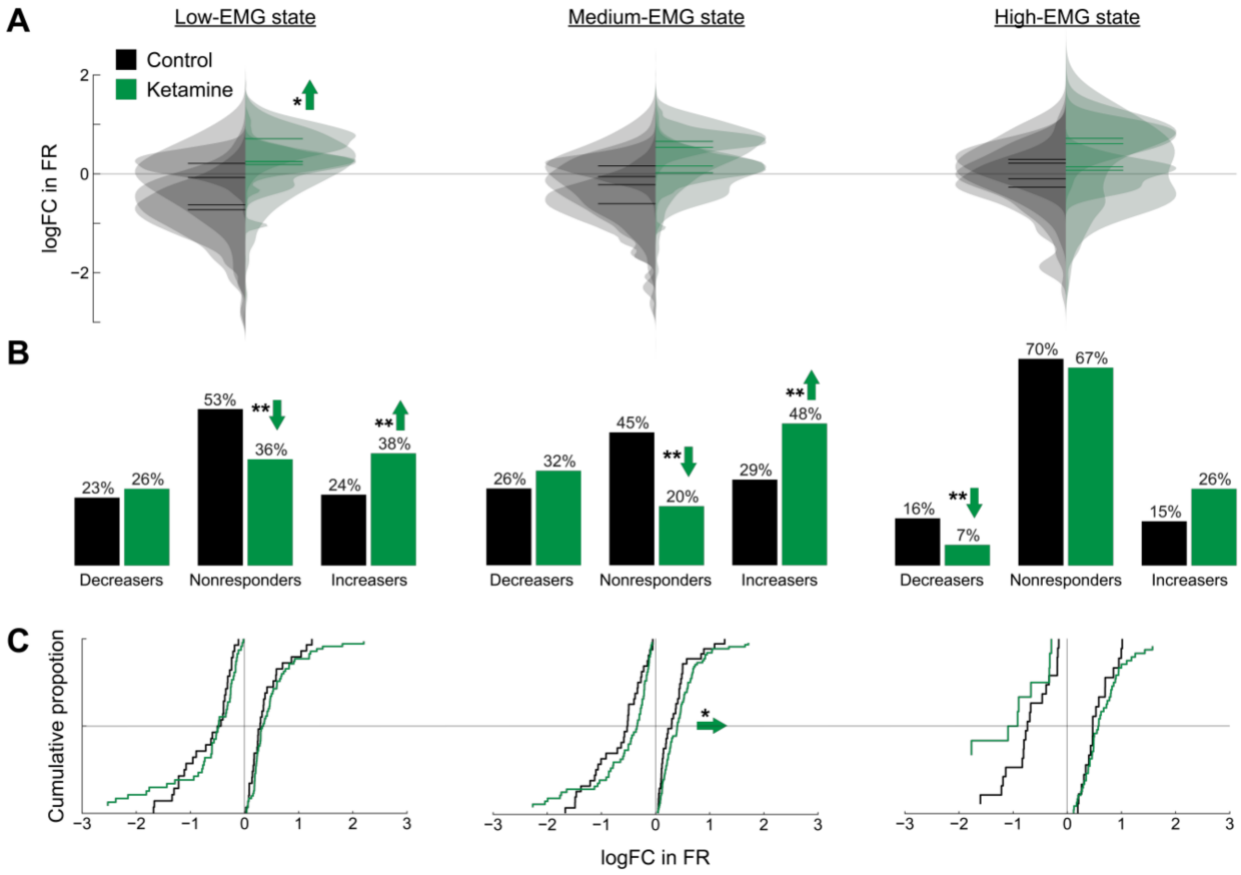


Figure 12: The effect of ketamine on spiking varies with pEMG state. (A) Separating spiking data by pEMG state reveals that specific to the low-EMG state is a significant increase in FR following ketamine but not saline (n = 4 comparisons). (B) Classification of units by individual response to treatment reveals similarities between the low- and medium-EMG states and a dramatically different distribution of responsiveness in the high-EMG state. (C)

Quantification of the responsive classes reveals similar patterns in the low- and medium-EMG states, but only the change specific to the medium-EMG state reaches significance. Horizontal line crosses medians of the distributions. Differences between control and ketamine are indicated with * ($p<.05$) or ** ($p<.005$).

The pEMG states differ also in ketamine-induced FR changes. The distribution of per-second FRs during each response period was again normalized in an improved fashion to the corresponding baseline mean using only times in a given pEMG state. While the pattern of differences in logFC in FR is similar to that of wake overall (Figure 10B), this targeted analysis reveals that the ketamine-induced increase in FR observed in representative recordings (Figure 10A) is greatest in the low-pEMG state such that only this state reveals differences significant under the strict test of differences in medians (Figure 12A, $p=.04$).

The classification of unit responses in each of the 3 pEMG states reveals the pattern of a smaller proportion of nonresponders and a greater proportion of increasers conserved between the low- ($p=.002$) and medium-pEMG ($p=.000003$) states and a highly divergent one in the high-pEMG state (Figure 12B). Notably, the proportion of nonresponsive units is far greater in both experimental conditions, and the effect attributable to ketamine is a decrease in the proportion of units that decrease in FR ($p=.002$).

Quantification of these changes in FR among the responsive units reveals that the greater increase in FR following ketamine (Figure 10D) is specific to the medium-pEMG state (Figure 12C, $p<.05$). Thus, the effect of ketamine on spiking, while similar between the low- and medium-pEMG states, is specific to median FR across all units in the low-pEMG state and to the distribution of logFC in FR among units that increase in response to ketamine in the medium-pEMG state.

### 3.7 Conclusion

We here reproduce known effects of antidepressant-dose ketamine on firing rate of pyramidal neurons and gamma power. We find that after ketamine, fewer neurons remain unchanged in their firing rates and more increase. Furthermore, the neurons that increase firing after ketamine do so more than with saline. We also identify the specific states of wake during which these immediate changes occur. In particular, we localize the ketamine-induced increase in theta power to a state of medium pEMG, we find that mean FR is influenced most strongly during the low-pEMG state, and we identify effects on both LFP and spiking that are unique to the high-pEMG state.

### 3.8 Discussion

Ketamine generally drove more neurons to increase firing than control conditions. This is consistent with gamma oscillatory states, which are often linked to higher pyramidal neuronal firing (Keeley et al., 2019; Adesnik & Scanziani, 2010; Lu et al., 2015). Additionally, when neurons increase firing, they do so more with ketamine than with control. This is consistent with findings of increased variance after ketamine (Cichon et al., 2023).

The most robust finding of this study was a ketamine-induced increase in gamma power that was unsurprising given its considerable documentation in this field (Pinault, 2008; Lazarewicz et al., 2010; Furth et al., 2017). This effect may be underlain by inhibition of specific neuronal populations (Amat-Foraster et al., 2018). That it is not observed in the high-pEMG state might suggest that sniffing, focusing on gathering information about the external world, is a state resistant to the antidepressant effect of ketamine. Perhaps this brain state is not amenable to induced changes. Relatedly, the quiet wake state may be more open to electrophysiological changes compared to active wake (Grønli et al., 2016). For these reasons, we believe it important to take into account divisions within wake in the investigation of the immediate effects of ketamine.

The observed increase in theta power, however, contradicts prior findings in humans (Lazarewicz et al., 2010). This may have to do with differences in how "background activity" was defined compared to our brain-state-based control.

We demonstrated a novel means by which to define brain state on the basis of pEMG. While video was scarce for this dataset, manual analysis reveals that the low-pEMG state is characterized by the animal remaining still, the medium-pEMG state is enriched for locomotion and rearing, and the high-pEMG state is attributable to head movement and sniffing. This suggests behavioral correlates of quiet wake, active wake, and craniofacial activity respectively. This is consistent with lower EMG in quiet wake than in active wake (Datta & Siwek, 2022) to a degree that it can be used to distinguish between the two in an automated fashion (Fraigne et al., 2023). Quiet and active wake appear to be distinct states, not merely ends of a spectrum; promoting quiet wake by administration of oxytocin suppresses active wake (Raymond et al., 2023). The high-pEMG state may reflect specifically sniffing behavior important in rodents. Sniffing is associated with exploration and reward anticipation among cognitive states (Wesson et al., 2008). It is tempting then to consider it a substate of active wake, but in truth this behavior

may lie outside the wake–sleep dichotomy entirely; sniffing has been observed in rats during sleep (Seelke & Blumberg, 2004). Perhaps the uniqueness of this behavioral state explains the degree to which ketamine's effect in this state differs from its effect during the other wake states.

The distribution of cell responses to ketamine differed with brain state. In the low- and medium-pEMG states, changes in spiking reflected a decrease in the proportion of cells nonresponsive to saline and a corresponding increase in the proportion of cells that increased in FR in response to ketamine. However, in the high-pEMG state, cells appear to be recruited from the subpopulation that decreases in response to saline to instead increase in response to ketamine. This differs from the net effect of ketamine, as the high-EMG state makes up a minority of the response period. It may be the case that non-treatment-responsive patients are enriched for this brain state, preventing ketamine from effecting the neuronal-activity-level changes that ultimately drive its antidepressant effects.

This study was limited by a lack of data on depressive-like behaviors, such as forced swim test or sucrose preference. As such, we are unable to directly determine whether brain states correlate with or dictate antidepressant effects (Moda-Sava et al., 2019). A related improvement would be the use of a rat model of depression as these rats were unstressed. It is possible that chronically stressed animals would have shown different neural responses given that they do show different behavioral responses (Fitzgerald et al., 2019). Moreover, treatment protocols are increasingly calling for the use of 20 mg/kg in rats, twice the dose we used. A stronger dose may reveal effects too small in this study to identify. Finally, the use of more animals would similarly increase power and, importantly, increase the count of inhibitory units to enable analysis across the two cell types.

Overall, we were able to replicate and also extend many findings regarding the effects of antidepressant-dose ketamine on neural spiking and LFP. Future work can further extend these findings by comparing control and stressed animals, adding behavioral testing, and investigating other measures of single-unit and network response, like bursting activity and functional connectivity, to deepen our understanding of the signatures of ketamine in PFC.

# Chapter 4 Discussion

## 4.1 Summary of conclusions

REM has 2 states based on eye movement, but one of its defining features is unimodal across these states and correlates with both eye movement and neuronal activity. Wake has 3 states based on pEMG, and the effect of ketamine on cortical electrophysiology varies across these states.

## 4.2 Theta frequency defines spiking across substates of REM

In our investigation of the temporal structure of REM, we discovered that despite its traditional binary division on the basis of eye movement, REM actually fluctuates between substates in a manner that concords with a continuous, oscillatory change in theta frequency. This link between a rhythm known to play a critical role in REM and the structure of REM itself offers a view of REM that is functionally relevant and greater in resolution than simple classification into pREM and tREM. Moreover, this fluctuation in theta aligns to a high degree of specificity with spiking activity in primary somatosensory cortex, with a peak in spiking corresponding to the pREM pole of this fluctuation. Across layers and cell types, units exhibit maximum spiking at or very near peaks in the fluctuation in theta frequency. Averaging across units, this peak also seen in mean spiking descends sinusoidally as the fluctuation approaches the tREM pole, with mean firing nearing zero. This pattern was not explained by pEMG, which might otherwise be expected to concord with spiking, or theta power.

Spiking reflects all neuronal processes, but a specific function that is known to be related to spiking during REM is learning and memory. The concordant fluctuation in mean firing rate may drive spiking-dependent plasticity facilitated in REM. The fluctuations in coordinated activity might reflect simple mass changes across neurons with similar properties, but the known roles of cell assemblies in sleep regulation and pattern completion could here manifest as reactivation of specific groups associated by sensory processing or memory in a manner that drops off as pREM transitions to tREM.

The increased primary somatosensory cortex (S1) spiking during pREM might also reflect dreaming, either generated in sensory cortex or initiated by a PGO wave. pREM behavior is known to reflect dreaming (Soh et al., 1992), and this seems to include the shifting of gaze that one would expect in a visual hallucination (Leclair-Visonneau et al., 2010; Senzai & Scanziani 2022). It is possible to imagine that rodent dreams include tactile hallucinations and that this internally generated whisker stimulus drives pREM-specific spiking in S1.

Future analyses might benefit from assessing this underlying fluctuation, which provides greater information about the state of the brain evidenced by significant, corresponding changes in single-cell and coordinated spiking activity. This improved understanding of state transitions in REM could inform detection of REM disturbances, particularly those that characterize the REM behavioral disorders that precede neurodegeneration and the disinhibition of pREM that is common in depression. The fluctuation in theta frequency represents not only a signal of greater resolution for examination of abnormal structure in REM but also a potential therapeutic target if it can be exogenously altered and in turn influence the tendency of the brain to remain in tREM or pREM.

### 4.3 The electrophysiological effects of ketamine vary with wake substate

In our investigation of the wake-enriched response period immediately following administration of antidepressant-dose ketamine, we identified three modes of pEMG and thus defined three substates. We observed that in the high-pEMG substate, the expected effects of ketamine on mPFC firing rate and gamma power were absent or greatly attenuated. Moreover, the distribution of responses across neurons was considerably changed. Assuming that the immediate electrophysiological changes induced by ketamine drive or enable its behavioral effects, animals in this state may be resistant to the therapeutic effect of ketamine. Existing work that does not take into account brain state may therefore underreport the effect of ketamine in mPFC.

It is well understood in clinical practice that mental state strongly moderates the efficacy of therapeutics; motivation, alertness, and outlook greatly influence the ability of the clinician to treat. Our findings suggest that even less-observable brain states can affect how responsive the brain is to external perturbation. In fact, sensitivity to external information (like sensory stimuli) might be considered a defining feature of brain states in wake just as it is in REM. Based in preliminary video analysis, the high-pEMG state corresponds to craniofacial muscle activity, like

chewing and sniffing. These might be considered goal-directed behaviors, and the brain state that favors them might in turn be less open to processing exogenous influences that would compete for the neural resources dedicated to these stereotyped behaviors. How this translates to humans is unclear, but it highlights the importance of taking into consideration minute-to-minute fluctuations in brain state as the clinician seeks to influence the brain. The use of EEG to determine optimal periods for ketamine delivery or therapy is a promising line of inquiry.

## 4.4 Limitations and future directions

### *4.4.1 Experimental models*

In these studies, we investigated neural oscillations and the neural activity that is thought to underlie them. However, we investigated behavior only in a limited context: eye movement during sleep and spontaneous behavior during wake. In the context of REM, it would be informative to determine the association between the whole-body twitches that are characteristic of REM and the fluctuation in theta frequency that varies continuously across REM. In the context of ketamine, we would like to investigate depressive-like behaviors like anhedonia as assessed through sucrose preference.

These studies were performed in normal rodents. Thus, while they have greater relevance to normal brain function as observed in typical humans, they are less relevant to populations we would like to treat: those with REM disorders and/or depression. These models would allow us to determine not only how brain state relates to atypical brain function but also how interventions like ketamine might be made more effective and how findings in this field can be translated for human work.

RBD can be modeled in rodents by inactivation of excitatory neurons in the pons (Garcia et al., 2017) or inhibitory neurons in the medulla (Garcia et al., 2018). Very specific models deliver fibrils of α-synuclein into the pons to recapitulate not just RBD symptoms but also the subsequent locomotor dysfunction (Shen et al., 2020), and these symptoms can be exacerbated by further delivery of these fibrils (Okuda et al., 2022). The fluctuation in REM theta frequency in RBD is an open question, and investigation of one of these models might allow us to determine whether the disorder is specific to pREM or tREM or continuously variable across these substates, potentially improving detection and treatment. These models are highly

translatable to humans using nuchal EMG (Silvani et al., 2017), which may also serve to reveal a trimodal distribution of craniofacial motricity as we observed in the ketamine study.

Rodent models of depression span genetic, developmental, pharmacological, and environmental interventions, reflecting the complex etiology of this disorder. Like humans, rats can exhibit a genetic predisposition to depression as in the Flinders sensitive line (Wegener et al., 2012; Steyn, 2025). Early-life stress, like handling and maternal separation, creates vulnerability to depression (Schmidt et al., 2010). Reserpine and corticosterone induce depression-like behavior amenable to antidepressant treatment (Becker et al., 2021). Chronic, unpredictable stress causes hallmark symptoms like learned helplessness and anhedonia (Antoniuk et al., 2019; Nollet, 2021; Slattery & Cryan, 2017). The effect of antidepressant-dose ketamine can be expected to differ in a rodent model of depression in terms of its influence on behavior, but its influence on neural activity may not. Differences in the electrophysiological effect of ketamine across brain states should be investigated in an animal model to enable better translation of our findings to the patient population.

We also have an interest in investigating substates of REM and wake in the context of learning. Waking experience has been shown to correlate with REM duration and theta power, and we expect that wake states differ in their contribution to and application during a learning paradigm.

We have set up a whisker-stim go/no-go task for which performance rises from chance to 80% accuracy in the course of a few weeks. While gradual increases in performance do not correlate specifically with prior-session accuracy, it may be that post-training sleep or more specific aspects of the prior training is a determinant of subsequent performance. Correlating subsequent performance against more specific features of brain state, like relative pREM and tREM duration or time spent in active wake during training, may reveal that mechanisms underlying task learning are specific to particular brain states.

### *4.4.2 Brain regions*

Retrosplenial cortex (RSC) has been shown to exhibit two substates in REM. We recorded in barrel cortex but would like to investigate the link by recording simultaneously in these regions to determine if this is identical to pREM and tREM and, if so, whether there is directionality or perhaps a common source, a pacemaker for REM that outputs to both sensory cortex and RSC.

We were able to record in both studies limited hippocampal data. Dedicated recording would allow investigation of hippocampal-specific rhythms and hippocampal–cortical coupling, which is especially important during sleep and likely underlies the theta observed during REM.

Finally, we would also like to record simultaneously in thalamus. Thalamocortical circuits are thought to generate some neural oscillations, gamma in particular, and so a combined recording would shine light on the role of this subcortical region in the effect of ketamine on gamma power. Because ketamine acts at the mPFC, it may be feedback from cortex that initiates the gamma-generating circuits.

### *4.4.3 Replication*

These findings would be strengthened with replication in more animals and, ideally, in the same rodent species for both lines of investigation followed eventually by work in humans. Because we studied LFP in both cases, it may be straightforward to noninvasively gather and compare EEG data in humans. We have performed preliminary investigation of human REM, finding that infraslow fluctuations in heart rate are greater in men with more greater depression symptomatology. If it is the case that the effect of ketamine is related to the change in gamma power that it induces, then recording patient brain activity during treatment might allow clinicians to predict the efficacy of a given dose or even tune the dose on a per-patient basis.

In future work, we will use the outcome of the present studies to refine our approach and analyses. Brain state should be considered not just as varying between wake and sleep but as inhabiting substates within these states and, along some axes of consideration, as having a fluctuation that might be mappable to specific electrophysiological features. Identifying the determinant of pEMG state was beyond the scope of this work, but it evidently modulates both behavior and responsivity to the NMDAR antagonist ketamine. Future work will further quantify the nature of these substates, including their temporal structure and transition probabilities, as well as assess how these traits might themselves change in response to ketamine. Perhaps ketamine induces a stereotyped sequence of brain states that supports its immediate and long-term changes.

Among the animals treated with ketamine, we are interested in examining changes in REM substates in the 24 hours following. Like other antidepressants, ketamine has been observed to decrease REM, partially rescuing the disinhibition of REM that characterizes depression (Kantor et al., 2023). Moreover, the effect of ketamine on early-night REM density is

a predictor of treatment response (Kheirkhah et al., 2025). Thus it is of interest how ketamine affects REM structure, and we can examine its effect not only specific to pREM and tREM but also as it relates to the infraslow fluctuation between the two.

Moreover, increasing our sample size would address limitations we encountered in the ketamine study: That the amount of data gathered demanded statistical thresholds restrictive enough that we were instead underpowered to detect expected differences in firing rate. A sufficient increase would also allow the specific analysis of putatively inhibitory (pI) units, which had to be excluded from the ketamine study on account of small sample sizes.

#### *4.4.4 On inhibitory neurons*

While we were able to record the activity of a large population of excitatory neurons and their response to ketamine, future analysis of inhibitory neuron activity may yield important new insights. Inhibitory neurons appear to play a critical role in the antidepressant effect of ketamine. In fact, it may be the action of ketamine on GABAergic interneurons, not glutamatergic putatively excitatory (pE) units, that underlies its antidepressant action in mPFC (Gerhard et al., 2019). In depression, GABAergic inhibition is reduced (Croarkin et al., 2011), particularly in prefrontal parvalbumin- and somatostatin-positive interneurons (Fuchs et al., 2017). The rapid effect of ketamine to inhibit these interneurons disinhibits the downstream excitatory neurons, enabling a surge of excitatory glutamate and metabolic pathways for plasticity (Zanos & Gould, 2018). Furthermore, the impairment in inhibitory control of excitatory neurons is thought to explain reduced gamma in individuals with depression (Liu et al., 2022) as generation of gamma relies on the interplay between well-behaved populations of inhibitory and excitatory units. In the present work, we observed an immediate increase in gamma power following ketamine treatment, suggesting a rapid induction of excitatory–inhibitory balance (EIB) that favors the generation of neural oscillations across this range of frequencies. This is consistent with a model in which ketamine blocks the NMDARs on pI units, disinhibiting pE units and producing the glutamate surge and downstream synaptic potentiation (Pham & Gardier, 2019). An analysis of pI spiking under our experimental paradigm and statistical approach would directly address the implication in this model that pI activity decreases in response to ketamine. Thus separate analysis of pI activity and its balance with pE activity is a critical future direction for this line of research.

### *4.4.5 On brain states*

One way to think of brain states is that gathering a small amount of information — like motor activity, dominant EEG rhythm, or pupil diameter — tells us considerably more information about the current tuning of the brain for specific functions or its sensitivity to perturbation by sensory stimulus or perhaps learning. Brain states thus represent not just ways of condensing and understanding the complex and dynamic brain but also ways to understand its mode of operation in the moment. Moreover, brain state can often be determined noninvasively, serving as a window into the brain even in humans and, importantly, patients.

The three pEMG substates represent an extension of existing knowledge about substates of wake. While separation of aWAKE and qWAKE on the basis of EMG is routine, our use of pEMG allowed us to specifically identify a state reflecting activation of the craniofacial muscles, primarily for sniffing. What this state reflects functionally is an open question.

Unsupervised behavior quantification identifies in rodents exploration, grooming, rearing, and feeding behaviors (Gris et al., 2017; Ziegler et al., 2020). Sniffing is an active sensory behavior that is often coordinated with whisking, which is also an active sensory behavior (Deschênes et al., 2012). These behaviors are related not just in function but also in time as they both lock to hippocampal theta (Kleinfeld et al., 2016). Interestingly, the coordination between sniffing and whisking is dependent on the animal's mode of interaction with the environment: Among the outbound, exploration, and inbound modes, the former two exhibit greater inter-modal correlation (Fonio et al., 2015).

Why might it be that the high-pEMG state is less amenable to ketamine-induced changes in spiking and LFP? Perhaps it is less perturbable in general. If this state is characterized by the gathering of olfactory information, then it may be the case that no processing power or metabolic energy remains to support the cascade of effects initiated by ketamine. Or perhaps the effect of ketamine requires the brain to carry out a set of functions or computations in circuits that are instead in use in service to sniffing. For the clinician, this could imply that ketamine treatment should be administered when the patient has low stress and mental load. However, our investigation cannot suggest whether efficacy might be highest when the patient focuses on a desired future mental state, the subjective effect of ketamine, the words of a therapist, or nothing at all.

### *4.4.6 On spiking*

What does it mean for firing rate to vary across substates of REM and wake and in response to ketamine?

In sensory cortex, firing rate can encode features of the external world. During REM, S1 activity largely continues to reflect whisking, but the alternation between high and low activation states may provide a substrate for memory-related processes (Boscher et al., 2024). It is known that the differences in baseline firing rate across sleep states do not simply reflect differences in responsivity, for example (Nir et al., 2015). Another hypothesis is that these changes in firing rate are driven by learning and culminate in lasting changes in FR among highly responsive, sparsely firing units in primary sensory cortex (Clawson et al., 2018).

In mPFC, spiking encodes behavioral response, outcome (Luk & Wallis, 2009), and environmental context (Hyman et al., 2012) in learned adaptive behavior (de Haan et al., 2018). This region may play a more general role in associating locations, events, and goal-directed responses, involving it in almost all memory and decision-making tasks (Euston et al., 2012). During wake, differences in firing rate across substate might therefore reflect differences in the animal's goals or perceived environment. The responsivity of firing rates to ketamine might then reflect the stability of those goals. Perhaps the high-pEMG state, being characterized by sniffing, is centered around exploration and reward-seeking and has little allowance for the offline, inward-directed processing that might be required for the antidepressant effect of ketamine.

#### *4.4.7 On coordinated spiking*

In our investigation of coordinated spiking, we adopted the method of Lopes-dos-Santos et al. (2013) for detection of cell assemblies and quantification of their activity. Assemblies may be detected by dimensional reduction (principal component analysis, independent component analysis, or nonnegative matrix factorization), network analysis (Markov chains or models), or group construction (Billeh et al., 2014). As temporal structure was beyond the scope of this investigation and the dataset was relatively large, we selected this method for efficiency without requiring that assemblies be orthogonal.

Another critical choice is the timescale on which to detect coordinated activity. We detected assemblies during REM and during specific phases of the theta fluctuation within REM with consistent results. It remains unclear what assemblies detected during wake might look like during REM and whether their activity is similarly variable across substates of REM. In a

learning context, we might expect assembly membership to change across sleep. The effect on its activity as related to REM is an open question as well.

Newer methods for assembly detection, validated empirically, may rely on efficient clustering (Watanabe et al., 2019) or biorealistic measures of synaptic connectivity (Asahina et al., 2022). The degree to which these methods concord with current standards has yet to be determined, but applying these methods to existing data for confirmation or alternative findings might reveal more about the structure of coordinated activity in REM.

### *4.4.8 On other metrics*

In our investigation of REM theta and ketamine during wake, we focused on the fundamental electrophysiological bases of brain function and behavior. However, just as coordinated spiking reveals more about the brain than single-unit spiking alone, metrics derived from the recorded data may further elucidate changes in the brain and the mechanisms by which it carries out its functions.

Burst firing is a rapid sequence of spikes that can be used as a mode for encoding information separate from what is encoded by normal spiking. For example, it could be used to quickly communicate information about stimulus intensity while normal spiking encodes stimulus specificity in an ongoing manner. In CA1, single spikes encode boundaries of place fields while bursting encodes position (Lowet et al., 2023).

Due to its short inter-spike intervals, bursting is more likely to elicit a postsynaptic spike (Zeldenrust et al., 2018), and its compressed timescale may also lend itself to driving synaptic plasticity (Payeaur et al., 2021) or neural oscillations (Shao et al., 2021). Bursting can be altered in pathological conditions. Notably, rodent models of depression exhibit an increase in bursting in the lateral habenula, an anti-reward center that mediates negative emotions, and optogenetically induced bursting in lateral habenula drives behavioral features of depression. Ketamine inhibits this bursting, disinhibiting downstream reward centers and rapidly elevating mood (Yang et al., 2018). Thus we have a particular interest in determining if ketamine's known inhibitory effect on PFC bursting (Shen et al., 2018) is similarly important in its antidepressant effect and whether this inhibition varies across the substates of wake.

Bursting also plays a critical role in REM. The cells that initiate PGO waves and associated eye movements rely on bursting (Nelson et al., 1983), and hippocampal bursting,

while rare in REM, may play a role in memory consolidation just as it does in NREM (Staba et al., 2002).

Excitation–inhibition balance is important for network stability and efficient coding (Zhou & Yu, 2018). It can be modified by homeostatic plasticity (Chen et al., 2022), and its impairment may contribute to psychiatric disorders, like autism (Sohal & Rubenstein, 2019). In depression, EIB is abnormal across PFC and the limbic system (Hu et al., 2023). Thus it may represent an important target for antidepressants, and the slow timecourse of SSRIs may be attributable to their delayed effect on EIB in mPFC (Yin et al., 2021), whereas ketamine both increases pE spiking and decreases pI spiking within just over an hour. In increasing the sample size of the ketamine experiment, we would enable a statistically robust investigation of EIB across substates, thereby contributing to the growing body of work on PFC EIB as a therapeutic target in a range of psychiatric disorders, including schizophrenia (Ferguson & Gao, 2018).

Criticality is the boundary between ordered and disordered states. In neural networks, information processing is optimal at criticality (Shew & Plenz, 2013), maximizing mutual information and minimizing energy consumption (Takagi, 2020). In depression, LRTC (a measure of criticality) in theta is abnormally high, and mindfulness training reduces it in a manner concomitant with changes in symptomatology (Gartner et al., 2017). Thus criticality may similarly represent a target for psychological and pharmacological treatments, and its future assessment in our dataset may prove useful in evaluating the important effects of ketamine in mPFC. Ketamine and other psychedelics may work by inducing transitions from depressed, noncritical states to critical ones.

In sleep, REM is characterized by subcriticality driven by changes in synaptic strength (Priesemann et al., 2013). It is unknown how pREM and tREM differ in criticality, but the lower arousal threshold of tREM suggests that it is more responsive to perturbation, a feature of criticality (Eremis et al., 2010). Analysis of our data using this measure may help elucidate the reason for these distinct substates in terms of information processing. However, because cortical state influences measures of criticality (Lotfi et al., 2020), care must be taken in such analyses to account for different states.

### 4.5 Summary

In these two investigations, we identified substates distinct in motor output, continuous in LFP, and either distinct or continuous in spiking. We found that the effect of an intervention

depended on substates, highlighting the need for better determination and consideration of brain states in neuroscience. This contribution to the study of sleep and of depression provides a more detailed conceptual basis for further investigation of REM and of wake, and its findings may be translatable for improved treatment of depression in humans.

### 4.6 Brain state across regions

While brain states are typically thought of as global, unitary descriptions of an animal's brain and related behavior, converging evidence suggests that brain states can vary across brain regions (Andrillon & Oudiette, 2023). Birds and aquatic mammals exhibit unihemispheric sleep, in which one cerebral hemisphere is engaged in sleep and the other allows vigilance (Mascetti, 2016). Dolphins use the awake hemisphere for intermittent breathing (Mukhametov et al., 1977) while birds use it as a defense against predation (Rattenborg et al., 1999) or even during flight (Rattenborg et al., 2016), perhaps to avoid collisions. Ostriches exhibit brainstem-mediated features of REM while their hyperpallium is in NREM (Rattenborg et al., 2019).

In humans, signatures usually attributed to wake and to sleep can coexist across cortical regions, perhaps explaining sleepwalking (Nobili et al., 2011). Neocortex and hippocampus exist in different states for up to a third of the night (Jang et al., 2022). Delta waves are distributed not uniformly across the cortex but with a bias for frontal regions (Finelli et al., 2001) and local use-dependent regulation (Krueger & Wisor, 2011). The regional specificity of delta has also been shown to relate to experience-dependent plasticity, changes in depth of sleep, and cognitive errors (Siclari & Tononi, 2017).

Lapses in attention are accompanied by sleep-like slow waves in frontal regions, and these waves precede the subjective experiences of mind wandering and mind blanking (Andrillon et al., 2021). In sleep-deprived humans, theta in task-related regions is correlated with impaired task performance (Bernardi et al., 2015). Selective attention seems to involve a desynchronized state induced locally in the region of cortex that represents the attended stimulus (Harris & Thiele, 2011). This local cortical state also predicts task performance (Engel et al., 2016).

In humans and rodents, unilateral sensory deprivation causes contralateral reduction in slow waves in the corresponding cortical region during subsequent sleep (Huber et al., 2006; Vyazovskiy et al., 2000).

Why is it that distinct brain states can co-occur? Current evidence points to it being driven by environmental demands or atypical circumstances like sleep deprivation, but this may reflect a mere lack of investigation in diverse species under normal conditions.

### 4.7 Neurochemistry

A key determinant of brain state is neuromodulation. Excitatory monoaminergic systems elicit transitions between wake and sleep (Saper et al., 2010), and pre-sleep behavior may promote a change from wake-promoting neuromodulatory tone to that necessary for sleep (Sulaman et al., 2023). While neurochemistry was not a focus of the present work, its role in brain state determination cannot be overlooked, and a comprehensive understanding of brain states must encompass their regulation and mechanisms of action.

### 4.8 More on brain states

Many brain states exist in addition to the ones discussed herein. Anesthetics and psychedelics induce states distinct in electrophysiology, responsivity to stimuli, and subjective experience. Substates of NREM, microarousals, and microsleep are well-characterized in humans (Halász, 1998). As with electrophysiology, techniques like fMRI can be used to decode brain state (Rué-Queralt et al., 2021). Thanks to its applicability to human research, fMRI can be used to define discrete cognitive and task states. A given movie elicits a similar sequence of states across participants (Meer et al., 2020). Gao et al. (2020) defines brain states as brain activity in response to a given stimulus and decodes them using fMRI data. Haxby et al. (2011) did this first and didn't call stimulus responses "brain states". Shinkareva et al. (2008) defines brain states that correspond to the perception of different objects, implying that a single percept might constitute a state. But this seems to broaden the definition to a point of uselessness. Converging evidence from the works cited and reproduced above suggest that a brain state is an ongoing regime that moderates stimulus responses and that these responses do not themselves constitute brain states. It is tempting to add a temporal range on this definition, to require that brain states be phenomena that last minutes to hours, but it is increasingly recognized that brain states may last milliseconds (Nir & de Lecet al., 2023), days, or even months — responsivity in attention and working memory tasks has been shown to vary across seasons, as does mood (Meyer et al., 2016).

Science is the practice of explaining phenomena, and the development of conceptual models like brain states is in service to the bettering of our understanding. As the range of phenomena we can observe grows, our models will necessarily change. Perhaps at some future point it will be useful to think of every possible combination of firing rates across billions of neurons as a distinct brain state. But at this time, it seems most practical for the systems neuroscientist and the clinician to conceptualize a handful of states and substates which differ in behavior, electrophysiology, and responsivity to perturbations like ketamine.

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