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Bridging single neuron dynamics to global brain states

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2 ABSTRACT

3 Biological neural networks produce information on backgrounds of multi-scale spontaneous
4 activity that become more complex in brain states displaying higher capacities for cognition, for
5 instance, attentive waking versus anesthetized states. Here, we review brain state-dependent
6 mechanisms spanning ionic currents (microscale) to the dynamics of brain-wide, distributed,
7 transient functional assemblies (macroscale). Not unlike how microscopic interactions between
8 molecules underlie structures formed in macroscopic states of matter, using statistical physics,
9 the dynamics of microscopic neural phenomena can be linked to macroscopic brain dynamics.
10 Beyond spontaneous dynamics, it is observed that stimuli produce collapses of complexity, more
11 remarkable over highly complex background dynamics present in conscious than unconscious
12 brain states. In contrast, complexity may not be further collapsed in already low-dimensional
13 unconscious spontaneous activity. We propose that increased complexity of spontaneous
14 dynamics during conscious states supports responsiveness, enhancing neural networks'
15 emergent capacity to robustly encode information over multiple scales.

16 **Keywords:** cerebral cortex, consciousness, computation, empirical, theoretical, statistical physics, mean-field model, manifold,
17 coupling, synchrony, regularity, complexity, dimensionality, entropy

INTRODUCTION

18 Brain activity transitions between healthy states, including stages of sleep, restful and aroused waking, as
19 well as pathological states such as epilepsy, coma, and unresponsive wakefulness syndrome. From such
20 a diversity of brain states, phenomenological categories encompassing similar spatio-temporal activity
21 patterns can roughly, but usefully, be defined: unconscious (e.g., sleep and anesthesia) and conscious
22 (e.g., waking and dreaming) brain states. At the macroscopic, global scale, unconscious brain states are
23 dominated by high voltage, low frequency oscillatory brain activity related to the microscopic alternation

24 of synchronous neuronal spiking and near silence (Steriade et al., 1993; Brown et al., 2010). Conversely,
25 conscious states are macroscopically characterized by low voltage, high frequency, complex "disorganized"
26 dynamics resulting from more asynchronous irregular (AI) microscopic network activity (Brunel, 2000;
27 Tsodyks and Sejnowski, 1995; Van Vreeswijk and Sompolinsky, 1996), thought to be important for neural
28 coding (Van Vreeswijk and Sompolinsky, 1996; Zerlaut and Destexhe, 2017; Skarda and Freeman, 1987;
29 Tononi and Edelman, 1998).

30 Much as different states of matter like solids, liquids, and gases emerge from interactions between
31 populations of molecules, different brain states may emerge from the interactions between populations
32 of neurons. Statistical physics provides a mathematical framework to uncover structures of microscopic
33 interactions underlying macroscopic properties. In this sense, macroscopically observed high synchrony,
34 low complexity brain signals recorded from unconscious states may be accounted for by an increased
35 coupling in the system's components, behaving more like a solid (Peyrache et al., 2012; Le Van Quyen
36 et al., 2016; Olcese et al., 2016; Nghiem et al., 2018a). In contrast, conscious brain states may be described
37 as higher complexity (Sitt et al., 2014; Engemann et al., 2018; Nghiem et al., 2018a), perhaps liquid-like.

38 Though quantitative expressions directly linking order and complexity are not straightforward, various
39 definitions and metrics of complexity have been described to vary between brain states. Reports of enhanced
40 complexity in conscious compared to unconscious states may be understood as increased dimensionality
41 (El Boustani and Destexhe, 2010), namely the number of degrees of freedom needed to capture a system's
42 dynamics. Intuitively, dimensionality relates, though is not reducible to, algorithmic complexity which
43 quantifies the length of a deterministic algorithm required to reproduce an exact signal. For a random signal
44 resulting from purely stochastic dynamics (similar to neural activity observed during conscious states),
45 the length of the algorithm would be as long as the signal itself. In contrast, a purely oscillatory signal
46 (reminiscent of unconscious brain dynamics) can be recapitulated by a shorter algorithm, easily described
47 by a periodic trajectory in few dimensions.

48 Here, we aim to connect spatial scales from microscopic (nanometers to micrometers - molecules to whole
49 neurons) to macroscopic brain activity (centimeters to meters - brain areas to individual subjects' brains),
50 describing both spontaneous and evoked dynamics. Toward linking interpretations of studies between
51 scales, mesoscopic data (micrometers to millimeters - populations of thousands to tens of thousands
52 of neurons) have been useful to inform models of neuronal assemblies. The perspective concludes by
53 discussing a hypothesis best tested with a multi-scale understanding of brain function: the global complexity
54 of neural activity increases in conscious brain states so as to enhance responsiveness to stimuli. We suggest
55 responsiveness may depend on the capacity of neural networks to transiently collapse the dimensionality
56 of collective dynamics - in particular neural assemblies sensitive to stimulus features - into evoked
57 low-dimensional trajectories supporting neural codes (Fig. 1A).

MACROSCOPIC SIGNALS VARY ROBUSTLY BETWEEN BRAIN STATES

58 Both spontaneous and evoked (Fig. 1A-B) neural signals vary macroscopically across brain states, as
59 demonstrated in electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic
60 resonance imaging (fMRI). In unconscious states, neural activity is dominated by low-frequency, high-
61 amplitude signals (Niedermeyer and da Silva, 2005). Accordingly, analyses of entropy (Sitt et al., 2014;
62 Engemann et al., 2018), complexity (Tononi and Edelman, 1998), and dimensionality (El Boustani and
63 Destexhe, 2010) during unconscious states indicate a relative simplicity of signals compared to conscious
64 states. In unconscious states, synchronous activity slowly sweeps across the cortex (Massimini et al., 2004)
65 along paths formed by cortical tracts (Capone et al., 2017). In both conscious resting and unconscious states,

66 the default mode network (Raichle et al., 2001; Boly et al., 2008) establishes a pattern of synchronization
67 between brain areas, producing correlations in ultra-slow (< 1 Hz) dynamics (Brookes et al., 2011).
68 Sustained, slow oscillations were initially reported in the thalamocortical system (Steriade, 2003), but are
69 also observed experimentally in isolated cortex, without thalamus (Timofeev et al., 2000; Sanchez-Vives
70 and McCormick, 2000). Thalamocortical connections shape slow wave dynamics (David et al., 2013;
71 Crunelli et al., 2015; Destexhe et al., 2007; Zucca et al., 2019; Poulet et al., 2012) although slow oscillations
72 appear to be the default state of cortical networks (Sanchez-Vives and McCormick, 2000; Sanchez-Vives
73 et al., 2017).

74 Patterns of neocortical regions activated in resting state networks have been successfully retrieved using
75 eigenmodes of the structural connectivity matrix, i.e. the possible oscillatory patterns at frequencies allowed
76 by white matter tract lengths (Atasoy et al., 2016). In active states, the executive control network replaces
77 the default mode (Fox et al., 2005), and the co-activation of different cortical regions is more strongly
78 controlled by correlations in external stimuli than by white matter structural connectivity (Gilson et al.,
79 2018), with patterns of activity propagating recurrently between low-level, sensory areas and high-level,
80 associative areas.

81 During conscious states, on the background of globally disorganized neural activity, transient patterns
82 emerge (Singer, 2013; Uhlhaas et al., 2009; Duncan-Johnson and Donchin, 1982; Goodin and Aminoff,
83 1984; Sur and Sinha, 2009; Luck and Kappenman, 2011; Sato et al., 2012; Chemla et al., 2019; Churchland
84 et al., 2012). Under an interpretation of brain states in analogy to states of matter, microscopic changes in
85 the interactions between neurons could permit the emergence of larger-scale structures in brain activity.

MICROSCOPIC MECHANISMS; BIOPHYSICS OF BRAIN STATES

86 Experiments have demonstrated that during unconscious brain states, the membrane potential (V_m) of
87 single cells slowly oscillates between hyperpolarized and depolarized potentials associated with alternating
88 periods of silence (Down states, also termed “OFF periods”) and AI-like firing (Up states, also termed
89 “ON periods”)(Steriade et al., 1993) (Fig. 2A). During conscious brain states, neurons show sustained but
90 sparse and irregular AI firing patterns (Vreeswijk and Sompolinsky, 1998; Destexhe et al., 1999; Steriade,
91 2000; Brunel, 2000; Renart et al., 2010; Dehghani et al., 2016; di Volo and Torcini, 2018). It was found
92 that, during AI states, excitatory (E) and inhibitory (I) synaptic inputs are near-balanced (Dehghani et al.,
93 2016), as predicted theoretically (Van Vreeswijk and Sompolinsky, 1996). In AI states, voltage fluctuations
94 drive neurons over the threshold for firing action potentials, resulting in irregular spiking dynamics, also
95 known as fluctuation-driven regimes (Destexhe, 2007; Destexhe and Rudolph-Lilith, 2012; Kuhn et al.,
96 2004). To understand mechanisms at work during fluctuation-driven dynamics, computational models have
97 further shown that three parameters are important to capture neuronal responses in this regime, the average
98 membrane voltage V_m , the amplitude of V_m fluctuations, and the conductance state of the membrane (Reig
99 et al., 2015; Zerlaut et al., 2016).

100 Neuromodulators, including acetylcholine, play important biological roles in modulating the membrane
101 properties of neurons (McCormick, 1992) and thus transitions between AI and slow oscillatory dynamics
102 through the regulation of membrane currents (Hill and Tononi, 2005). Neuromodulators are present
103 at higher concentrations during conscious states (McCormick, 1992; Jones, 2003) and, most generally,
104 inhibit potassium (activity-dependent and leak K^+) channels, which leads to depolarization of cells and
105 suppression of *spike-frequency adaptation*. At low neuromodulatory concentrations, during unconscious
106 states, K^+ leak channels are constitutively open and activity-dependent K^+ open when neurons spike,
107 allowing K^+ ions to exit the cells thus hyperpolarizing cells. Accumulating self-inhibition in the form

108 of spike-frequency adaptation during Up periods results in the transition to Down states. Conversely,
109 spike-frequency adaptation wears off during Down states, allowing noise fluctuations (present ubiquitously
110 (Destexhe and Rudolph-Lilith, 2012)) to trigger transitions to Up states (Destexhe, 2009; Jercog et al.,
111 2017; di Volo et al., 2019; Nghiem et al., 2018c) (Fig.2B). Computationally speaking, for high values of
112 spike-frequency adaptation, bistability can be observed, with solutions at firing rate zero (Down state)
113 and non-zero (Up state) values (di Volo et al., 2019; Holcman and Tsodyks, 2006). The more chaotic
114 dynamics of AI states associated with states of consciousness allows for more reliable stimulus encoding
115 (D'Andola et al., 2017), more reliable propagation (Zerlaut and Destexhe, 2017), and more sustained
116 responses (Nghiem et al., 2018c) to stimuli over time. In contrast, during unconscious states, neuronal
117 responses are more unreliable and vary greatly depending on the stimulus amplitude and whether cells
118 receive inputs in Up or Down periods (Rosanova and Timofeev, 2005; Reig et al., 2015).

119 The Ising model for spin glasses (Jaynes, 1982) fitted to neural data (Schneidman et al., 2006) has
120 revealed divergent types of emergent neuronal dynamics in conscious and unconscious states. While
121 neuronal interactions are pairwise in wakefulness (Nghiem et al., 2017), coupling becomes population-wide
122 in deep sleep compared to wakefulness (Nghiem et al., 2018b; Tavoni et al., 2017). In particular, inhibitory
123 neurons organize synchronous activity across populations (Nghiem et al., 2018b; Zanoci et al., 2019),
124 especially during deep sleep (Peyrache et al., 2012; Le Van Quyen et al., 2016; Olcese et al., 2016) where
125 inhibitory neurons regulate rhythms of slow wave dynamics (Compte et al., 2008; Zucca et al., 2017; Funk
126 et al., 2017; Zucca et al., 2019).

127 To summarize, between unconscious and conscious brain states, microscopic data appear intuitively
128 related to macroscopic data: synchronous microscopic Up and Down states resulting from constitutive
129 and activity-dependent, hyperpolarizing currents due to reduced neuromodulation correspond to relatively
130 simple, high-amplitude macroscopic dynamics observed in unconscious states. Active, disorganized,
131 desynchronized, AI, low adaptation, high neuromodulation conditions correspond to low amplitude,
132 complex, conscious brain signals. On backgrounds of differing spontaneous dynamics, generalizable
133 patterns of activity (a.k.a. neural graphoelements) are observed. Cash et al. have shown that K-complexes
134 (graphoelements characteristic of sleep stage 2) are complementarily observed both at microscopic and
135 macroscopic scales (Cash et al., 2009). Other identifiable patterns also begin to emerge in empirical and
136 theoretical data, including phase cones (Freeman and Barrie, 2000) and interacting traveling waves (Sato
137 et al., 2012; Chemla et al., 2019). Since statistical physics has successfully described neuronal interactions
138 for different brain states, we ask next whether mesoscale methods from statistical physics can help represent
139 spontaneous and evoked dynamics of neuronal populations, thus formally linking knowledge between
140 micro- and macroscopic scales.

MESOSCALE BRIDGES; POPULATIONS OF NEURONS

141 Brain dynamics at mesoscopic scales, describing thousands of neurons, are investigated empirically by
142 electrophysiology and more recently, voltage-sensitive dyes (Arieli et al., 1996; Chemla and Chavane,
143 2010). At mesoscales, brain activity follows the trend of increasing complexity of spontaneous activity
144 with consciousness (Fig.2A). Studying the effects of inputs at the mesoscale, studies have shown that
145 perturbations during deep sleep states induce slow waves, but, during waking states, perturbations can result
146 in chains of phase-locked activity (Pigorini et al., 2015) leading to causal global interactions (Rosanova
147 et al., 2018).

148 *Mean-field* models offer a formalism for scaling up microscopic detail to collective macroscopic dynamics
149 using few equations, offering a computational advantage for simulations. In describing states of matter,

150 mean-field models simplify the probabilistic behavior of molecules to the relatively more predictable
151 behavior of macroscopic states (Kadanoff, 2009). A rich literature has begun to develop mean-field models
152 of neuronal populations, showing that global variables describing population activity can be usefully
153 derived from the biophysics of neurons and their interactions (Ohira and Cowan, 1993; Ginzburg and
154 Sompolinsky, 1994; El Boustani and Destexhe, 2009; Buice et al., 2010; Dahmen et al., 2016). Mean-field
155 models have qualitatively reproduced temporal features of spontaneous dynamics including AI (El Boustani
156 and Destexhe, 2009), Up and Down dynamics (Compte et al., 2003; Jercog et al., 2017; Tartaglia and Brunel,
157 2017; di Volo et al., 2019), and transitions between these states (Tort-Colet et al., 2019; di Volo et al., 2019).
158 In addition, connecting mean-fields provides a tool for simulating the propagation of patterns through time
159 and space, across mesoscale structures. For example, recent work deriving mean-field models of networks
160 with conductance-based synapses has reproduced the suppressive interaction between travelling waves
161 observed in visual cortex during conscious states, a biological phenomenon that could not be captured by
162 current-based networks (Chemla et al., 2019).

163 Mean-field models have highlighted that, while complicated to apply mathematically in the framework of
164 conductance-based models (di Volo et al., 2019), voltage-dependent interactions constitute a significant
165 non-linearity in the membrane evolution equations. Voltage-dependent interactions appear to be important
166 for explaining non-trivial responses of biological neurons, through the mean and fluctuations of the cells'
167 membrane voltage (Reig et al., 2015). In fact, while these results do not imply that this effect is due only
168 to conductances, they show that voltage dependent synapses play a role in the nonlinear state-dependent
169 response of a neural network. As shown in Fig.2C, various levels of membrane conductance, regulated by
170 voltage-dependent synapses, are shown to differently shape population responses.

171 Finally, renormalization group theory, a method of coarse-graining microscopic detail to obtain
172 macroscopic laws helping to understand how order can emerge from apparent disorder (Cardy, 1996;
173 Goldenfeld, 2018; Wilson, 1979) has recently begun to be applied to neural assemblies (Meshulam et al.,
174 2019), laying further foundation for the formal connection of our understanding of brain function across
175 scales.

DISCUSSION

176 In this paper, we briefly reviewed work on the measurement and modeling of brain states at different
177 scales, from single neurons to cell assemblies and global brain activity, considering both spontaneous and
178 evoked dynamics. In particular we highlighted that increased complexity in the dynamics of conscious
179 brain states relates to changes in single-neuron biophysics, tuned by neuromodulation. In unconscious
180 states, reduced neuromodulation promotes activity-dependent self-inhibition of excitatory neurons as they
181 spike, leading to alternating, synchronous transients of silence and firing, that produce high-amplitude, low-
182 complexity, synchronous signals, on resonant frequencies of the structural connectome. During conscious
183 states, neuronal discharges are asynchronous, irregular and fluctuation-driven, resulting from sustained
184 membrane depolarization in cortical neurons, promoting effective neural communication.

185 Beyond conscious and unconscious categories proposed here for the sake of brevity, important differences
186 exist within categories of unconscious and conscious states (Brown et al., 2010; El Boustani and Destexhe,
187 2010; Nghiem et al., 2018a). Unlike healthy wakefulness and sleep, epileptic networks display both
188 excessively high conductance and strongly synchronized, regular dynamics (El Boustani and Destexhe,
189 2010). Further, brain signals in coma are both low-amplitude and low-complexity, in contrast to high-
190 amplitude signals observed in other unconscious states, but also to complex signals observed in conscious
191 states (El Boustani and Destexhe, 2010). Such anomalous deviations from the overall trend of coordinated

192 changes in complexity and amplitude may illuminate mechanisms underlying disease-causing deviations
193 from healthy brain states (Mackey and Glass, 1977).

194 To characterize brain states, it has been useful to consider not only spontaneous dynamics but also patterns
195 evoked by perturbations. It was found that macroscopic responsiveness highly depends on brain state and
196 different patterns of responses are evoked in conscious versus unconscious states (Massimini et al., 2005).
197 Such state-dependent responsiveness can also be seen at the level of local networks *in vivo* and *in silico*,
198 for example in the different reliability of responses to perturbations given during Up and Down periods of
199 slow waves (Reig et al., 2015; Zerlaut and Destexhe, 2017). In simulations, different responsiveness could
200 be accounted for by three parameters: membrane voltage, voltage fluctuation amplitude, and membrane
201 conductance (Reig et al., 2015). These parameters could be well described by mean-field models (di Volo
202 et al., 2019), able to capture fundamental properties of spontaneous dynamics and also state-dependent
203 responses at mesoscales. As such, the data-driven connection of such mean field models may serve as
204 natural candidates for modeling the emergence of mesoscopic and macroscopic-scale patterns.

205 Transient collapses of dimensionality found in encoding networks were also discussed as substrates
206 potentially supporting neural codes. Such collapses in complexity have been observed in active ensembles
207 at scales spanning microscopic (Churchland et al., 2010; Fairhall, 2019) to macroscopic (Quiroga et al.,
208 2001; Zang et al., 2004) activity. This echoes recent work studying recordings of neural populations which
209 highlighted that neural representations of stimuli may lie on low-dimensional manifolds (Gallego et al.,
210 2017; Stringer et al., 2019; Chaudhuri et al., 2019; Sadtler et al., 2014; Golub et al., 2018; Chaudhuri
211 et al., 2019; Churchland et al., 2012; Zhao and Park, 2017; Recanatesi et al., 2019). Indeed neurons do
212 not fire independently, which would yield dynamics of dimensionality as high as the number of neurons,
213 but instead follow constrained trajectories of activity that can be captured by descriptions of much lower
214 dimensionality that depend on spontaneous and evoked dynamics. For example, a neural population firing
215 in synchrony could be fully described by a periodic orbit trajectory constrained to a low-dimensional space
216 (Churchland et al., 2012). Since spontaneous global network activity increases in dimensionality during
217 conscious states, we ask whether the transient collapse of complexity in specific networks, translating the
218 emergence of simpler dynamical structures from disorder, may be associated to neural codes.

219 As an analogy, windmills facing all in one direction display low complexity, but can only be synchronously
220 active or inactive. Windmills facing in random directions, in contrast, are a higher complexity configuration
221 able to represent wind from any direction through the activity of a subset. The activity of an ensemble
222 of windmills tuned to a particular direction of wind could represent a collapse of complexity and the
223 generation of information by that subset (in this case, about the direction of wind). Similarly, enhanced
224 dimensionality associated with conscious states could subserve neural information through the collapse of
225 complexity in neural assemblies tuned to encode particular representations.

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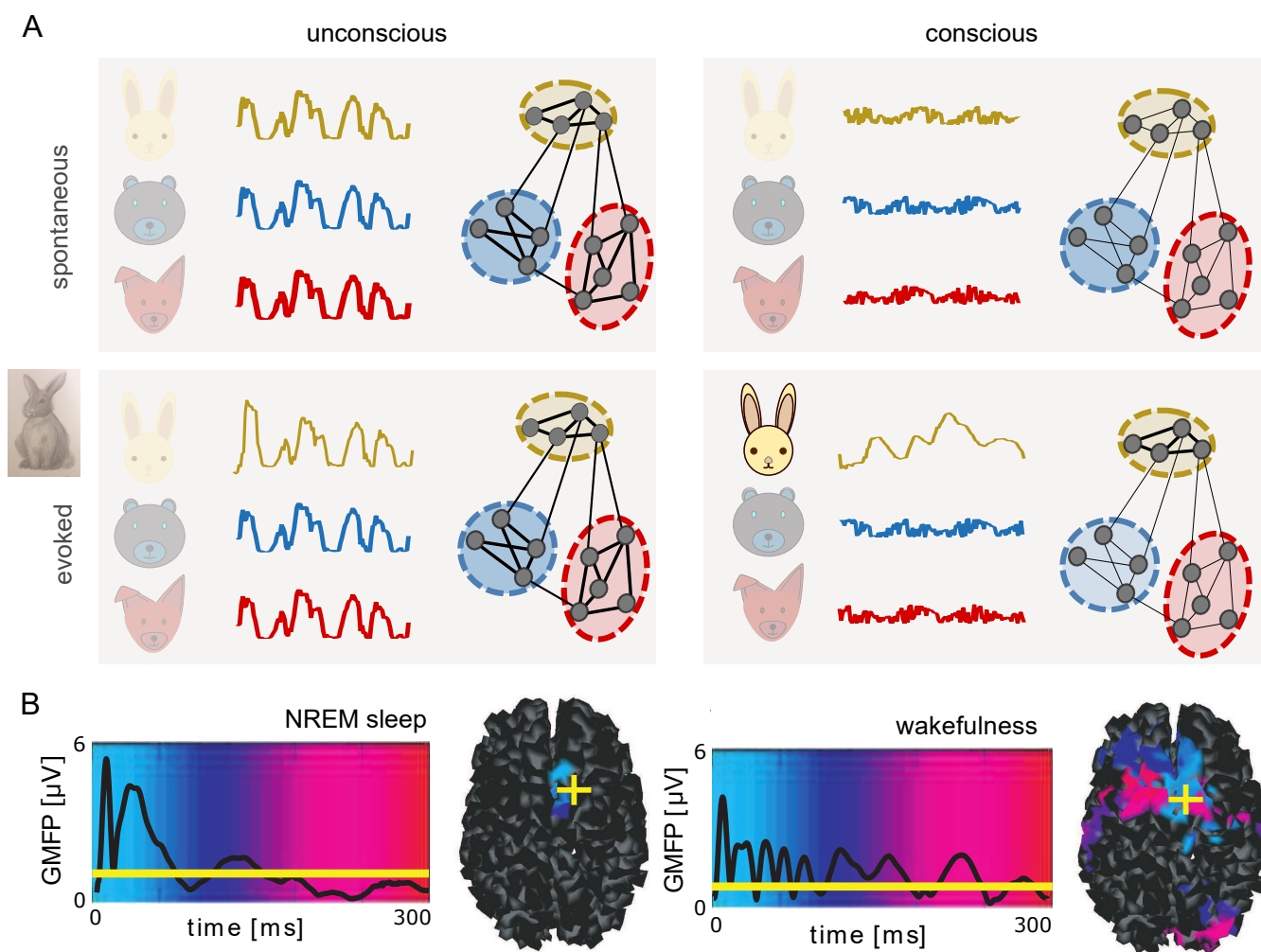


Figure 1. Complex dynamics associated with conscious brain states provide a potential substrate for neural coding. **A** Schematics of spontaneous (top) and evoked (bottom) dynamics in connected neuronal assemblies encoding different related concepts (different colors) in unconscious (left) and conscious (right) brain states. In unconscious brain states, slow, synchronous, large amplitude oscillations are observed. Stimuli delivered during unconscious states evoke large amplitude, transient responses similar to spontaneous activity. In contrast, during conscious states, asynchronous, irregular firing of neurons results in macroscopically desynchronized, low amplitude signals. Only networks recruited by the perturbation (here, a rabbit) produce lower-dimensional patterns that propagate relatively further in time and space. **B** Global mean field power (GMFP) recorded with EEG in response to transcranial magnetic stimulation, during deep, non-rapid eye movement (NREM) sleep versus wakefulness. Mean EEG signal is represented by black traces. Background colors represent temporal latency (light blue, 0 ms; red, 300ms) of maximum current sources, also shown in cortical space on the right, where yellow crosses represent the location of stimulation (right dorsolateral premotor cortex). Reprinted with permission from AAAS (Massimini et al., 2005). If brain dynamics between states may be described in analogy to states of matter, perturbing unconscious brains results in large, brief signals perhaps akin to a small perturbation of a solid, which can displace the solid briefly, but will not modify its internal structure. In contrast, the same perturbation delivered during conscious, liquid-like brain states results in smaller but more complex patterns that propagate further in time and space. Under this interpretation, in coding networks, responses evoked during conscious states could represent a form of transient 'crystallization', consistent with neural trajectories lying on low-dimensional manifolds.

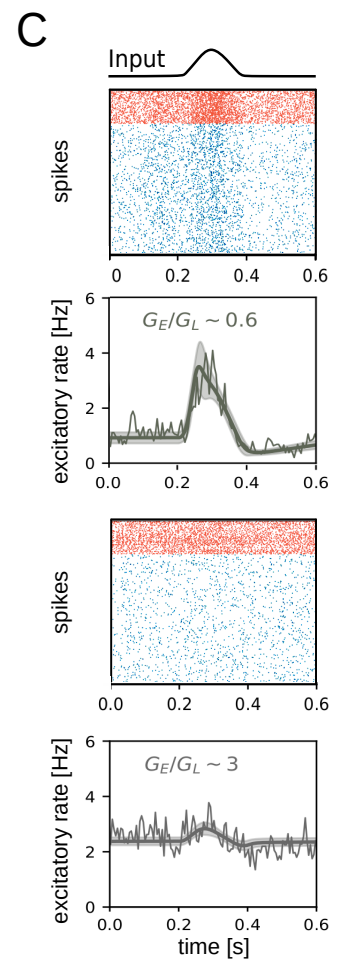
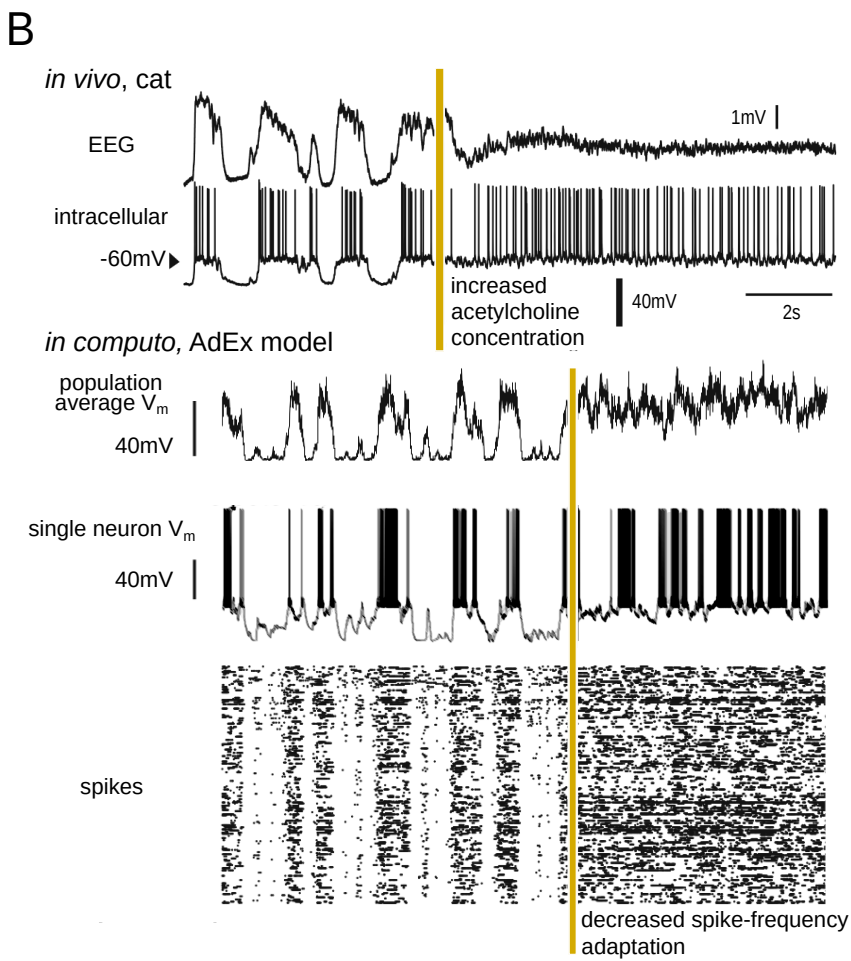
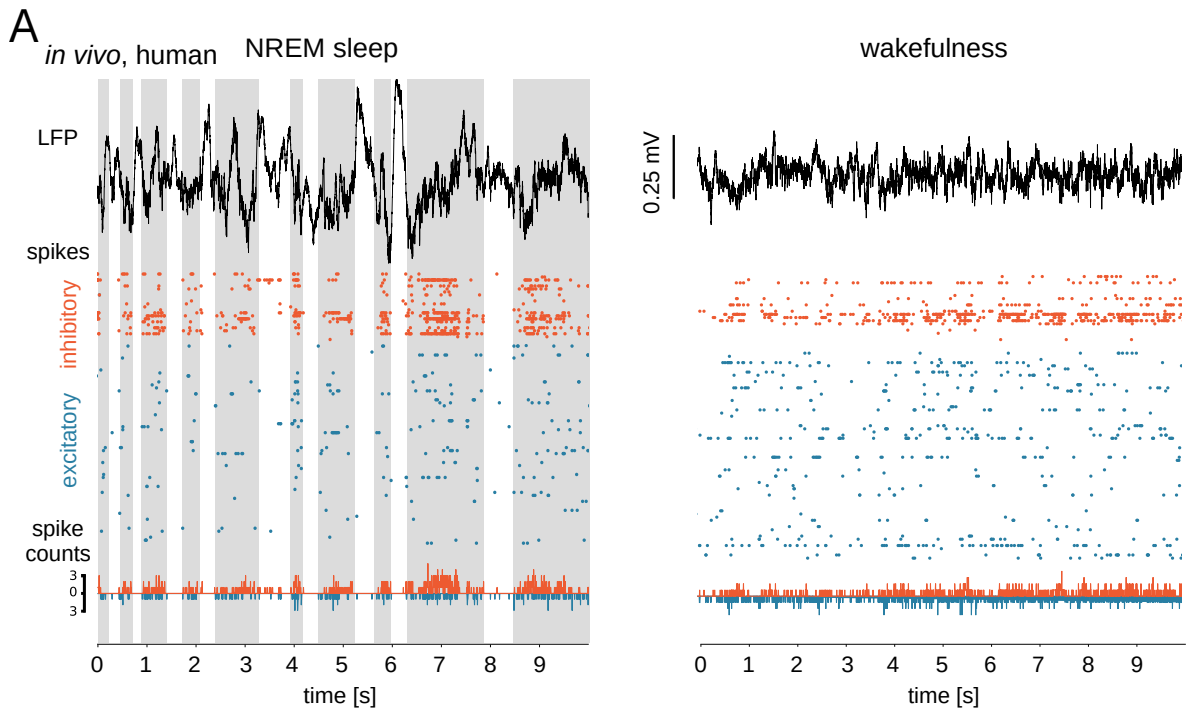


Figure 2. Simple, high-amplitude signals in unconscious brain states are associated with synchronous regular neuronal firing, whereas complex, low-amplitude signals in conscious brain states emerge from asynchronous irregular firing. **A** Data sample from (Peyrache et al., 2012; Le Van Quyen et al., 2016; Teleńczuk et al., 2017; Dehghani et al., 2016; Nghiem et al., 2018b), containing local field potential (LFP; top), spike times (action potentials; middle), and spike counts (bottom) recorded from a human subject during NREM sleep (left) and wakefulness (right). Spikes from inhibitory (orange) and excitatory (blue) neurons were separated and spike counts were calculated in bins of 5ms. Up states shaded in the left panel. **B** Transition between slow-wave (unconscious) and activated (conscious) state dynamics *in vivo* (top) and *in silico* (bottom). Experimentally the transition is generated by electrical stimulation of acetylcholine neurons in the pedunculopontine tegmentum (PPT) in anesthetized cat (Volgushev et al., 2011), triggering awake-like, desynchronized dynamics in cortex (Rudolph et al., 2005). A prominent consequence of enhancing cholinergic signaling in cortex is a reduction of spike-frequency adaptation (McCormick, 1992). *In silico*, a similarly desynchronizing effect can be generated by reducing the parameter responsible for spike-frequency adaptation. Simulated traces shown in the bottom were modified from (Destexhe, 2009), which used a network of adaptive exponential integrate-and-fire neurons. The average V_m of the network, the V_m of a randomly chosen neuron, and the raster plot of the network are shown. Reproduced with permission from (Destexhe, 2009). **C** State dependence of network responsiveness. The responsiveness of two spiking networks to a sinusoidal pulse is shown. Raster plots display spike times of excitatory (blue) and inhibitory (orange) neurons connected by voltage-dependent synapses. Population activity (spike counts, thin line), as well as mean (thick line), and standard deviation (shaded area) of population firing rate generated by a mean field model developed in (di Volo et al., 2019). Responsiveness is found to vary between levels of conductance, obtained by changing the ratio of the time-averaged global excitatory conductance (G_E) (Destexhe et al., 2003) to membrane leakage conductance (G_L) from low (top) to high values (bottom).

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