

Spontaneous Fluctuations and Non-linear Ignitions: Two Dynamic Faces of Cortical Recurrent Loops

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<http://dx.doi.org/10.1016/j.neuron.2015.09.018>

Recent human neurophysiological recordings have uncovered two fundamental modes of cerebral cortex activity with distinct dynamics: an active mode characterized by a rapid and sustained activity (“ignition”) and a spontaneous (resting-state) mode, manifesting ultra-slow fluctuations of low amplitude. We propose that both dynamics reflect two faces of the same recurrent loop mechanism: an integration device that accumulates ongoing stochastic activity and, either spontaneously or in a task-driven manner, crosses a dynamic threshold and ignites, leading to content-specific awareness. The hypothesis can explain a rich set of behavioral and neuronal phenomena, such as perceptual threshold, the high non-linearity of visual responses, the subliminal nature of spontaneous activity fluctuations, and the slow activity buildup anticipating spontaneous behavior (e.g., readiness potential). Further elaborations of this unified scheme, such as a cascade of integrators with different ignition thresholds or multi-stable states, can account for additional complexities in the repertoire of human cortical dynamics.

Introduction: Two Modes of Cortical Function

Traditionally, research of human cortical function has focused on mapping the neuronal activations triggered by supra-threshold stimuli and well-defined tasks. Similar to numerous studies in animal models, measurements in the human cortex also revealed that the central characteristic of optimal neuronal responses consists of rapidly emerging bursts of neuronal activity. Taking the human sensory cortex as a well-researched example, cortical activations to optimal stimuli were shown to be reflected in bursts of high firing rates in single neurons recorded invasively in patients undergoing clinical diagnosis for epilepsy (e.g., Bitterman et al., 2008; Nir et al., 2007), in an increase of broadband gamma power during invasive electrocorticography (ECoG) recordings in patients (Nir et al., 2007; Manning et al., 2009), in large blood-oxygen-level-dependent (BOLD) responses in fMRI scans (e.g., Heeger and Ress, 2002; Mukamel et al., 2005), and in electroencephalography (EEG) and magnetoencephalography (MEG) as reflected in large event-related potential (ERP) responses (e.g., Hämäläinen et al., 1993; Gao et al., 2013).

Particularly for sensory systems, it was assumed that in the absence of a stimulus (e.g., in complete darkness), the sensory cortex enters an uninformative, low-level baseline mode. However, following the pioneering research of Arieli et al. (1996) in anesthetized animals, paralleled with BOLD fMRI recordings in the human motor cortex by Biswal et al. (1995), numerous studies have, by now, established that in the absence of a stimulus or task—in what has been termed the “resting state”—cortical networks enter into a highly informative mode of spontaneous activity. In contrast to the active mode, these so-called

resting-state fluctuations are characterized by low-amplitude modulations of activity and ultra-slow (<0.1 Hz) dynamics. Although most research on resting-state fluctuations has relied on BOLD imaging, subsequent research has confirmed their existence also in firing-rate modulations (Nir et al., 2008), ECoG recordings (He et al., 2008; Nir et al., 2008), and scalp EEG (Schurger et al., 2015), following on the seminal studies of Berger and colleagues (e.g., Niedermeyer and da Silva, 2005).

Importantly, the slow spontaneous fluctuations are not confined to specific resting-state networks but emerge in each and every cortical site that has been studied so far. For example, the human visual cortex shows widely spread and highly structured spontaneous BOLD fluctuations in the absence of visual inputs (e.g., Arcaro et al., 2015; Nir et al., 2006). The structure of the spontaneous fluctuations appears to be highly informative and likely reflects the statistics of the natural environment and cognitive traits (Berkes et al., 2011; Hamelech and Malach, 2013). The structure and ubiquity of these fluctuations suggest that they may constitute an important mode of cortical function.

Figure 1 compares the two modes of cortical function as revealed in single units recorded in the auditory cortex of patients in the course of diagnostic procedure for epilepsy (modified from Bitterman et al., 2008; Nir et al., 2008). Shown are stimulus-driven, active responses (Figure 1A) versus resting-state spontaneous fluctuations in firing rates (Figure 1B). The most striking difference that can be readily appreciated is the transition from rapid-burst dynamics in the active mode—in which bursts develop within a fraction of a second in a response to an auditory stimulation—to low-amplitude ultra-slow fluctuation dynamics during resting mode, when there is no auditory stimulus and

Active and resting state modes
reflected in neuronal firing in human auditory cortex

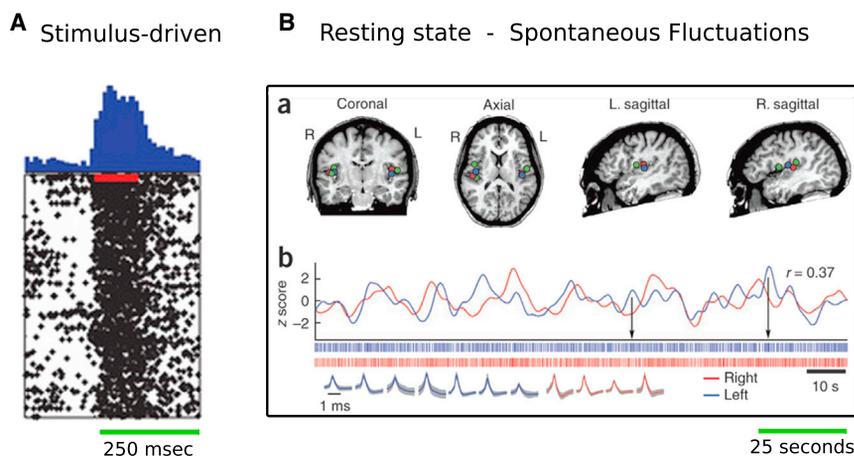


Figure 1. Two Modes of Cortical Function
Examples of active and resting-state spontaneous modes reflected in firing of the same neurons recorded from human auditory cortex.
(A) Responses to tones of specific frequency (modified from Bitterman et al., 2008).
(B) Spontaneous activity generated in the absence of auditory stimulation. Note the strikingly different timescales characterizing the two phenomena (modified from Nir et al., 2008).

the patients rest in a quiet room. Here, we hypothesize that these two modes, which seem to have such drastically different dynamic properties, may originate from the same network mechanism of excitatory reverberatory loops.

Neuronal Mechanisms Underlying the Active Mode

At least within the domain of sensory system neurophysiology, a number of experimental results suggest that, in addition to the well-documented bottom-up and top-down flow of information, there is a third major component that consists of strong reverberatory interactions relying on lateral connections. Such lateral recurrent interactions can readily lead to highly non-linear positive-feedback dynamics.

An important cortical phenomenon that appears to reflect such non-linear behavior concerns the threshold nonlinearities observed in the input-output relationship between a sensory stimulus and the neuronal response. A consistent observation when gradually increasing the intensity of a weak sensory stimulus—for example, by constraining participants to view a briefly presented stimulus interrupted by a mask (“backward-masking” method reviewed in Kouider and Dehaene, 2007; Figure 2A)—is that the neuronal response is not linearly related to the increase in strength of the physical stimulus (e.g., exposure duration or target-mask delay) but shows a highly non-linear, typically steeply sigmoid function (e.g., visual awareness with EEG contrast response in Del Cul et al., 2007; and with contrasted BOLD activity in Grill-Spector et al., 2000; or auditory awareness in Gutschalk et al., 2008). Thus, there is a range of values, both low and high, in which changing the stimulus intensity only marginally affects the neuronal response, while in a rather narrow range of values (which are termed the sensory “threshold”), minimal changes in the stimulus intensity lead to greatly amplified neuronal activity. Such neuronal response non-linearity has been demonstrated across all measurement modalities from BOLD imaging (Bar et al., 2001; Grill-Spector et al., 2000; Hesselmann and

Malach, 2011), MEG and EEG recordings (Lamy et al., 2009; Sekar et al., 2013; Wyart et al., 2012), ECoG recordings (Fisch et al., 2009), and even single-unit recordings in medial-temporal lobe structures (Quiroga et al., 2008). Even for a fixed stimulus presented close to threshold, the neural response may be bimodal, indexing the subject’s report: high activity is observed on trials when the subject reports perceiving the stimulus, and low or no activity is observed

when he or she reports being unable to perceive it (Fisch et al., 2009; Quiroga et al., 2008; Sergent et al., 2005).

A second informative aspect of these non-linear responses is their sustained nature: once a neuronal response crosses the threshold, changing or even removing the sensory input does not shut off the neuronal response, which remains at a high value for durations of up to a few hundred milliseconds. This phenomenon is illustrated in Figure 2, which depicts a typical backward-masking paradigm (Figure 2A) and two examples of threshold phenomena revealed during backward masking. In Figure 2B (modified from Fisch et al., 2009), ECoG recordings from face-selective sites in patients show that, at threshold, the very same stimulus (a briefly flashed face) can lead to a highly amplified signal when reported as perceived (red line) and to much a smaller response when reported as unperceived (blue line). In Figure 2D (modified from Dehaene and Changeux, 2011), depicting BOLD-fMRI signals recorded from the word-form area, a striking amplification of the signal is evident at threshold for consciously perceived versus non-perceived words (Dehaene et al., 2001). Furthermore, the sustained nature of the “ignited” response can be appreciated in Figure 2B by noting that the neuronal response upon perceiving the target lasts for several hundreds of milliseconds, while the target-stimulus duration itself was less than 20 ms. It should be noted that this sustained “ignition” effect cannot be attributed merely to the first stages of the cortical hierarchy. It has been demonstrated that non-linear responses in high-order cortical areas can emerge in the absence of such effects in earlier cortical stages (Bar et al., 2001; Del Cul et al., 2007; Fisch et al., 2009; Grill-Spector et al., 2000; Kouider et al., 2013).

Mechanisms Underlying the Ignition Threshold

The respective roles of local versus global long-distance network phenomena in such ignitions are not fully established and remain

Neuronal and behavioral evidence for threshold non-linearities

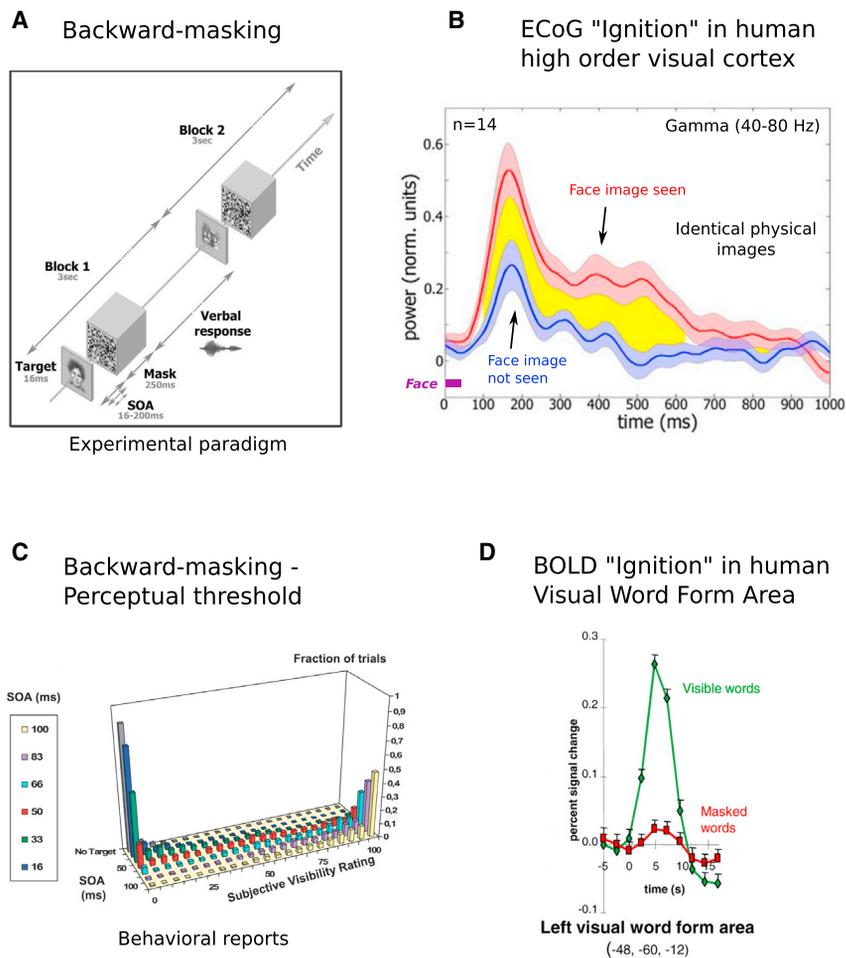


Figure 2. Neuronal and Perceptual Evidence for Threshold Non-linearity Ignition in the Human Visual System

(A) The backward-masking experimental paradigm, which allows precise timing of stimulus presentation and has been used extensively to uncover ignition dynamics (modified from Fisch et al., 2009). SOA, stimulus-onset asynchrony.

(B) Intracranially recorded ECoG responses from human high-order, face-selective sites, showing activation to perceived and non-perceived face stimuli at threshold. Note the high signal amplitude and relatively sustained responses, which far outlast the duration of the presented stimulus (indicated by the purple bar; modified from Fisch et al., 2009).

(C) Behavioral evidence of an all-or none perceptual response during the backward-masking paradigm. Despite gradual changes in stimulus strength, both objective and subjective responses show a clear bifurcation into visible and non-visible states (modified from Del Cul et al., 2007).

(D) BOLD-fMRI responses from the human visual word-form area demonstrating the highly nonlinear amplification of BOLD signal associated with crossing the perceptual threshold during visual perception of words (modified from Dehaene and Changeux, 2011). Error bars indicate means \pm SEM.

a matter of debate (Lamme, 2006). Empirically, both local and global ignitions are revealed under various conditions (e.g., Dehaene and Changeux, 2005; Fisch et al., 2009; Noy et al., 2015). A plausible model for their generation is readily suggested by noting the dense lateral intra- and inter-areal connections that characterize cortical networks (e.g., Amir et al., 1993; Douglas and Martin, 1991; see review by Felleman and Van Essen, 1991). These lateral connections are mainly excitatory, making them highly susceptible to entering into a positive feedback reverberatory dynamics, once the net excitatory drive overcomes the strong inhibitory and leakage control. Such net excitation, emerging in densely and reciprocally connected networks, can readily lead to a fast and non-linear ignition. Figure 3 illustrates, using a simulation of a minimal one-dimensional dynamic system (see formal description in Supplemental Experimental Procedures and also see Figure S1), how such non-linear ignitions emerge naturally in a recurrent network (Figure 3A, top). The dynamic consequences of having the net excitation exceed the inhibitory suppression (Figure 3A, bottom left) are depicted in Figure 3B. Note the sustained and high activity that follows

a short time constant during the ignition, does not necessarily imply a short-latency response following, e.g., a visual stimulus. Thus, an ignition can occur after a long delay of “dormant” activity. Indeed, bursts of visual responses were shown to emerge in the human medial temporal lobe only after rather a long period (>300 ms in Quiroga et al., 2008). Such long delays may be due either to long subliminal buildup time following the stimulus presentation (discussed later) or to a long chain of intermediate links.

Simulations suggest that NMDA glutamate receptors, with their slow dynamics, may play a specific role in inducing a prolonged ignited state (Wong and Wang, 2006). In Dehaene and Changeux’s (Dehaene et al., 2003; Dehaene and Changeux, 2005) simulations, NMDA receptors were specifically allocated to recurrent top-down connections. This hypothesis was recently borne out experimentally, as late sustained activity in V1 was selectively affected by NMDA receptor blockers (Self et al., 2012), while the early feed-forward wave was spared.

It should be noted that recurrent networks tend to self-ignite even in the absence of inputs, as observed both in simulations

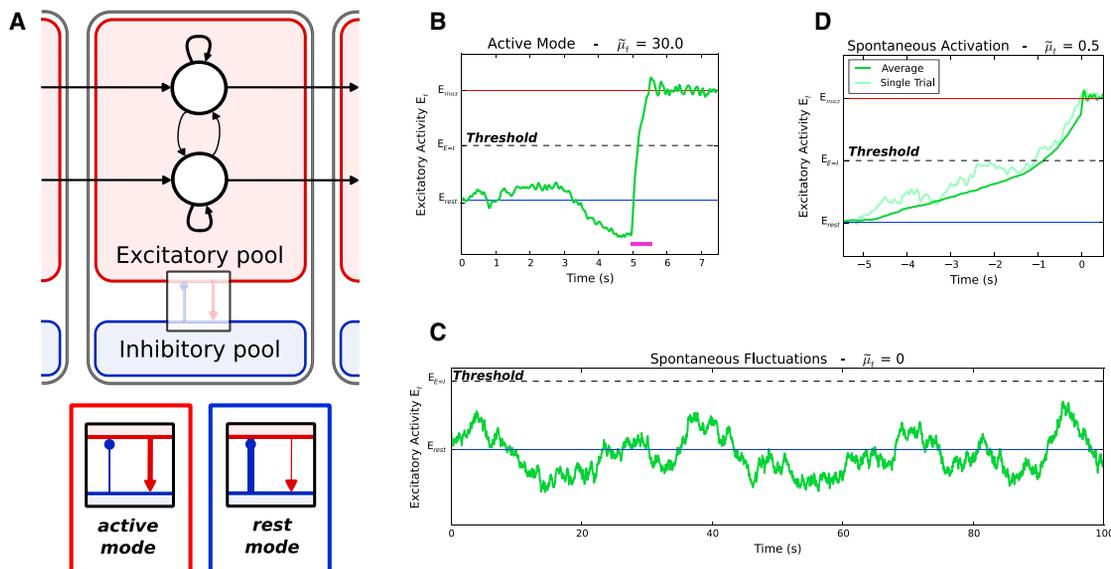


Figure 3. Illustration of the Network Dynamics Below and Above the Ignition Threshold

(A) The structure of the local recurrent network used for the illustration; the parameters of the network were specifically chosen to demonstrate the feasibility of the observed dynamics (inspired from Marti et al., 2008).

(B) Illustration of the active ignited dynamics. Note the steep buildup and sustained high activity associated with crossing the threshold.

(C) Illustration of the resting-state, spontaneous dynamics. Note that the same network enters ultra-slow fluctuation dynamics when below the ignition threshold.

(D) Long anticipatory build-up. Even in the absence of external driving input, the slow fluctuations may spontaneously cross the ignition threshold initiating a rapid signal amplification. Dark green indicates an average over 50 trials; light green indicates a single-trial example.

(Dehaene and Changeux, 2005) and in isolated neural tissue (e.g., Eytan and Marom, 2006). Thus, both modeling work and characteristic cortical circuitry point to reverberatory network activity as a prominent mechanism that could drive the non-linear ignition process. However, we emphasize that the assignment of the non-linear ignition to reverberating connections is tentative at this point. Other neurobiological mechanisms based on inhibitory loops (e.g., Lo and Wang, 2006) or on non-linear dendritic events (Larkum, 2013) may play important roles as well. Particularly interesting is the observation of a zone for the initiation of calcium action potentials (Ca^{2+} spikes) in the apical dendrites of layer 5 pyramidal neurons (Larkum and Zhu, 2002), which is described as “a tremendously explosive engine, driving the L5 pyramidal cell to fire repetitively when ignited” (Larkum, 2013, p. 141). Recurrent feedback from distant cortical areas is ideally suited to trigger this dendritic ignition phenomenon, as such feedback lands simultaneously onto supragranular apical and on infragranular layers (van Kerkoerle et al., 2014), thus simultaneously contacting the apical and somatic dendrites of pyramidal L5 cells in the target area. There is direct evidence that this top-down mechanism plays a causal role in the late ignition of somatosensory cortex in response to a tactile stimulus in mice and that interfering with it suffices to prevent the perception of tactile inputs (Manita et al., 2015).

Behavioral Correlates of Neuronal Ignitions

A significant issue, which can be studied particularly effectively in humans, concerns the perceptual correlates of the ignition dynamics. The threshold non-linearity which is a major “signature” of the ignition process finds a ready counterpart in the highly

nonlinear input-output relationships observed in sensory psychophysics (e.g., Sergent and Dehaene, 2004; Wilson and Bergen, 1979). Figure 2C (modified from Del Cul et al., 2007) depicts a detailed illustration of such psychophysical threshold derived from backward masking. Note the highly non-linear transition in subjective visibility reports from seen to unseen targets, despite a gradual change in the physical stimulation parameter. Importantly, both objective and subjective behavioral effects appear to follow such threshold non-linearity. Thus, the threshold non-linearity was evident even when participants’ reports were based on subjective, graded evaluations.

The all-or-none character of conscious perception has been observed in a variety of paradigms, including masking (Del Cul et al., 2007; Grill-Spector et al., 2000), visual search (Aly and Yonelinas, 2012), attentional blink (Sergent and Dehaene, 2004; Wierda et al., 2012), attentional selection in time and space (Vul et al., 2009), working memory retrieval (Zhang and Luck, 2009), and long-term memory recollection (Harlow and Donaldson, 2013).

Brain imaging and neurophysiological research has examined the relationship between psychophysical and neuronal thresholds, establishing tight links between these two manifestations of threshold non-linearity. Thus, in BOLD imaging, Grill-Spector et al. (2000) have demonstrated, during the backward-masking paradigm, that BOLD activation in object-selective cortical sites was amplified at threshold, in parallel with the participants’ ability to correctly recognize the briefly presented images. Crucially, following perceptual training, which lowered the recognition threshold, Grill-Spector et al. were able to demonstrate that the BOLD ignition threshold covaried with the induced changes

Box 1. Current Status of the Field

- Each cortical site may be subject to two fundamental modes of cortical dynamics: fast, high-amplitude, task-driven activity and ultra-slow, low-amplitude, resting-state activity.
- During sensory stimulation, a linear increase in stimulus parameters may be associated with a non-linear ignition dynamics, in which crossing a threshold leads to signal amplification and sustained activity, seen in all modalities of brain recording (EEG, BOLD-fMRI, intracranial ECoG recordings, and single-unit recordings).
- Behavioral evidence is compatible with the existence of an all-or-none state of conscious perception in a variety of paradigms, including masking, visual search, attentional blink, attentional selection in time and space, working memory retrieval, and long-term memory recollection.
- Ultra-slow resting-state fluctuations have been demonstrated in fMRI, EEG, ECoG, and single-unit recordings at every cortical site.
- Spontaneous behaviors such as decision to move, free recall, and spontaneous pupillary dilations are all characterized by a slow buildup of neuronal activity “anticipating” the spontaneous decisions.

in perceptual thresholds. In both BOLD-fMRI and scalp EEG studies, crossing of the perceptual threshold during backward masking is concomitant with a non-linear amplification of the BOLD and ERP signals (Dehaene et al., 2001; Del Cul et al., 2007). Using ECoG recording in face-selective sites in patients during such backward-masking paradigms, Fisch et al. (2009) were able to demonstrate that crossing the perceptual recognition threshold was linked to a robust amplification of neuronal activity (Figures 2A and 2B). Finally, a highly non-linear firing of medial temporal neurons was reported by Quiroga et al. (2008) to be closely associated with patients' recognition threshold, even on a trial-by-trial basis.

To summarize (see Box 1, “Current Status of the Field”), studies of perception and neuronal activity converge in pointing to a clear correspondence between the ignition and psychophysical thresholds. Simply stated, these studies suggest that the dividing line between conscious and subconscious processes is delineated by the neuronal threshold leading to ignition.

Neuronal Mechanisms Underlying the Spontaneous, Resting-State, Mode

In striking contrast to the rapidly evolving, high-amplitude ignitions associated with stimulus-driven neuronal activations, the resting-state mode is characterized by ultra-slow fluctuations of activity, often taking seconds to develop (see Figure 1A). Detailed analysis of the power spectra of these resting-state activity fluctuations conducted in invasive recordings in patients reveal a scale-free power-law function (He et al., 2008; Nir et al., 2008; Podvalny et al., 2015). While, in BOLD imaging, the spontaneous fluctuations appear to be similar in amplitude to task-driven activations (Nir et al., 2006; Raichle and Mintun,

2006), it is important to caution that it is difficult to infer, from such amplitude comparisons, the firing rates of the underlying neuronal populations. Specifically, short, high firing-rate bursts may produce lower amplitude BOLD activations than low but sustained neuronal activations. Single-unit recordings comparing optimal auditory stimulation with the fluctuations during silent rest reveal that sensory-driven activations produce significantly higher firing rates than the no-stimulus spontaneous fluctuations (Nir et al., 2008), but clearly, additional single-neuron data are needed to validate the generality of this observation. However, the power-law function characterizing spontaneous fluctuations, while highlighting the important contribution of ultra-slow fluctuations, also reveals some contributions from higher frequencies as well. In fact, indications for such faster contributions have been recently reported in BOLD-fMRI measurements (e.g., Chen et al., 2015).

A fundamental feature of spontaneous fluctuations is their ubiquity across the cortex. A large and rapidly growing body of research reveals that, remarkably, each and every cortical site has the potential to exhibit such spontaneous fluctuations, albeit with a different level of correlation to other cortical loci (e.g., Damoiseaux et al., 2006; Fox and Raichle, 2007). This is an important observation, not only because of its potentially clinical significance as a method that “self-diagnoses” each cortical network (e.g., Greicius et al., 2004; Hahamy et al., 2015; Han et al., 2011; Harmelech and Malach, 2013), but because it indicates that the spontaneous dynamics may reflect a common or even canonical cortical phenomenon. Thus, revealing the neuronal machinery that generates the spontaneous resting-state fluctuations will constitute a major advance in our understanding of cortical function.

A central challenge when considering the neuronal mechanisms that underlie the spontaneous fluctuations is to explain their extremely slow timescales, which likely point to a large memory capacity of the fluctuating network. At present, similar to the case of the ignition dynamics, the exact biophysical mechanisms that generate spontaneous resting-state fluctuations remain unknown. However, a number of modeling studies have begun to unravel possible neuronal mechanisms, specifically relying on experimentally observed network structures, that could account for the experimentally observed resting-state fluctuations (Deco et al., 2011; Honey et al., 2007).

Interestingly, models that attempted to simulate slow neuronal dynamics have proposed a reverberatory circuit mechanism as the source of such persistent activity (Martí et al., 2008; Okamoto et al., 2007; Schurger et al., 2012; Wang, 2002). Notably, the slow dynamics could not be explained in such models by isolated cellular synaptic mechanisms and depended on the presence of strong excitatory reverberations. In Figures 3A and 3C, we illustrate how a simple one-dimensional simulation of a recurrent network generates the slow stochastic dynamics typical of the resting mode (compare Figure 3C with Figure 1B). Additionally, homogeneous, balanced networks of uniformly connected excitatory neurons cannot computationally explain the slow spontaneous fluctuations, but homogeneous clustered networks can (Litwin-Kumar and Doiron, 2012). The latter architectural constraint of clustered connectivity is, of course, typical of cortical architecture (Perin et al., 2011; Song et al., 2005; Amir

et al., 1993; Rockland and Lund, 1983). Other direct attempts at network simulations of spontaneous fluctuations again relied on clustered recurrent activations but emphasized the importance of long-range, large-scale connectivity (Chaudhuri et al., 2014; Deco et al., 2011; Ghosh et al., 2008). Finally, it is important to clarify that the ultra-slow spontaneous fluctuations do not represent the entire repertoire of spontaneous, self-generated phenomena in the brain. As we argue later, the slow, spontaneous fluctuations can sometimes lead to spontaneous ignitions. However, in clear distinction from externally generated ignitions, such self-generated ignitions are often preceded by a slow buildup of subliminal activity.

To summarize, both modeling and experimental results raise the possibility that the long timescales typical of ultra-slow spontaneous fluctuations are generated by neuronal accumulators implemented by recurrent reverberations in excitatory cortical circuits. As the spontaneous fluctuations appear to involve each and every human cortical network, this suggests that the recurrent accumulator mechanism is operating not only in specific, well-studied, accumulator circuits, e.g., in parietal and frontal cortex, but in fact is a canonical property of most, if not all, cortical areas (although with distinct timescales; Chaudhuri et al., 2014; He et al., 2008).

Hypothesis: A Common Network Mechanism Underlying Ignition and Resting-State Spontaneous Fluctuations

When considering together the possible mechanisms underlying the activation threshold, the ignition and the spontaneous fluctuations, it becomes evident that, despite their drastically different dynamic nature, they could both potentially rely on the same network mechanism: excitatory reverberatory loops. Under such a hypothetical unification, the different dynamics are explained as resulting from their relationship to the ignition threshold. Thus, when the overall excitation of the reverberating network exceeds the inhibitory or leakage “quench,” the network ignites, i.e., rapidly enters into the active mode. Once such a network is in the ignited mode, its activity can remain sustained through the intrinsic network reverberations and no longer depends on the feed-forward drive (Barak and Tsodyks, 2007; Dehaene and Changeux, 2005; Wong and Wang, 2006). The observed return of such network to its pre-ignition baseline may be explained by various mechanisms of adaptation, inhibitory drive, or synaptic depression (e.g., Tsodyks et al., 1998). By contrast, when the network activity remains below the ignition threshold, the reverberating excitatory connections act essentially as a low-pass filter with a long time constant (Goldman et al., 2009), endowing the network with slow, persistent activity that integrates the rapidly varying input noise typical of cortical circuits (e.g., Marom, 2010) over long timescales.

Considering, side by side, the ignition dynamics that is apparent during the active mode in response to a sensory stimulation or task and the resting-state dynamics that emerges in the absence of any stimulus or task, it thus appears that both can be explained by the same mechanism: reverberatory network dominated by excitatory connections. Under this hypothesis, the transition between these drastically different modes of cortical dynamics is set by the ignition threshold. Whenever the overall network activity is driven above the posi-

tive-feedback threshold (even in the absence of any stimulus), it leads to the active mode. On the other hand, when there is minimal input drive, the excitatory feedback is too weak to overcome the inhibitory balance but is nevertheless sufficient to impose long timescales in the storage of the intrinsically weak noise fluctuations (Deco et al., 2011; Wang, 2002). The link between the strength of input drive and fluctuations’ time constants appears to be a natural property of recurrent networks, although, in the case of sensory stimulation, there is a general shortening of timescales (e.g., Wong and Wang, 2006).

It should be emphasized that this unifying attempt—attributing the active and resting-state dynamics to a single mechanism—does not rule out the possibility that additional factors may differentiate the active from the rest states. In particular, attention and arousal mechanisms are enhanced during active states and contribute to modulate network interactions. Such attentional effects, involving the release of acetylcholine and other neuromodulators, have been suggested to affect the distance of intra-cortical communication, which, in turn, could modulate the amplitude and dynamics of cortical network fluctuations (Pinto et al., 2013). Indeed, in support of such effects, studies in behaving primates have revealed that attentional modulation can directly affect the amplitude of spontaneous fluctuations of cortical neurons (Churchland et al., 2010; Cohen and Maunsell, 2009; Mitchell et al., 2009).

Consequences of the Proposed Hypothesis

Our proposed hypothesis points to the neuronal ignition threshold as the critical parameter that separates the slow, quasi-linear, accumulator dynamics (manifested in ultra-slow resting-state fluctuations) from the rapid rise of non-linear bursts of activity manifested during the active mode. Crucially, ignition is also postulated to relate to conscious perception. Specifically, it has been previously proposed that, when ignition occurs in a network of cortical neurons, the corresponding content becomes subjectively available for conscious report. Alternative models emphasize a global neuronal workspace (GNW) that broadcasts a neural representation to many cortical sites (Dehaene and Changeux, 2011; Dehaene et al., 2003), or a more local framework where the subjective content depends mainly on ignition in content-selective representations (e.g., Noy et al., 2015). The neuronal ignition threshold would, therefore, be the physiological correlate of the threshold for content-specific perceptual awareness, as defined psychophysically. This hypothetical scheme leads to three main consequences. First, it implies that any neuronal activity that occurs below this threshold should remain subliminal, below the level of the participant’s awareness. Under the present hypothesis, the spontaneous fluctuations, provided that their amplitude remains below the ignition threshold, should, therefore, not be directly correlated to reportable conscious events. This view, therefore, predicts that, despite their robust and widespread nature, as revealed in numerous BOLD imaging studies, resting-state activity fluctuations should not be associated with a conscious feeling, inasmuch as they remain at low subthreshold amplitude.

Several recent studies appear to support this counterintuitive outcome of our hypothesis. Ramot et al. (2011) showed that when participants rest with their eyes closed, the spontaneous,

resting-state BOLD fluctuations are significantly coupled to slow, drifting eye movements that emerge spontaneously upon eye closure. Despite this significant BOLD-oculomotor link, participants were completely unaware that such BOLD and oculomotor fluctuations were actually taking place.

An even more striking demonstration of the subliminal nature of the spontaneous fluctuations has been demonstrated by [Shibata et al. \(2011\)](#). This group used a real-time multivariate neurofeedback procedure in which participants were rewarded whenever their spontaneous fluctuations matched a target pattern associated with a specific visual stimulus. Remarkably, participants were able to enhance the probability of appearance of the target BOLD pattern and, furthermore, showed improved perceptual sensitivity to the trained visual stimulus. However, crucially, the participants were completely unaware of the occurrence of the spontaneously emerging BOLD pattern (despite the fact that they were continuously rewarded for this pattern). When prompted, they remained at chance in identifying the reward pattern (e.g., deciding whether the biofeedback was elicited by the activation pattern corresponding to a vertical or horizontal grid).

A second strong consequence of our hypothesis, related to the conjecture that the same reverberatory circuit could mediate both spontaneous fluctuations and the network ignition, concerns the transition between the spontaneous and active states. Under the present hypothesis, if the spontaneous fluctuations are high enough to approach the ignition threshold, then they may cross it, initiating an ignition on the one hand and an overt cognitive or behavioral event on the other.

A significant support for this conjecture is the finding that a consistent signature of spontaneous or “voluntary” behaviors (i.e., behaviors that do not depend on external sensory stimuli) is an ultra-slow buildup of activity preceding such voluntary behaviors. In a model with continuously accumulating fluctuations, this phenomenon is very natural: prior to crossing a threshold for voluntary decision, the stochastic fluctuations must have accumulated more or less steadily up to the threshold level ([Schurger et al., 2012](#)). Such an event is illustrated in our simulation in [Figure 3D](#). Note the slow buildup anticipating the threshold crossing under the “free-behavior” mode. Such phenomena were studied particularly intensively in the case of voluntary decisions to move, starting with the pioneering research of [Kornhuber and Deecke \(1965\)](#), followed by [Libet et al.’s \(1983\)](#) series of “free-will” studies. This research showed, using EEG recordings, that a slow potential—the so-called “readiness” potential—anticipates the decision of participants to initiate a movement (see also [Schurger et al., 2012](#); [Figure 4B](#)). While some anticipatory buildup is to be expected in any dynamical system, a consistent observation is that such buildup is strikingly slower when generated freely, compared to when generated following an external cue.

The aspect most relevant to our hypothesis, one that has been repeatedly documented, is that participants are unaware of this slowly developing neuronal build-up. Under our hypothetical framework, such lack of awareness is readily explained by the fact that the anticipatory signal remains below the ignition threshold. These results have been further confirmed in single-unit recordings in patients ([Fried et al., 1997](#)). Recent studies

have revealed similar anticipatory buildups in BOLD imaging, often lasting several seconds in duration ([Bode et al., 2011](#); [Soon et al., 2008](#)).

Significantly, the phenomenon of slow anticipatory buildup prior to “voluntary” decisions is not confined to the motor domain. Thus, recording single-neuron responses in medial temporal lobe structures during free recall of previously shown video clips, [Gelbard-Sagiv et al. \(2008\)](#) found an anticipatory increase in neuronal firing rate that preceded the recall event by several seconds. Importantly, such long anticipatory buildup was abolished when the participants directly viewed rather than freely recalled the video clips ([Gelbard-Sagiv et al., 2008](#)). This result is depicted in [Figure 4A](#).

In direct relation to our present hypothesis, it has been proposed by [Schurger et al. \(2012\)](#) that the intriguing slow buildup before voluntary decisions to move is compatible with the assumption that these decisions occur when slow, spontaneous fluctuations cross the decision threshold, thus simultaneously entering awareness and leading to the motor response ([Schurger et al., 2012](#)). The slow dynamics of the anticipatory signal is then explained by the inherent ultra-slow character of the spontaneous fluctuations ([Figure 4B](#)). [Schurger et al. \(2012\)](#) supported their hypothesis by demonstrating that unexpected interrupting cues delivered during high activity peaks of the spontaneous fluctuations resulted in accelerated responses, supporting the notion that these fluctuations actually contribute, subliminally, to voluntary decisions. Recently, in agreement with this view, the influence of the slow fluctuations on the timing of awareness was further described in a Libet-like experiment: transcranial direct current (DC) stimulation in the angular gyrus and the primary motor cortex increased the neuronal excitability and the spontaneous fluctuations’ amplitude, leading to faster awareness of conscious motor intentions ([Douglas et al., 2015](#)).

A valid critique of the use of voluntary paradigms to study the role of spontaneous fluctuations is that such paradigms do not represent a true resting state, since the participants are involved in a demanding (albeit voluntary) task. To circumvent this problem, while indirectly monitoring the cognitive state of participants, [Yellin et al. \(2015\)](#) opted to measure spontaneous fluctuations in pupil diameter while subjects were resting with their eyes open. Extensive previous research has documented direct links between pupil diameter and cognitive load ([Eldar et al., 2013](#); [Kahneman and Beatty, 1966](#); [Kloosterman et al., 2015](#)), so that examining pupil diameter fluctuations during rest and their relationship to spontaneous activity fluctuations could potentially reveal some indication of the cognitive state of individuals without interfering with their resting state.

The results of this study confirmed and extended previous observations of free behavior and are in line with our hypothesis: pupil dilation events (presumably indexing spontaneously emerging conscious thoughts) were preceded by a slow buildup of BOLD activity in areas belonging to the default-mode network (DMN) ([Yellin et al., 2015](#)). The DMN has, indeed, been previously implicated in mind wandering and intrinsically oriented thoughts ([Mason et al., 2007](#); [Preminger et al., 2011](#)). Furthermore, testing various models with different dynamics led to the conclusion that the model that best fit the observed correlation between BOLD and pupil diameter was, indeed, a

Ultra-slow anticipatory buildup during spontaneous/free behaviors

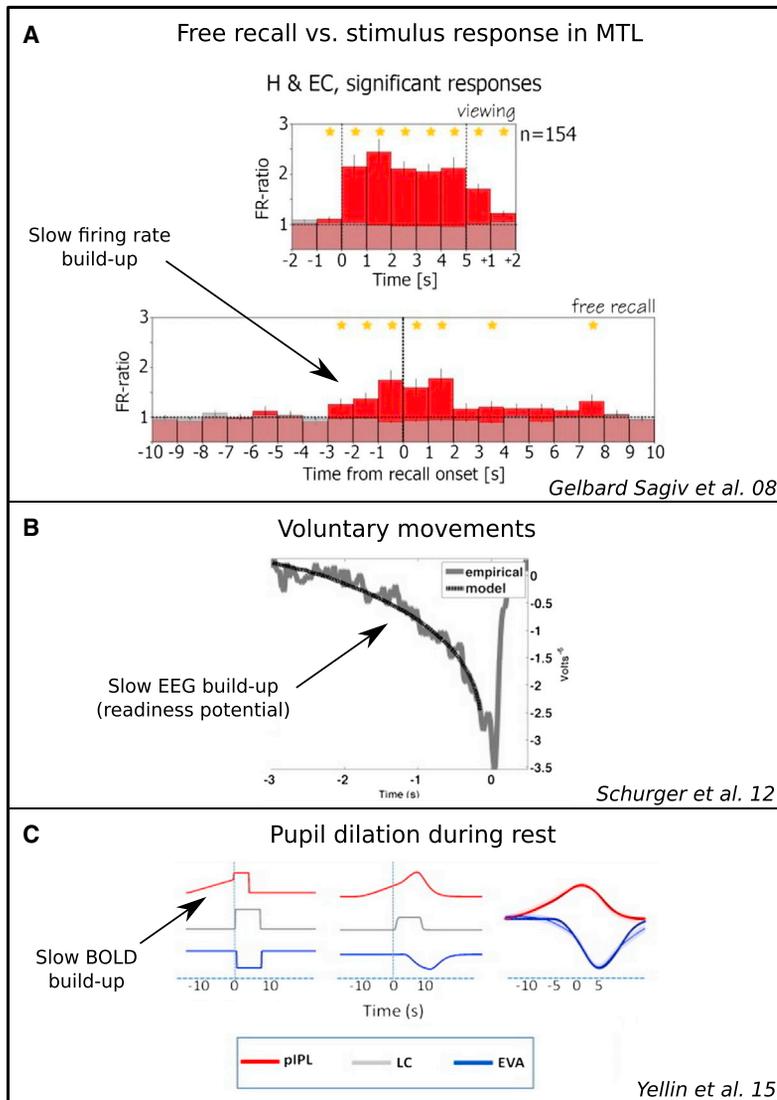


Figure 4. Three Examples Illustrating the Slow Buildup of Activity Characteristic of Spontaneous, Free Behaviors

(A) Slow buildup of single-neurons' firing rate prior to free recall of previously viewed videos in human middle temporal lobe (MTL) (modified from Gelbard Sagiv et al., 2008). Note the strikingly slower dynamics of the signal prior to free recall (bottom) compared to the neuronal response following actually presented video (top). H, hippocampus; EC, entorhinal cortex.

(B) Slow buildup of EEG signal (readiness potential) that has been extensively studied during free decisions to move (modified from Schurger et al., 2012).

(C) Slow buildup of BOLD-fMRI signals recorded in the human default mode network prior to spontaneous pupil dilation during rest, presumably associated with the generation of spontaneous thoughts during rest (modified from Yellin et al., 2015).

the extremely short evolution of sensory- or task-driven responses (compare, e.g., the active and free modes in Figure 4A). This striking difference between the active aware state on the one hand and the ultra-slow, subliminal preparatory signals on the other—which have also been a focus of intense cognitive and even philosophical debates (Dennett, 2003; Libet, 1985; Shadlen, 2014)—is nicely explained by our present hypothesis. In the absence of external inputs, the ultra-slow spontaneous fluctuations are proposed to contribute to the initiation of voluntary “free” decisions based on slow accumulator-like anticipatory signals of which participants remain unaware. By contrast, upon external sensory or task activation, the reverberating network is rapidly driven above the ignition threshold, leading to its intense activation concomitant with cognitive awareness.

slow buildup of neuronal activity up to a threshold followed by rapid neuronal activation (Yellin et al., 2015; Figure 4C). This model is nicely compatible with the notion that subliminal non-conscious spontaneous fluctuations become cognitively relevant upon crossing a high-amplitude threshold. Thus, we find converging lines of evidence suggesting that the ignition phenomenon is not confined to sensory-driven representations but can be detected in intrinsic networks as well, being linked then to spontaneously emerging awareness of internal cognitive processes such as spontaneous thoughts and free recall. Note that, in this respect, our model extends the possibility of spontaneous, self-generated ignitions to the domain of spontaneously emerging conscious thoughts. As in the case of other spontaneous behaviors, such thoughts are likely to be preceded by a slow buildup of subliminal activity.

This set of converging findings consistently contrasts ultra-long timescales during buildup of spontaneous behavior with

A third consequence of the current hypothesis concerns the differential circuit dynamics found across cortical areas. While we have so far emphasized the “canonical” principles that are common across the entire constellation of human cortical networks, a potentially robust outcome of our hypothesis relates to differences in neuronal dynamics across different cortical areas and networks. Even at the level of anatomical connectivity, which, under the present hypothesis, should play an important role in mediating the reverberation dynamics, such differences are evident. For example, examining the anatomical spread of lateral anatomical connections at different levels of the visual hierarchy in the monkey brain reveals a gradual increase in the anatomical span as one moves to higher levels of the cortical hierarchy (e.g., Amir et al., 1993). In the same line of ideas, in the human brain, pyramidal cells become more branched and spinous from the occipital lobe to the temporal lobe and from the latter to the prefrontal lobe (Elston et al., 2001). A

Box 2. Future Directions

- Can a realistic model circuit integrate the concepts of evidence accumulation and ignition, specifically demonstrating (1) accumulation of noisy neuronal signals in a quasi-linear manner, (2) threshold crossing, and (3) ignition dynamics?
- How can we account for local ignition-like events that apparently are dissociated from awareness (e.g., V1 bursts of activity)?
- Can the concept of ignition be reconciled with the graded nature of neural firing and the apparent dissociations between signal reduction (e.g., adaptation) and perceptual awareness?
- What are the neuronal mechanisms by which an ignition is “broadcast” to the rest of the cortex?
- Can a causal relation be demonstrated between ultra-slow spontaneous fluctuations in neuronal activity and the generation of free, self-generated, spontaneous behaviors, such as free motor movements, free associations, and spontaneously emerging insights?

straightforward consequence of such changes in anatomical circuitry is an increasingly slower (more persistent) timescale of the circuit storage mechanism. If, indeed, our hypothesis that the slow spontaneous fluctuations and the supra-threshold sensory activations are derived from the same reverberatory loops is right, we should expect that, despite the striking differences in the frequency contents of the two phenomena, changes in the characteristic dynamics of the spontaneous fluctuations across cortical sites should parallel similar changes in the dynamics of their task-driven responses. A suggestion that this, indeed, may be the case has been recently provided (Honey et al., 2012). The authors recorded both ECoG responses (Honey et al., 2012) and BOLD-fMRI responses (Stephens et al., 2013) and demonstrated a hierarchy of increasingly slower accumulator dynamics in neuronal responses to naturalistic stimuli leading from auditory cortex to DMN structures. In agreement with our hypothesis, they found a significant correlation between the stimulus-driven dynamics and the ones found during resting-state spontaneous fluctuations. Thus, cortical regions that responded in a sluggish manner to the naturalistic stimuli also expressed slower frequencies in their spontaneous activity fluctuations during rest. A similar relationship between the dynamics of resting and task activations was found in a meta-analysis of neuronal activity responses in monkey cortex (Murray et al., 2014). It should be noted in this respect, that in our framework, the sluggish nature of the frontal circuits will predict longer subliminal buildup prior to active ignitions. Nevertheless, such sluggish buildup should not preclude the crossing of the ignition and awareness threshold in these slow circuits as well.

However, a more extensive analysis of the relationship between task-driven and spontaneous dynamics will be needed to better establish the possible common source of these two modes of cortical activity. It will be particularly informative to examine the dynamics of those aspects that may be more diagnostic of the storage capacity of the network; for example, the

duration of the sustained activity following brief stimulus presentations (e.g., Fisch et al., 2009).

Elaborations

Given the extreme complexity of cortical circuits, and the many parameters that impact on their dynamics, the proposed hypothesis should naturally be viewed as an oversimplification. Thus, additional experiments (see also Box 2, “Future Directions”) and elaborations of the basic scheme proposed here should be considered. Here, we point out three particularly prominent ones and attempt to show how a simple extension of our hypothesis could account for these complications.

A major indication that the all-or-none ignition hypothesis is an oversimplification comes from the many observations that the neuronal response during the active state can be graded. In the perceptual domain, certain perceptual dimensions appear to be continuous, such as motion velocity, contrast levels, and so forth. In the neuronal domain, a ubiquitous case is the phenomena of adaptation and “repetition suppression,” in which the amplitude of neuronal responses to optimal stimuli can be significantly reduced upon stimulus repetition (Grill-Spector and Malach, 2004; Grill-Spector et al., 2006; Krekelberg et al., 2006; Malach, 2012). Such graded responses indicate that additional parameters, such as network excitability levels on the one hand and synaptic depression (e.g., Tsodyks and Markram, 1997) on the other, should be added to the simple all-or-none feedback network activations. A plausible, more nuanced elaboration of the all-or-none ignition model could be implemented in networks expressing multi-stable levels (e.g., Ghosh et al., 2008; Hansen et al., 2015). Furthermore, as noted earlier, synaptic depression mechanisms may account for the termination of the ignition response that, otherwise in a simple point-attractor-like model, would persist indefinitely.

A second major discrepancy with the present hypothesis is the observation that the neuronal buildup during voluntary behaviors does not always lead to an ignition in the accumulator network itself. For example, the readiness potential leading to a voluntary decision to move does not appear to be followed by a non-linear neuronal event that is associated with movement awareness (Fried et al., 1997; Libet et al., 1983). Again, such observations indicate that the assumption that accumulation and ignition must always occur in the same network is likely an oversimplification. A plausible scenario, also suggested for perceptual decisions under uncertainty (Gold and Shadlen, 2007) and for voluntary behavior in rodents (Murakami et al., 2014), is that the voluntary decision may involve a cascade of reverberatory loops, in which an upstream network may possess a higher ignition threshold than its target area. Under such a scenario, network fluctuations that remain below the ignition threshold in one cortical area may, nevertheless, drive a downstream area above its own (lower) ignition threshold, leading to voluntary behavior associated with an ignition event that is anatomically separated from the accumulator network. In a related proposal, Lo and Wang (2006) propose that the readout of threshold-crossing events could occur subcortically; for instance, in the superior colliculus.

An interesting observation that may appear to contradict the notion that high signal activity should correspond to conscious

awareness concerns sleep states. In particular, it is well established that, during non-rapid eye movement sleep (NREM), peak neuronal activity does not diminish compared to the REM and awake states (see, e.g., Nir et al., 2011; Ramot et al., 2013). A plausible explanation for the lack of reportable experiences during NREM sleep could be the frequent off-states, which are characteristics of NREM sleep. Such off-states may quench the ability of local high-amplitude signals to cascade into a global brain-scale ignition, thus gaining access to memory networks and, hence, preventing conscious recall (Nir et al., 2011). A similar fragmentation of brain activity into locally preserved but globally incoherent states has been described with intracranial recordings during human anesthesia (Lewis et al., 2012).

Finally, while our model emphasizes the dynamic role of excitatory connections and assumes a largely stationary impact of the inhibitory drive, this is clearly an oversimplification, as many studies have demonstrated a tight link between averaged excitatory activity and neuronal inhibition (see, e.g., the reviews Buzsáki et al., 2004; and Zhang and Sun, 2011). Thus, a more realistic rendition of network activation under rest and sensory-driven modes should consider a more dynamic and balanced behavior of network inhibition.

To summarize, we propose here that a common mechanism, recurrent positive-feedback loops, may account for two drastically different cortical dynamics. The ubiquity of these dynamics across the cortex suggests that they reflect a canonical cortical characteristic, i.e., common phenomena across all cortical circuits. They highlight the networks' ignition threshold as a critical aspect of cortical decision making and conscious awareness.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and one figure and can be found with this article online at <http://dx.doi.org/10.1016/j.neuron.2015.09.018>.

ACKNOWLEDGMENTS

The authors declare that they have no conflicts of interest. The research leading to these results has received funding from the European Union (EU) Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 604102 (Human Brain Project). C.M. and S.D. received additional support from INSERM, CEA, Université Paris Saclay, and the Spoelberch Foundation. R.M. received additional support from the Helen and Martin Kimmel Award for Innovative Investigation, the EU (FP7 VERE), and the ISF-ICORE.

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