

CHAPTER 22

Roles of multiscale brain activity fluctuations in shaping the variability and dynamics of psychophysical performance

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Abstract: Spontaneous brain activity across many time scales influences sensory perception and human cognitive performance. Empirical insight into the underlying systems-level mechanisms has, however, remained fragmented. We review here recent studies on how wideband scale-free and scale-specific neuronal activity fluctuations together bias sensory processing and perceptual performance. We posit that these fluctuations constitute the neurophysiological foundation for both the trial-to-trial behavioral variability and the scaling laws governing psychophysical performance.

Keywords: infra; slow; fluctuation; EEG; MEG; fMRI; BOLD; resting state; intrinsic connectivity; network; oscillation; critical; scaling; phase; synchrony; cross frequency; interaction; attention; perception.

Introduction

Human psychophysical and cognitive performance is highly variable at all time scales even under constant experimental conditions and even in responses to simple stimuli. It has been known since the early 1950s that human behavior is autocorrelated in time scales from seconds to tens or hundreds of seconds so that psychophysical performance in any given trial is similar to the performance in preceding trials (Verplanck

et al., 1952, 1953). Many later studies have extended these observations and shown that human perceptual or cognitive performance in a wide range of tasks is not only autocorrelated but is so in a scale-free, aperiodic, and fractal-like fashion (Gilden, 2001; Gilden and Wilson, 1995; Monto et al., 2008).

This kind of scale-free behavioral dynamics is salient in psychophysical data collected in diverse continuous performance tasks (CPTs) where the subject performs a given task for minutes or, preferably, tens of minutes without interruption. We will suggest here that a specific subset of CPTs, threshold-stimulus detection tasks (TSDTs), are

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particularly informative for probing how spontaneous brain activity influences behavioral performance. In TSDTs, the subject is presented weak constant-intensity sensory stimuli and the subject reports whenever a stimulus is perceived. Prior to the experiment, the stimulus intensity is calibrated to a level that yields the desired detection rate, often 50%. The time series of behavioral performance in TSDTs reveal complex dynamics where the detected (Hits) and undetected (Misses) stimuli are clustered and have scale-free cluster-size distributions, long-range temporal correlations, and positive autocorrelations extending over hundred seconds (Fig. 1; Monto et al., 2008). The term scale-free here thus indicates that these clusters of Hits and Misses do not have a preferred size and consequently also that the underlying brain states have scale-free life times. If a preferred scale existed, it would have been reflected in the cluster

sizes having a well-defined mean and an oscillatory autocorrelation. Importantly, long-term monitoring of rat mobility has revealed that similar scale-free power-law dynamics characterize the animals' activity across intervals of several days (Antenodo and Chialvo, 2009), which indicates that scale-free behavioral fluctuations arise also in natural settings and well beyond the time scales of human CPTs. However, although power-law scaling laws often characterize psychophysical data, their provenance and relevance for understanding psychological processes are under debate (Farrell et al., 2006). Most importantly, their biological basis has remained unknown (Kello et al., 2010). In addition, the fact that numerous complex systems from sand piles (Bak et al., 1987) to earthquakes (Bak et al., 2002), stock markets (Stanley et al., 2002), and genetic regulatory networks (Balleza et al., 2008) exhibit similar dynamics, raises the question of whether

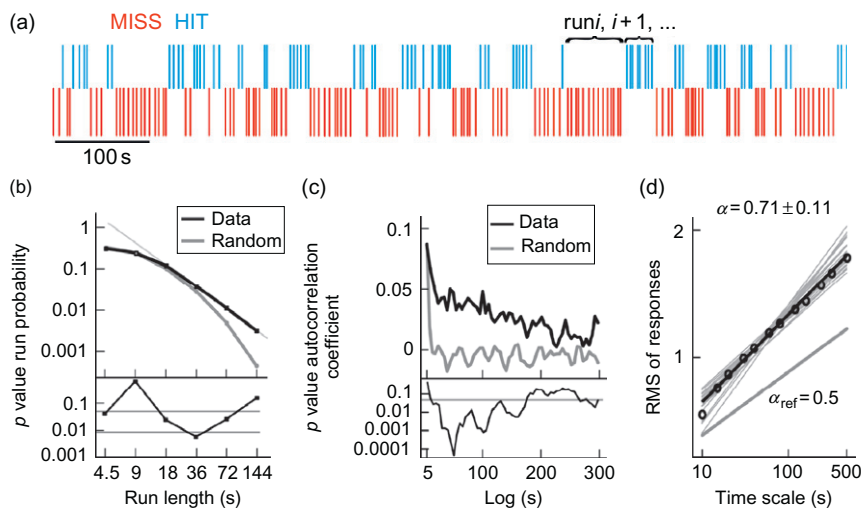


Fig. 1. Scale-free infraslow fluctuations (ISFs), or “behavioral avalanches,” are a salient and fundamental characteristic of human psychophysical performance. (a) An example of a single experiment shows that psychophysical performance in a threshold-stimulus detection task (TSDT) with constant-intensity somatosensory stimuli is clustered into runs of Hits (detected stimuli, blue upward ticks) and Misses (unperceived stimuli, red downward ticks). (b) Run probability decays as a power-law function of Run length and is significantly different from the exponential decay of randomized data. (c) The sequences of Hits and Misses are autocorrelated for more than 100 s. (d) Detrended fluctuation analysis (Linkenkaer-Hansen et al., 2001) shows that the behavioral data exhibit scale-free long-range temporal correlations. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this chapter.) Adapted from Monto et al. (2008).

fractal behavioral or neuronal dynamics are an epiphenomenon without functional relevance.

What can we learn about the brain or behavior from dynamics they share with a pile of sand? We argue here that this dynamics has a profound impact on human action, perception, and cognition. Understanding the neuronal underpinnings of behavioral scaling laws is critical for understanding the relation of spontaneous brain activity and psychophysical performance. At the phenomenological level, fractal self-similarity, power-law-like scaling laws, and “ $1/f$ noise” are typical for systems exhibiting “avalanche dynamics” and operating in a critical (Werner, 2009, 2010) or self-organized critical state (Bak et al., 1987). A large amount of data does, in fact, show that brain dynamics from cultured single neurons to whole brains *in vivo* exhibit spatiotemporal self-similarity, long-range correlations, and power-law scaling behavior, which strongly suggests that the brain is akin to a system in a critical state (Linkenkaer-Hansen et al., 2001; Plenz and Thiagarajan, 2007; Werner, 2009, 2010). It would thus be tempting to draw a direct link between the scaling laws of behavioral and neuronal fluctuations. Nevertheless, while scale-free fluctuations are ubiquitous in neurophysiological recordings and also correlated with behavior, there is little direct experimental evidence to indicate a relationship at the level of scaling laws.

In this review, we examine the hypotheses that (i) variability in psychophysical and psychological time series is caused by concurrent fluctuations in collective neuronal activity and that (ii) the fractal properties of psychophysical time series are directly related to the fractal characteristics of underlying brain activity. We assess recent studies along three lines of questions: First, what kind of neuronal fluctuations operate in the frequency range and have scale-free temporal structures similar to those of psychophysical data? Second, are these neuronal activity fluctuations correlated with behavioral performance? Third, is there evidence for a causal relationship between neuronal and behavioral variability and how could that be obtained?

Infraslow spontaneous brain activity fluctuations in fMRI

The waxing and waning of spontaneous brain activity in the time scales of tens to hundreds of seconds is readily observed with functional magnetic resonance imaging (fMRI) as infra-slow fluctuations (ISFs; 0.01–0.1 Hz) in the blood-oxygenation-level-dependent (BOLD) signal (Biswal et al., 1995). BOLD ISFs are correlated among networks of brain regions, which is defined to reflect interareal functional connectivity. These correlations have an architecture similar to but not fully explained by the underlying structural connectivity (Honey et al., 2007, 2009). A majority of fMRI research on functional connectivity has been performed with the subject in resting state and hence, the interconnected brain regions are often called “resting-state networks.” However, as similar network dynamics characterize also neuronal activity during cognitive tasks (Golland et al., 2007), these networks have also been termed “intrinsic connectivity networks” (ICNs; Sadaghiani et al., 2010a).

ICNs are typically extracted with independent components analysis (ICA) but a number of other correlation mapping approaches have been shown to yield very similar ICN divisions. ICNs can be divided into task-positive and -negative networks of which the latter comprise the default-mode network (DMN). Brain regions belonging to DMN show negative BOLD responses during task performance and are thought to underlie internally oriented brain activity (Raichle et al., 2001). Task-positive networks, on the other hand, comprise brain regions where sensory, cognitive, or motor tasks enhance the BOLD signal and include, for example, sensory, motor, attentional, executive, and alertness networks, of which at least the dorsal attention network (DAN) is anticorrelated with DMN (Fox et al., 2005; Fig. 2a) but with complex and directed connectivity (Uddin et al., 2009). In line with modeling studies (Deco et al., 2009; Honey et al., 2007), recent fMRI data also show

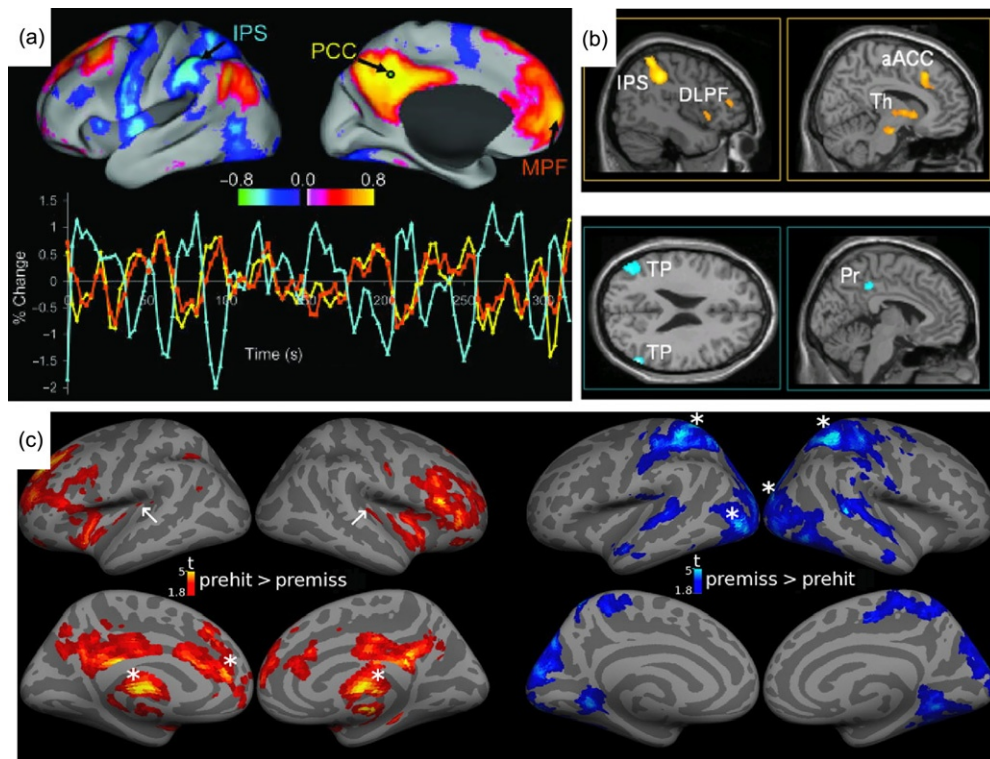


Fig. 2. Spontaneous brain activity fluctuations predict the behavioral outcome in somatosensory and visual TSDTs. (a) Fluctuations of attentional (blue) and default-mode (red) intrinsic connectivity networks are anticorrelated in resting-state fMRI data. Adapted from Fox et al. (2005). (b) Positive BOLD-signal dorsal attentional regions and suppressed signal in the default-mode regions predict Hits in a somatosensory TSD task (Boly et al., 2007), but (c) a partially opposite pattern is observed in an auditory TSD task (Sadaghiani et al., 2009).

that there is dynamic variability in the relationships of ICNs and shifts between correlated to anticorrelated states (Chang and Glover, 2010). Although the dichotomous division and the notion of anticorrelated functional networks has persisted (Fox et al., 2009), ICNs appear not to be atomic entities. Data-driven functional connectivity mapping techniques corroborate the modularity revealed in prior studies but suggest also that ICNs and functional connectivity have a scale-free anatomical architecture wherein each network can be further divided into smaller constituents and where the spatial correlations decay according to a power law

(Benjaminsson et al., 2010; Expert et al., 2011; Ferrarini et al., 2009; van den Heuvel et al., 2008). Nevertheless, a large body of data converges on showing that the levels of neuronal activity in discrete cortical networks fluctuate in the same infraslow frequency range as psychophysical performance.

Several investigations have characterized the temporal structure of the BOLD ISFs, which is not revealed by the conventional functional connectivity analyses. These data show that in addition to having a power-law amplitude spectrum, the BOLD fluctuations are scale-free, fractal (Suckling et al., 2008; Wink et al., 2008) and have

temporal correlations that decay with a power law (Expert et al., 2011). The BOLD ISFs fluctuations thus match also the dynamical fingerprint of psychophysical time series.

Correlation of BOLD-signal fluctuations with behavioral dynamics

Antagonistic fluctuations of task-positive and negative networks would be an attractive candidate for explaining behavioral variability in cognitive tasks (Clare Kelly et al., 2008). Alternating windows of externally and internally oriented states could dominate psychophysical dynamics in especially in TSDTs where the overall attentiveness or alertness can be a decisive factor and where sensory stimuli are weak and need only to be detected rather than inspected (Monto et al., 2008). Indeed, in DAN and DMN, the prestimulus BOLD signals are positively and negatively, respectively, correlated with Hits in a somatosensory TSDT (Boly et al., 2007; Fig. 2b). Conversely, it is conceivable that tasks involving stimulus-content specific perceptual decisions and suprathreshold stimuli challenge the sensory systems directly (Sadaghiani et al., 2010a). A series of studies corroborate this idea and show that the level of prestimulus BOLD signal is positively correlated with perceptual performance specifically in limited task-specific sensory regions (Hesselmann et al., 2008a,b; Mennes et al., 2011). Further, the concept was recently expanded to the more complex cognitive task, the Stroop task. Prestimulus activity in the task-specific sensory region was again positively correlated with behavioral performance, but in addition, the activity in frontal regions underlying the suppression of distracting information was also positively correlated while the activity in sensory regions processing the distracting information was negatively correlated with performance (Coste et al., 2011). Taken together, there is a salient and task-dependently coordinated correlation between spontaneous BOLD-signal and behavioral performance fluctuations. The task

susceptibility is further highlighted, in recent auditory TSDT data (Sadaghiani et al., 2009), where DMN was positively and DAN negatively correlated with successful stimulus detection, which corroborates the overall correlation of slow neuronal fluctuations with behavior but indicates that one cannot attach static or context-independent functional roles to ICNs (Fig. 2c). These data thus show that the brain state set by spontaneous activity may have salient predictive value on the behavioral outcome of concurrent or subsequent stimulus processing.

Taken together, slow spontaneous brain activity fluctuations reflected in BOLD-signal dynamics satisfy the two first requirements for a neuronal process to underlie both the behavioral variability and the fractal nature of behavioral time series: these neuronal phenomena are correlated with behavioral performance and exhibit scale-free dynamics that match those of behavioral fluctuations.

Electrophysiological characterization of infraslow fluctuations

Electrophysiological oscillations or fluctuations in the infraslow frequency range of the behavioral and BOLD-signal fluctuations can be studied with direct current (DC) recordings and were, in fact, identified already in the 1950s in human EEG (Aladjalova, 1957) and have later also been observed in rat hippocampus and basal ganglia (Allers et al., 2002; Penttonen et al., 1999; Ruskin et al., 2003). ISFs in EEG did not receive much attention because typical LFP/EEG recordings utilize alternating current amplifiers, non-DC-stable electrodes, and/or discard signals below ~ 1 Hz by high-pass filtering. Moreover, much of the EEG research has focused on evoked responses on one hand and time-averaged spectral analyses on the other, which both are based on the idea that task-related processing is independent of noise-like spontaneous activity and thus observable through averaging across trials

or time. Thus, both of these research paradigms discard the rich information contained in temporal structures and trial-to-trial variability. Recent human EEG studies have shown that robust and large-amplitude ISFs indeed characterize human ongoing brain activity both during sleep (Vanhatalo et al., 2004) and during somatosensory-TSDT performance (Monto et al., 2008). These studies were the first to attribute a clear functional significance to EEG ISFs. During sleep, ISF phase was correlated with the probability of transient EEG events, K complexes, and interictal epileptic events as well as with the continuous amplitude fluctuations of spontaneous >1 Hz oscillations (Vanhatalo et al., 2004). Also in awake subjects, the ISF phase was correlated with the amplitudes of EEG activities from 1 to 40 Hz (Monto et al., 2008). Most importantly, the detection performance of somatosensory stimuli was strongly correlated with and predicted by the ISF phase (Fig. 3).

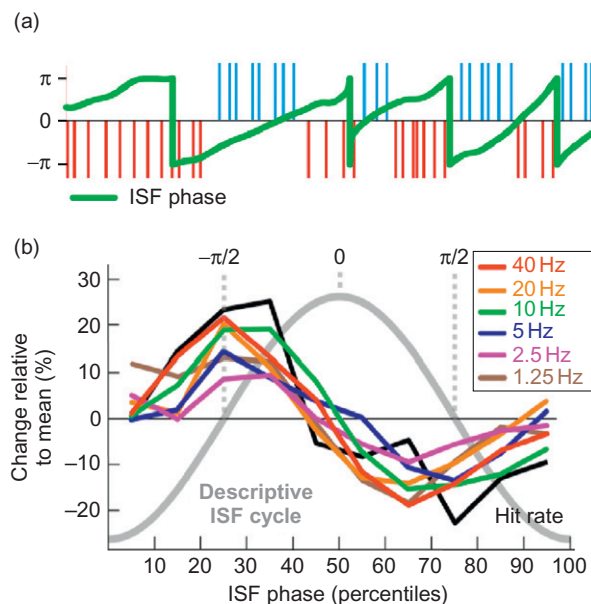


Fig. 3. The phase of infraslow oscillations (ISOs) in human EEG (a) predicts behavioral performance in somatosensory TSD task and (b) is correlated with the amplitudes of faster ongoing EEG oscillations. Adapted from Monto et al. (2008).

These data converge on that ISFs reflect gross cortical excitability fluctuations and it is tempting to speculate that they also reflect the ICN fluctuations observed with fMRI. Direct evidence for this correlation, however, remains to be found. What mechanisms generate the EEG ISFs? Large-scale depolarization of the apical dendrites of cortical neurons has been proposed as one mechanism, but the generation of EEG ISF signals may also involve nonneuronal mechanisms and possibly a direct contribution from hemodynamics *per se* (Vanhatalo et al., 2003; Voipio et al., 2003). Nevertheless, in invasive microelectrode recordings, ISFs are salient in the activity of underlying neuronal circuitry (Allers et al., 2002; Penttonen et al., 1999; Ruskin et al., 2003). Cellular mechanisms producing periodicity in the infraslow frequency band have also been recently identified in thalamic preparations *in vitro* (Lorincz et al., 2009b). Future studies are needed to resolve the role of these mechanisms in ISFs *in vivo* as well as the contributions that the slow amplitude dynamics of fast >1 Hz neuronal activities (Deco et al., 2011; Linkenkaer-Hansen et al., 2001) have in shaping the ISFs and ICN fluctuations.

EEG ISFs are not associated with a peak in the power spectrum (He et al., 2010; Monto et al., 2008; Vanhatalo et al., 2004) and hence do not reflect oscillations in a classical sense. This has led to a suggestion that a large part of ongoing brain activity would be fundamentally aperiodic and scale-free (He et al., 2010). Nonetheless, not only the >1 Hz oscillations but also the ISFs may be generated through scale-specific cellular mechanisms (Lorincz et al., 2009b) that on their own produce periodic phenomena. While the reasons for why transient neuronal periodicity leads to scale-freeness and apparent aperiodicity at the systems level or in data collapsed across of time may be debated, two lines of evidence support the concept of oscillations also when referring to ISFs. First, it is the *phase* of EEG ISFs, which predicts perceptual performance (Monto et al., 2008) and occurrence of fast neuronal events (Vanhatalo et al., 2004). Second, even

within the infraslow band, functional connectivity is phase dependent and emerges dynamically in narrow frequency bands (Chang and Glover, 2010). The fact that phase is a critical parameter in defining the physiological and behavioral significance of these neuronal processes indicates that they can be considered to be oscillations, regardless of whether the rhythmicity is periodic or aperiodic.

In conclusion, the EEG ISFs are the primary electrophysiological correlate of slow neuronal activity fluctuations in the human brain. EEG ISFs share the time scales and fractal nature of psychophysical dynamics and are 1:1 correlated with psychophysical performance. Hence, like BOLD ISFs in specific cortical structures or ICNs, the EEG ISFs reflect a neuronal process that is tightly linked with psychophysical dynamics.

Zooming-in on neuronal oscillations

fMRI has superior spatial accuracy but is restricted to the 1+ second time scales of hemodynamic signals and, moreover, the relationship of BOLD signals with the underlying neuronal activity is complex (Raichle, 2010). Also the EEG ISFs are, by definition, confined to these same time scales and are a rather indirect reflection of neuronal activity. Cognitive operations and neuronal activity *per se* involve time scales from a few to some hundreds of milliseconds. Hence, the physiological basis of the slow fluctuations in cognitive performance must be understood in terms of the collective dynamics of fast neuronal activity.

In electrophysiological studies, 1–200 Hz oscillations appear to be ubiquitous throughout the nervous system from *in vitro* slice preparations to local field potential recordings in animals *in vivo*, invasive depth electrode (stereotactical EEG, SEEG) recordings in humans, and to the macroscopic signals recorded noninvasively from scalp with magneto- and electroencephalography (M/EEG; Buzsaki, 2006; Varela et al., 2001). Such “non-scale-free” or

scale-specific, correlated activity emerges through numerous interacting scale-specific mechanisms such as the time constants of postsynaptic currents, axonal conduction delays, and network connectivity motifs (Bartos et al., 2007; Lorincz et al., 2009a,b). Synchronization of neuronal population activity into transient oscillations has two profound functional consequences at the cellular level. First, synchronized synaptic excitation is much more likely to evoke an action potential in a downstream neuron than temporally uncorrelated inputs (Uhlhaas et al., 2009) and synchronization endows a neuronal population an advantage in the competition of engaging their target neurons. Second, rhythmic membrane potential fluctuations facilitate neuronal excitability in one phase of the cycle and suppress it in the other. Such excitability windows may be powerful temporal regulators of both local neuronal processing and interareal interactions. Neuronal oscillations may thus play the key mechanistic role in coordinating interareal communication (Fries, 2005) and collective neuronal action.

The coexistence of scale-free and scale-specific (oscillatory) dynamics (Linkenkaer-Hansen et al., 2001; Petermann et al., 2009) in brain activity is enigmatic and lacks predecessors in other physical critical-state systems. A critical state endows the system tolerance against perturbations, and at the same time, susceptibility and capability to exhibit rapid configuration changes or phase transitions. A critical state also maximizes the system's representational capacity for information (Shew et al., 2011). What is the role of fast oscillations in slow scale-free brain dynamics? We suggest here that neuronal oscillations regulate transiently the intrinsic temporally scale-free dynamics into a succession of meta-stable states that support externally oriented and task-relevant behavior in environmentally appropriate time scales. Specifically, the role of oscillatory synchronization could be in the brief stabilization of neuronal assemblies within each meta-stable state in between the network reconfigurations that are scale-free or driven by slower oscillations.

Direct effects of oscillation phase on behavioral dynamics

Fluctuations in behavioral performance have so far been considered in time scales of 1–100+ seconds. In the subsecond range, there is little data to suggest that behavioral effects were scale-free. On the contrary, several experiments have revealed perceptual, attentional (VanRullen and Koch, 2003; VanRullen et al., 2005, 2007), and motor (Gross et al., 2002) phenomena that are associated with a limited range of temporal scales (25–200 ms) and are thus scale-specific. These findings suggest that sensory data are attended and perceived and also actively acquired in discrete time windows that could be physiologically achieved by correlated neuronal oscillations in sensory, attentional, and motor systems (Schroeder et al., 2010).

The prestimulus phase of broadband ongoing activity in MEG (Palva et al., 2005a,b; Fig. 4a and b) and of theta/alpha-band oscillations in EEG (Busch and VanRullen, 2010; Busch et al., 2009; Mathewson et al., 2009; Fig. 4c) is correlated with successful perception in TSD tasks. In a prestimulus time window of just some hundreds of milliseconds, the EEG oscillation phase accounts for 11–14% of the total behavioral variability (Busch and VanRullen, 2010; Busch et al., 2009) in visual TSDT. While this effect is smaller than the ~40% effect of EEG ISFs (Monto et al., 2008), it is robust and salient in single-trial EEG. Importantly, the strength of this phase effect is dependent on attention and its anterior scalp-potential topography (Busch and VanRullen, 2010) is suggestive of generators in the frontal attention controlling brain regions. These results imply that neuronal oscillations indeed have a direct role in periodic perceptual sampling as. Because in TSDTs the stimuli are presented at unpredictable times, the task thus reveals by random sampling a periodic opening of a sensory-attentional-communication channel that depends critically on exact timings of neuronal activities in the sensory and attentional

networks, which is possibly achieved by synchronization of these networks (Palva et al., 2005a,b, 2010a).

Neuronal oscillations also regulate sensory processing and implement an attentional bias under conditions where sensory stimuli are presented at suprathreshold levels and at a constant rhythm. Such periodic stimuli can entrain cortical delta-frequency band (1–4 Hz) oscillations in a dynamic fashion so that the phase of delta oscillations is dependent on the direction of attention and can be switched between auditory and visual modalities (Lakatos et al., 2008). The entrained oscillations are also phase correlated with the amplitude of faster oscillations (Lakatos et al., 2008) as well as with behavioral performance in macaques (Lakatos et al., 2008) and humans (Stefanics et al., 2010). Via sustained attention, it is thus possible to voluntarily modify the endogenous multiscale neuronal dynamics in order to facilitate task performance.

Taken together, the scale-free behavioral fluctuations appear to arise as an envelope of scale-specific behavioral states and temporally discrete sensorimotor processing. While the EEG- and BOLD ISFs are associated with the slow behavioral fluctuations, the phases of 1–40 Hz neuronal oscillations reflect discrete excitability windows that bias psychophysical performance in subsecond time scales.

Amplitude dynamics link neuronal oscillations and ISFs

ISFs are vastly different in their temporal scale when compared to 1–200 Hz oscillations. One ISF cycle comprises 100–1000 alpha-oscillation cycles. How are ISFs and neuronal oscillations related?

MEG and EEG data show that similarly to the BOLD ISFs, the amplitude fluctuations of neuronal oscillations in at least in the theta- (4–8 Hz), alpha- (8–14 Hz), and beta- (14–30 Hz) frequency bands have a fractal structure governed by

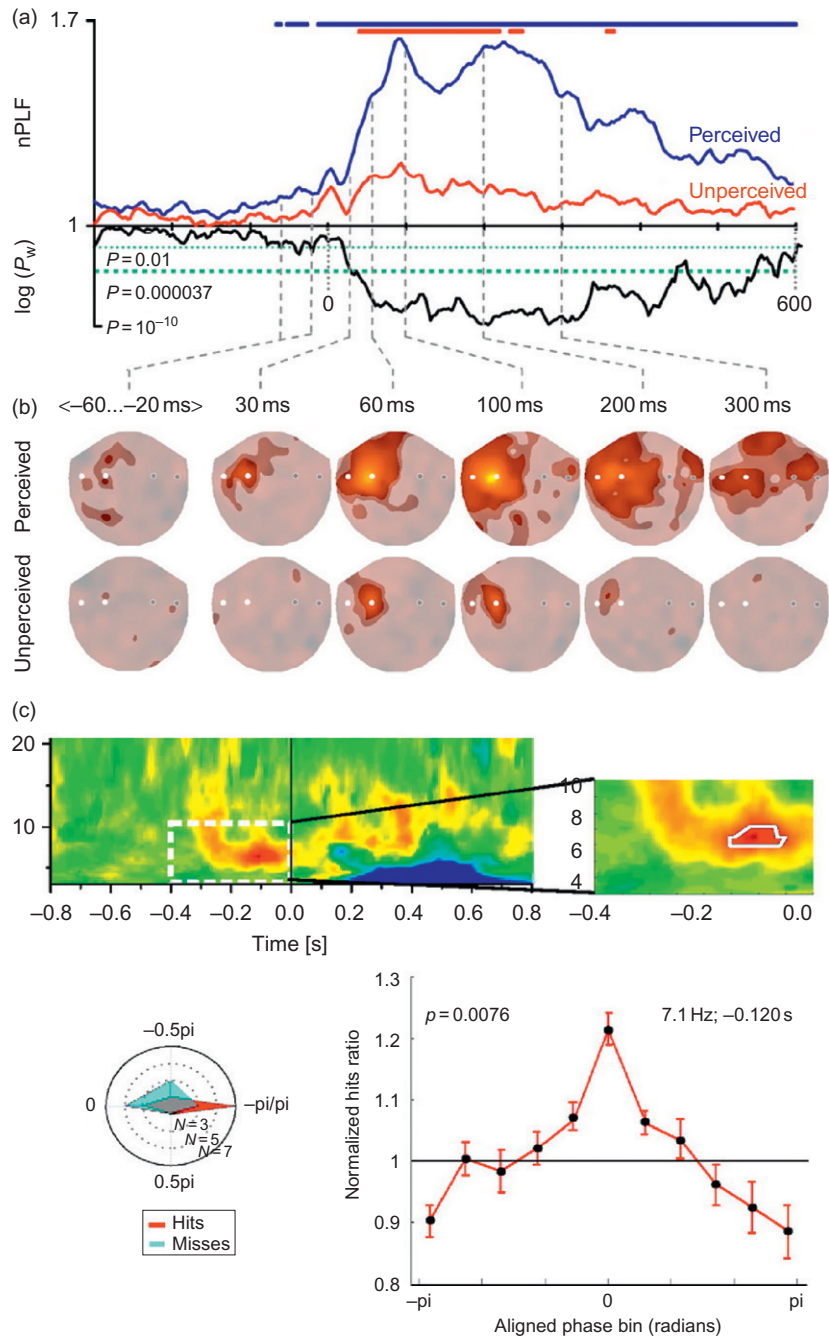


Fig. 4. Scale-free infraslow neurophysiological and psychophysical dynamics coexist with scale-specific temporal microstructure set by fast neuronal oscillations. (a) The phase of ongoing cortical broadband activity predicts conscious stimulus detection. Stimulus

power-law scaling and long-range temporal correlations lasting up to hundreds or thousands of oscillations cycles (Linkenkaer-Hansen et al., 2001, 2005). Like ICNs, these amplitude dynamics are also correlated between hemispheres in homotopic cortical regions (Nikouline et al., 2001). These data, together with the joint locking of >1 Hz oscillation amplitudes with phase of EEG ISFs in humans (He et al., 2010; Monto et al., 2008; Vanhatalo et al., 2004) and in rats (Allers et al., 2002) point to that the amplitude fluctuations of fast neuronal oscillations could be a link between fast scale-specific oscillations and slow scale-free ISFs and ICN dynamics. Indeed, several recent studies show that fMRI ICN fluctuations are correlated with amplitude fluctuations of oscillations ranging from 1 to >100 Hz in both humans (de Pasquale et al., 2010; He et al., 2008; Sadaghiani et al., 2010b) and monkeys (Scholvinck et al., 2010). A joint infraslow amplitude modulation of 1–100 Hz oscillations is also evident in MEG data showing that in the resting state, positive cross-frequency (CF) amplitude–amplitude correlations among narrow-band oscillations throughout this frequency range are highly significant and widespread (Palva et al., 2005a,b).

Covarying oscillation amplitude fluctuations thus appear to be an important signature of spontaneous brain activity and a direct link between ISFs and fast oscillations. In line with fMRI data (Boly et al., 2007; Sadaghiani et al., 2010b), a large body of electrophysiological data on TSDT performance indicate that prestimulus oscillation amplitudes in several distinct frequency bands predict a fraction of the behavioral variability (Busch et al., 2009; Linkenkaer-Hansen et al., 2004; Mathewson et al., 2009; Wyart and Tallon-

Baudry, 2009; Zhang and Ding, 2010). Of these frequency bands, amplitudes in the alpha-band are suggested by recent transcranial magnetic stimulation (TMS) studies to causally reflect visual input regulation (Capotosto et al., 2009; Romei et al., 2010) and have been suggested to do so via periodic (Klimesch et al., 2007) or “pulsing” inhibition (Mathewson et al., 2009). In fact, modulation of oscillation amplitudes with TMS provides the first evidence for a causal link between spontaneous brain dynamics and behavioral performance. It has, however, remained unclear whether ISFs *per se* can be manipulated with TMS.

What are the mechanisms driving the ICN and amplitude covariance? Amplitude is a characteristic that is easily related neither to the underlying cellular-level mechanisms nor to the functional roles of the oscillation. Even if one assumes the amplitude of the population oscillation to reflect the degree of synchrony in the population or the fraction of participating neurons, it is not clear what kind of neuronal interactions could mediate amplitude–amplitude interactions. Simulations using realistic structural brain connectivity suggest that the actual cycle-by-cycle neuronal interactions, or in other words, phase–phase coupling, would lead to emergent amplitude–amplitude interactions and ICN fluctuations similar to those observed in fMRI data (Honey et al., 2007). Future studies using M/EEG, source reconstruction techniques, and interareal interaction mapping (Palva et al., 2010a) or direct SEEG recordings (Jerbi et al., 2010) would be needed to establish links between phase–phase and amplitude–amplitude correlations. Such data could also shed light on whether long-range temporal correlations in amplitude data (Linkenkaer-Hansen et al., 2001) arise emergently

locking is also more robust after the stimulus onset for the detected than for the undetected stimuli in MEG data on a somatosensory TSDT, which suggests that the to-be-conscious perceptual processing is associated with a rapid, large-scale phase transition in the brain state. Adapted from Palva et al. (2005a,b). (b) The phase locking of ongoing brain activity to the detected stimuli spreads rapidly from contralateral somatosensory (white dots) to frontal (up) and parietal (down) brain regions whereas the activity related to Misses remains restricted to the somatosensory regions. (c) The phase of ongoing EEG oscillations at electrode Fz predicts subsequent conscious perception in a visual TSDT, which indicates a direct link between the phase of large-scale neuronal oscillations and the perceptual processing. Adapted from Busch et al. (2009).

from long “memory” of fast neuronal activity or through active control by slower processes such as neuronal oscillators in the ISF frequency range.

Cross-scale binding by CF phase-amplitude and phase–phase interactions

As brought up already, the phase of ISFs and the amplitudes of >1 Hz oscillations are robustly correlated (Monto et al., 2008; Vanhatalo et al., 2004). This relationship is a specific kind of a CF interaction called phase–amplitude correlation. Studies of CF interactions are becoming increasingly popular and are motivated, in part, by the unique potential of CF phase interactions to act as mechanisms for cross-scale integration (Lakatos et al., 2005; Palva et al., 2005a,b). Neuronal processing for cognitive operations is scattered not only anatomically but also temporally and spectrally. By coordinating neuronal activity among distinct frequency bands, CF interactions thereby inherently also bind activities in different time scales. Moreover, CF interactions can also bind neuronal processing in different spatial scales because the frequency of neuronal oscillations is to some extent correlated with the spatial scale of the population so that slow oscillations can engage larger neuronal populations than fast oscillations. Neuronal mechanisms connecting different spatial and temporal scales have a special role in the coordination of brain activity at the systems level—CF interactions are the prime candidates to serve such cross-scale integration (Palva et al., 2005a,b).

While amplitude–amplitude CF correlations (Bruns and Eckhorn, 2004; Palva et al., 2005a,b) might be more a consequence than a cause, phase–amplitude (Canolty and Knight, 2010; Lakatos et al., 2005) and phase–phase (Palva et al., 2005a,b) CF interactions can be readily linked to physiological mechanisms because the phase of population oscillations is related directly to underlying neuronal membrane potentials and

excitability, and thereby to the timing and likelihood of neuronal firing (Schroeder and Lakatos, 2009). An accumulating body of data shows that phase–amplitude interactions are, indeed, highly robust among between ISFs and 1–200 Hz oscillations (Monto et al., 2008), among the 1–200 Hz oscillations (Canolty et al., 2006; He et al., 2008, 2010; Lakatos et al., 2005, 2008), dynamically modulated during task performance (Tort et al., 2008), and correlated with the behavioral learning during task repetition (Tort et al., 2009). Phase–amplitude interactions are thus both prevalent and functionally significant.

Phase–phase CF interactions, of which $n:m$ -phase synchrony is the most well known, are fundamentally distinct from phase–amplitude interactions. $n:m$ -phase synchronization indicates phase locking of oscillations in frequency bands f_x and f_y of which the ratio is defined by the integers n and m so that $nf_x = mf_y$ (Tass et al., 1998). Importantly, while phase–amplitude correlations may exist between arbitrarily separated frequency bands, n and m need to be small because the stability of $n:m$ -phase synchrony is inversely related to the sum $n^2 + m^2$ (Wacker and Witte, 2011). From the physiological point of view, phase–phase CF interactions are in a position to coordinate neuronal communication analogously to 1:1-phase synchrony (Fries, 2005) because, by definition, the neurons in the slow oscillation fire at a specific phase of the fast oscillation (Palva et al., 2005a,b). This temporal accuracy is unavailable in phase–amplitude correlations where the slow oscillations are uncorrelated with the phase of fast oscillations even if they reflect excitability modulations in time scales of multiple fast cycles. Phase–amplitude and phase–phase CF interactions may thus play complementary roles in cross-scale coordination and communication.

In human resting-state MEG and EEG data, 1:2-phase synchrony is observable among 3–100 Hz oscillations (Palva et al., 2005a,b) and salient among theta-, alpha-, and beta-frequency bands (Nikulin and Brismar, 2006; Palva et al.,

2005a,b; Schack et al., 2005). Observations that these 1:2 interactions as well as 1:3-, 1:4- (Palva et al., 2005a,b), and 1:6- (Hamidi et al., 2009) phase synchronies between the alpha and gamma bands are associated with working memory processing suggest that they also are functionally significant.

Taken together, these data suggest that ongoing brain activity is composed of numerous neuronal oscillations from 0.01 to more than 100 Hz that create nested, spatiotemporally tree-like excitability windows to regulate and bias multi-scale neuronal activity according to exo- and endogenous processing demands. Indeed, it has been often speculated (He et al., 2010; Lakatos et al., 2005; Palva et al., 2005a,b) that CF interactions would have a hierarchical structure that spans the entire spectrum of brain activity. While the data are convincing on that pairwise interactions exist, there are little data to indicate the presence of a hierarchy beyond the pairwise connections. Such higher order correlations in the ordering of CF interactions along with the directionality of the interactions and possible scaling laws remain to be explored. Discoveries of such relationships could help in understanding how the cycle-by-cycle oscillation phase dynamics and short-time scale neuronal mechanisms underlie the slow ICN dynamics and long-range temporal correlations in amplitudes across hundreds or thousands of cycles. It is also up to future research to reveal the functional significance of CF interactions in TSDT-like tasks. Nonetheless, at this point, CF interactions appear to be the primary mechanistic link between millisecond-range neuronal activity and the long time scales of scale-free behavioral fluctuations.

Dissection of causal from correlated

Even with analyses of directionality and trial-by-trial behavioral performance, it is difficult to attribute the causal roles to specific neuronal activities or interactions. At least to some extent, the causal

effect of neuronal activity on behavior can be investigated by using targeted perturbations by noninvasive TMS in healthy subjects or with invasive microstimulation in patients or experimental animals (Driver et al., 2009). TMS and microstimulation can perturb (Driver et al., 2009; Massimini et al., 2009; Romei et al., 2010) or entrain (Hamidi et al., 2009) neuronal activity in targeted brain regions for a short period of time. The impacts of TMS and microstimulation on ongoing neuronal interaction networks have, however, remained largely unknown because very few studies have so far mapped networks of phase-phase synchronized neuronal oscillations with either M/EEG and source localization or with SEEG, respectively. Human brain networks defined by structural and functional connectivity (Bullmore and Sporns, 2009; Hagmann et al., 2008; van den Heuvel et al., 2008) or by cortical phase synchrony (Palva et al., 2010b) exhibit a fractal structure where a few brain regions act as network hubs and are critical for the connectivity in the network. Such scale-free networks are robust against attacks on random nodes but are highly vulnerable to attacks on the hubs (Albert et al., 2000). Using *a priori* knowledge of network topology for the targeting exogenous perturbations could thus pave way for a novel research paradigm for identifying the causal effects that specific interactions mediate.

Conclusion

Human psychophysical performance is autocorrelated for hundreds of seconds and fluctuates in a scale-free fashion but displays also scale-specific periodic modulations in time scales of tens to hundreds of milliseconds. We argue that scale-free activity fluctuations in brain networks account for scale-free behavioral fluctuations and that phase-phase coupled neuronal oscillations, on the other hand, account for discrete meta-stable states in action, attention, and perception. In this framework, within- and

CF phase interactions are the key physiological mechanisms that hierarchically coordinate multi-band neuronal oscillations and give rise to the emergent slow global dynamics reflected in the ISFs. These fractal and nested excitability fluctuations imposed by brain rhythms both occur spontaneously and can be coordinated by volition to meet exogenous demands.

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Abbreviations

BOLD	blood-oxygenation-level-dependent
CF	cross-frequency
CPT	continuous performance task
DAN	dorsal attention network
DMN	default-mode network
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
ICA	independent components analysis
ICN	intrinsic connectivity network
ISF	infraslow fluctuation
M/EEG	magneto- and electroencephalography
MEG	magnetoencephalography
SEEG	stereotactical EEG
TMS	transcranial magnetic stimulation
TSdT	threshold-stimulus detection task

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