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Imaging the temporal dynamics of brain states with highly sampled fMRI

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Abstract

The spontaneous dynamics of the brain modulate its function from moment to moment, shaping neural computation and cognition. Functional MRI (fMRI), while classically used as a tool for spatial localization, is increasingly being used to identify the temporal dynamics of brain activity. fMRI analyses focused on the temporal domain have revealed important new information about the dynamics underlying states such as arousal, attention, and sleep. Dense temporal sampling – either by using fast fMRI acquisition, or multiple repeated scan sessions within individuals – can further enrich the information present in these studies. This review focuses on recent developments in using fMRI to identify dynamics across brain states, particularly vigilance and sleep states, and the potential for highly temporally sampled fMRI to answer these questions.

Brain states fluctuate across seconds, minutes, hours and days, dynamically shaping neural computation. This state-dependence of brain function allows flexible behaviors across behavioral contexts. One striking example is how our responses to the environment are dramatically altered when we fall asleep; however, the effects of brain states are evident within the awake brain as well, due to fluctuations in attention, mood, arousal, and circadian and seasonal rhythms. Approaches that can identify brain states are thus critical for understanding variability in behavior and cognition, and determining how ongoing brain dynamics modulate neural computation.

Tools for assessing brain states are rapidly evolving. Large-scale coupled activity across distributed brain regions was discovered through temporal correlations in fMRI signals, termed ‘functional connectivity’ [1]. Although the origins and nature of spontaneous activity are still incompletely understood, studies using direct neural recordings have confirmed that brainwide, large-scale dynamics are strongly coupled to ongoing sensory processing and

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behavior [2–9], and can reflect offline cognitive processing such as replay and memory consolidation during sleep [10–14]. In humans, many questions about dynamic brain states have been primarily studied using EEG, which provides high temporal resolution to resolve rapid activity and oscillatory markers of distinct brain states such as sleep, but lacks spatial resolution and is not sensitive to deep brain structures. In recent years, fMRI has once again provided a new avenue for assessing brain states with whole-brain resolution, in particular through approaches that focus on its temporal dynamics.

fMRI is an indirect measure of brain function, sampling blood-oxygenation-level-dependent (BOLD) signals linked to neural activity [15,16]. Task-driven BOLD changes are related to induced neural activity [17], and human and animal studies have also confirmed links between spontaneous neural dynamics and hemodynamic signals within the resting state [18–24]. Because of the relatively slow sampling rates of conventional fMRI protocols (~2−3 s), and the presumed sluggishness of the hemodynamic response, BOLD fMRI has been extensively used to investigate activity at slow timescales. Major applications have included spatially mapping responses to cognitive tasks on long timescales (>2 s), or tracking spontaneous signals at very low frequencies (<0.1 Hz). However, two recent lines of research have developed highly temporally sampled approaches that support fMRI investigations of changes in brain state. First, repeated scanning of single individuals, in sessions across multiple days or months, has been used to identify how neural states and dynamics shift over time. Second, advances in acquisition technology such as simultaneous multislice imaging [25–28] have enabled researchers to acquire whole-brain images with sampling rates of hundreds of milliseconds. These fast fMRI approaches offer the potential to capture rapidly varying neural activity and fast dynamics within single scan sessions, while simultaneously providing the spatial coverage of fMRI to assess interactions between multiple areas across the whole brain.

These advances have now enabled neuroscientists to investigate multiple aspects of brain states, such as the functional properties of spontaneous BOLD signals observed in the temporal domain, and altered brain function within individuals across minutes, days and months. In particular, high temporal sampling within individuals – whether rapid sampling within a scan session, or repeated sampling across many sessions – has revealed significant new information about the temporal dynamics of brain states. This review will focus on recent advancements in highly temporally sampled fMRI and its potential for understanding the dynamics of human brain states.

The temporal sampling of fMRI studies has advanced

The original whole-brain fMRI studies used repetition times (TRs) of around 2 3 s, limiting imaging to slow timescales. This slow imaging was originally not thought to be a major constraint, as the fMRI signal temporal resolution is ultimately determined by the timescale of the hemodynamic response. The hemodynamic response unfolds relatively slowly, peaking several seconds after neural activation, and conventional models, therefore, originally predicted that fMRI signals would only contain slow dynamics, with little added benefit from faster sampling. However, even early studies showed signs of potentially faster dynamics [29], scanning rapidly by acquiring just a few slices rather than whole-brain

images. New fMRI acquisition strategies based on simultaneous multislice imaging – also termed multiband imaging – have matured in the last decade [30], enabling whole-brain data to be acquired in just a few hundred milliseconds. These multiband techniques were adopted by large-scale consortia such as the Human Connectome Project [114], which scanned 1200 individuals using a TR of 720 ms, setting a new standard for fMRI temporal resolution.

Taking advantage of this increased temporal resolution, multiple resting-state fMRI studies demonstrated that higher-frequency signals are present in the BOLD fMRI signal than were originally predicted, well above 0.1 Hz [31–35]. To elucidate the neural basis of fast fMRI signals, a task-based study then used visual stimuli test the temporal resolution of fMRI signals in a controlled manner, by inducing neural oscillations of known frequency, and determined that signals of up to 0.75 Hz, that is, subsecond dynamics, could be detected [36]. Subsequent task studies have used this fast sampling to detect even faster signals in rodents [37], and to identify fast fMRI dynamics linked to language and autonomic function [38,39]. High temporal sampling thus does not just provide more data, but can also enable detection of faster dynamics in the fMRI signal.

In addition to faster imaging, recent studies have used long-term, repeated imaging of individual participants to track changes in brain state over time. The Midnight Scan Club is one such project, in which individuals were imaged 10 times each [40]. Many Midnight Scan Club papers have now been published and demonstrate the insights that can be achieved with repeated measures within individuals – in particular, measuring dynamics across multiple days allows investigation of which brain state dynamics are stable or evolving on long timescales [41,42].

High temporal sampling provides three key advantages when imaging the dynamics of brain states. The first is simple: higher temporal sampling means more data (Figure 1a,b). fMRI datapoints are correlated over time, so doubling the sampling rate or number of sessions does not double the amount of information present, but does increase it. Multiband imaging can provide higher statistical power and better estimation of physiological noise [43–45]. Second, when examining dynamics underlying distinct brain states, the brain states themselves can fluctuate; imaging more rapidly or for longer periods enables capturing these fluctuations over time. Third, increasing evidence demonstrates that complex temporal features of the fMRI signal carry information about brain function, and these temporal features can often be better identified with higher temporal resolution data (Figure 1c,d).

Many aspects of spontaneous temporal dynamics carry information about brain function

These high-temporal-sampling approaches for fMRI provide a substantial advantage for assessing neural dynamics across brain states. Many of the first investigations of dynamic changes in brain states focused on dynamic functional connectivity: using sliding time windows to test how functional connectivity measures change over time [46,47]; see Ref. [48] for a review. Simultaneous EEG–fMRI recordings demonstrated that dynamic functional connectivity is coupled to neurophysiological state [49,50]. Increased temporal sampling can substantially improve measures of dynamic connectivity (Figure 1), by

allowing smaller time windows to be used for connectivity calculations (effectively increasing the temporal resolution) and by enhancing separation of physiological signals and detection of faster fMRI dynamics. Because of autocorrelation of the fMRI signal, window sizes cannot be made arbitrarily small and caution is still needed in interpreting dynamic signals [51], but even when holding window length constant the increased sampling can enable more accurate estimation of correlations.

Beyond dynamic functional connectivity, increasing evidence demonstrates that other temporal properties of fMRI signals may carry essential information about brain states: for example, individual activation events, or faster components of the BOLD signal. An intriguing line of work is the development of techniques to identify individual events across networks in the BOLD signal, that may drive correlation metrics [52,53]. These events may be linked to specific sequences of neural activity, and rapidly sampled fMRI could improve event detection and enhance future studies aiming to understand the link between these dynamics and cognitive states. A related approach is to identify temporal sequences of brain states, as was done in a recent study using Hidden Markov models to identify distinct brain states and their corresponding temporal occupancy and transition probabilities [54]. Furthermore, while parcellations of specific cortical regions are often used to extract signals within each region, a recent study demonstrated that the parcellations themselves are state-dependent [55•]. This observation further complicates the analysis of cortical dynamics, but also intriguingly suggests that functional parcellations may be temporally dynamic features of brain activity.

Further studies of temporal dynamics of the BOLD fMRI signal are a promising approach for understanding the underlying neural activity, as the interpretation of functional connectivity is quite complex. For example, a study in mice revealed that silencing of the prefrontal cortex led to paradoxical brain-wide resting state fMRI overconnectivity linked to increased interareal delta coherence [56]. By this logic, increased slow waves during sleep might also be expected to increase functional connectivity, despite representing decreased neuronal activity and perhaps corresponding to disrupted effective connectivity. Such findings bring up the challenges of using functional connectivity as a unidimensional indicator of brain-wide communication, and emphasize the importance of rhythmic activity to the establishment of apparent functional coupling. Incorporating distinct temporal features of the fMRI signal, such as spectral frequency content or event structures, may help shed light on these other aspects of neural coupling, and studies linking neural dynamics and synchrony to fMRI signals [23,53,57,58] will be important to aid with their interpretation.

fMRI dynamics across distinct arousal and cognitive states

Many of the investigations of brain arousal states with fMRI have focused on sleep, due to its profound modulation of behavior and cognition. Sleep studies typically use EEG to identify sleep stages, and then analyze the associated fMRI dynamics. Simultaneous EEG–fMRI sleep studies demonstrated that functional connectivity is modulated across the stages of non-rapideye-movement (NREM) sleep [59–61,115–118] and connectivity and activity measures are further coupled to individual EEG events such as sleep spindles and slow waves [62–64]. These dynamics can in fact be used to predict sleep stage [65], and applying

this prediction to a larger public dataset led to the important observation that many resting state fMRI studies likely include some sleeping participants.

More recently, more detailed temporal properties of the fMRI signal have been identified in sleep. The amplitude of spontaneous fMRI fluctuations increases in low arousal and light sleep [66], and is modulated by arousal regulatory circuits [119••]. This property may confound the interpretation of functional connectivity measures, as higher amplitude signals will inflate correlation values, suggesting that should be taken into account when analyzing fMRI dynamics. Chang *et al.* [67] developed an 'arousal template' — a spatial map of fMRI signal amplitude that predicts arousal over time (Figure 2a). This study developed a new approach to fingerprinting brain state not just through slow correlations, but through brainwide activity patterns at a moment in time.

Moving to this time-varying, dynamic perspective, is an important shift for studying sleep. While classic studies have categorized sleep into stages using 30 s time windows, it has long been known that brain states in fact fluctuate dynamically and gradually [68,69], sometimes punctuated by individual neurophysiological events or arousal state changes (Figure 2b). Recent fMRI studies have in turn identified subcortical networks linked to specific arousal events [70,71] demonstrating that these event structures are rooted in brainwide network engagement that can be detected via fMRI. Higher temporal sampling in future studies will further enhance these measures by allowing detection of more rapid events and fluctuations in state.

While sleep represents a drastic shift in behavior and cognition, studies have also identified fMRI dynamics underlying more subtle behavioral states in the awake brain as well. For example, sustained attention and fluctuating cognitive performance can be predicted by connectivity dynamics [72,73••,74,75,76], as well as network topology dynamics [77]. Attentional impairments after sleep deprivation are also linked to altered fMRI dynamics [78], as well as spontaneous fluctuations in pupil diameter, which covaries with alertness [79]. Multiple techniques have recently been developed to examine these dynamic changes in network state on faster timescales [80,81], and have observed rapid network-scale shifts linked to cognitive state [82].

Taken together, these studies demonstrate major shifts in the temporal properties of fMRI signals across cognitive states, and identify large-scale fMRI network dynamics that can predict electrophysiology and behavior. Interpreting the neural origins of these fMRI dynamics is often challenging, and continued multimodal studies using electrophysiology to understand these signals will be of high importance.

Longer term modulation of brain states

Highly temporally sampled fMRI can also reveal brain state shifts at longer temporal scales. A remarkable study conducting 13 imaging sessions within a day demonstrated that task-driven responses are coupled to the circadian rhythm [83]. A recent study found that spontaneous fMRI amplitudes decrease throughout the day [84•], which is a paradoxical finding given that fMRI amplitude typically increases in low arousal states, and points

to rich circadian variation in brain physiology that could be investigated with densely temporally sampled fMRI. In addition, seasonal variation in cognition and behavior is well known [85] and a cross-sectional fMRI study has also demonstrated seasonal variation in responses [86]; future studies densely sampling across a year within individuals could potentially reveal more information about these dynamics.

Repeated imaging also enables protracted manipulation of brain states. A fascinating recent study used daily imaging over three months to study the effects of movement restriction on dynamics in motor cortex [87••]. They discovered spontaneous activity pulses occurring focally in motor cortex during temporary casting and disuse of an arm (Figure 2c). This work demonstrates that focal brain states can be induced through sensorimotor manipulations, and identifies temporal dynamics that share some characteristics with low arousal states. Previous electrophysiology studies have demonstrated the phenomenon of 'local sleep', in which individual cortical areas can exhibit sleeplike dynamics while the rest of the brain remains awake [88,89]; how focal arousal states such as these related to disuse phenomena remains an intriguing question in need of further study.

The role of systemic physiology and neurovascular coupling in imaging brain states

The interpretation of fMRI signals in the context of brain states is complicated by the fact that distinct neural states are also often marked by altered neurovascular coupling and systemic physiology. First, since fMRI relies on blood oxygenation signals, its dynamics will be altered by changes in neurovascular coupling. Low arousal states such as sleep are associated with altered cerebral blood flow [90], and these baseline changes could be expected to alter the BOLD signal. Intriguingly, a recent study in mice demonstrated that neurovascular coupling is strengthened in NREM sleep, as compared to wakefulness [91], suggesting that fMRI's ability to track neural dynamics may be enhanced during low arousal. In addition, neuromodulatory substances such as noradrenaline, which modulate brain state and neuronal function, also modulate vascular tone and can directly induce vasodilation or vasoconstriction [92]. This vascular effect of neuromodulation suggests that attentional and emotional states may also modulate neurovascular coupling, but the degree to which this occurs is not yet clear.

In addition, systemic physiological dynamics, such as cardiac and respiratory signals, covary with brain state and modulate fMRI signals [93–96], both via motion (e.g. pulsation with the heartbeat) as well as via their effects on oxygenation and vascular tone. Accounting for these effects can be quite complex. For example, neural slow waves (including K-complexes) measured in the EEG during stage N2 sleep are associated with widespread cortical deactivation in the fMRI signal [97], consistent with the widespread neuronal suppression measured through invasive recordings [98,99]. However, systemic vasoconstriction also co-occurs with neural slow wave events [100], and thus dissecting the respective contributions of neural versus systemic physiological factors on the measured fMRI signal is not straightforward; both factors likely contribute to some degree. While common practice is often to regress out physiological signals to attempt to account for this issue, this regression-

based approach will also remove any signal of neural origin that is collinear with the physiological signals – which is often the signal of interest when studying brain states. Notably, systemic physiology alone can predict arousal state and even specific EEG features and cognitive correlates [101–105], and thus cannot simply be removed from fMRI signals. Even CSF flow is sometimes correlated with neural dynamics [97], suggesting that common preprocessing approaches such as regressing out the signal in the ventricles may sometimes have unintended effects. Similarly, an intriguing recent study demonstrated that motion is coupled to neural arousals [106••], suggesting that motion regression may remove some arousal-related neural dynamics as well.

An additional advantage of fast fMRI is that cardiac and respiratory signals no longer alias into low frequency bands — they can be separately resolved in their respective frequency bands and show distinctive spatiotemporal patterns [107,108]. This reduces direct noise contamination of fMRI signals from cardiac and respiratory cycles, although the influence of slow modulations in these signals, such as the 0.1 Hz envelope of the respiratory signal, nevertheless remain [93,109]. In addition, careful statistical analysis of fMRI signals will be important for resolving many of these questions. Statistical analyses are affected by the autocorrelation and physiological noise in fMRI signals, which is modulated by sampling rate [110]; techniques designed to account for this are being developed to enhance accuracy with highly sampled fMRI [111–113]. Analyzing physiological dynamics, in concert with experiments with interventions to modulate physiology directly, will be a key area for addressing these questions of how to account for systemic physiology in fMRI studies of brain dynamics.

Conclusions

Examining fMRI signals in the temporal domain has revealed new aspects of brain function, and is a promising approach for identifying how brain states modulate neural function. Recent work has identified multiple temporal features of fMRI signals that are relevant for brain function, as well hemodynamic and physiological factors that should be taken into account when analyzing these data. Sleep, attention, and other changes in brain state are associated with significant alterations in the temporal properties of fMRI signals, and these are coupled to electrophysiological and behavioral dynamics. Future studies taking full advantage of the increasing speed and sensitivity of fMRI, to obtain densely temporally sampled measures, hold major potential for understanding how these states support the flexibility of behavior and cognition in the human brain.

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• of special interest

•• of outstanding interest

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•• The authors demonstrated that the same functional connections that predict overall sustained attention ability can significantly predict attention changes observed over minutes, days, weeks, and months. The authors suggest that fluctuations in the same network structure can reflect state-like or trait-like differences in attentional performance. This work presents a proof-of-concept of a neuromarker for attention that translates across timescales.

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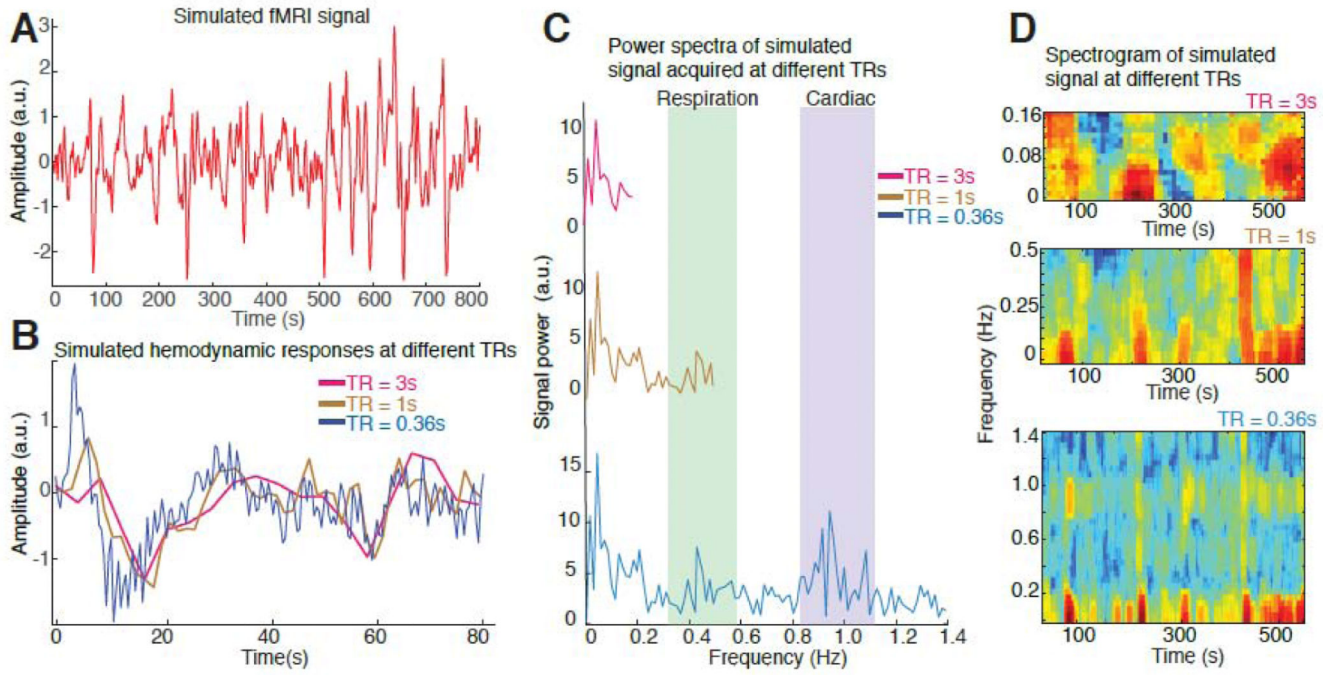

Figure 1.

Distinct temporal dynamics can be detected with higher temporal sampling.

This simple simulation illustrates the temporal properties of fMRI signals across sampling rates. (a) A simulated fMRI signal was generated with 0.3 Hz and 1 Hz oscillations representing the respiratory and cardiac cycles, and individual events representing large task-related hemodynamic responses. This simple simulation does not include the effects of sampling rate on SNR. (b) Example timeseries of the hemodynamic response as captured by different TRs (events beginning at 0 s and 60 s). Richer temporal information can be detected with short TRs. (c) The power spectrum at each TR value. Respiratory fluctuations are missed with the longest TR, and the cardiac fluctuation is detected only with the shortest TR. (d) The spectrogram of the simulated signal demonstrates the aliasing properties and detectability of high-frequency fluctuations.

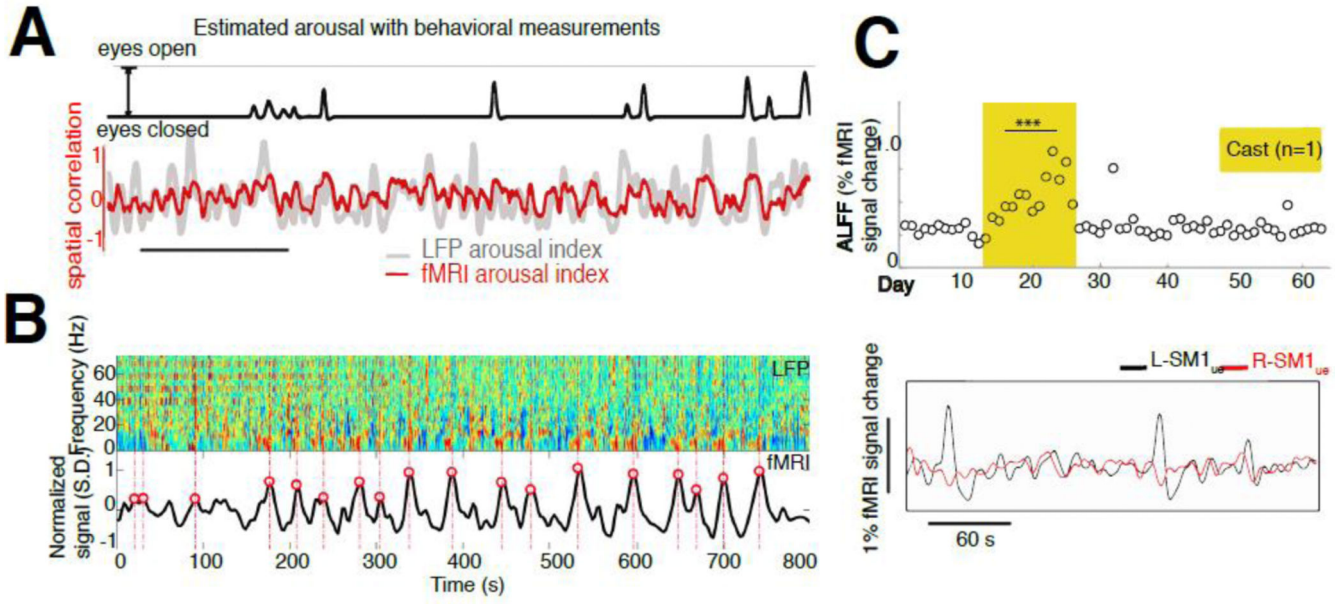

Figure 2.

Identifying fMRI temporal dynamics across brain states.

An array of studies have identified specific temporal properties of the fMRI signal coupled to brain state. (a) Chang *et al.* developed a time-varying arousal index that can predict brain state from fMRI signals. Figure reprinted from Ref. [67]. (b) Liu *et al.* identified events in the fMRI signal associated with distinct electrophysiological sequences. Figure reprinted from Ref. [70]. (c) Newbold *et al.* observed spontaneous event pulses in cortical areas representing a limb undergoing a temporary cast manipulation. Figure reprinted from Ref. [87••].