State-related neural influences on fMRI connectivity estimation

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Abstract

The spatiotemporal structure of functional magnetic resonance imaging (fMRI) signals has provided a valuable window into the network underpinnings of human brain function and dysfunction. Although some cross-regional temporal correlation patterns (functional connectivity; FC) exhibit a high degree of stability across individuals and species, there is growing acknowledgment that measures of FC can exhibit marked changes over a range of temporal scales. Further, FC can covary with experimental task demands and ongoing neural processes linked to arousal, consciousness and perception, cognitive and affective state, and brain-body interactions. The increased recognition that such interrelated neural processes modulate FC measurements has raised both challenges and new opportunities in using FC to investigate brain function. Here, we review recent advances in the quantification of neural effects that shape fMRI FC and discuss the broad implications of these findings in the design and analysis of fMRI studies. We also discuss how a more complete understanding of the neural factors that shape FC measurements can resolve apparent inconsistencies in the literature and lead to more interpretable conclusions from fMRI studies.

1. Introduction

Functional magnetic resonance imaging (fMRI) is well-suited for mapping large-scale network organization of the human brain. Patterns in the temporal associations between fMRI signals (functional connectivity; FC) not only can differentiate and identify subjects with high accuracy but can also predict measurable behavioral outputs such as fluid

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intelligence, sustained attention, symptom severity in psychiatric illness, and personality traits (Finn et al., 2015; Rosenberg et al., 2016; Hsu et al., 2018). This ability to capture meaningful behavioral variance illustrates the utility of FC and related metrics as potential biomarkers of behavior or disease.

Alongside these discoveries, open questions remain regarding the interpretation and reproducibility of fMRI-derived FC measures. Marked changes in FC, extending beyond transformations linked to maturation and aging, have been identified both across and within participants and scan sessions. These observations raise questions about the factors that shape the magnitude of FC and its underlying fMRI fluctuations at any given moment (Hutchison et al., 2013; Lurie et al., 2020). While some variability may stem from non-neuronal sources such as head motion and physiological artifacts, neural variability tied to state changes can also substantially modulate fMRI signal characteristics. Natural variations in arousal, perceptual state, attention, mind-wandering, and mood can shape fMRI connectivity measures (Sadaghiani et al., 2015; Kucyi, 2018; Mirchi et al., 2019; Liu and Falahpour, 2020; Song and Rosenberg, 2021). Neural activity is also known to undergo diurnal variations (Orban et al., 2020), and altered connectivity associated with task performance can persist post-task and affect subsequent resting-state connectivity measures (Gordon et al., 2014; Gaviria et al., 2021).

The extent to which fMRI connectivity measures reflect stable inter-individual traits and structural pathways, as opposed to internal state and daily variation, has been a matter of ongoing dialogue and investigation (Geerligs et al., 2015; Laumann et al., 2017; Gratton et al., 2018). Indeed, fMRI scans capture not only the unique “fingerprint” of an individual but also the state of the brain during image acquisition, where the latter effects may be most pronounced at short time scales and in brief scans. Unmodeled neural variability can also introduce inconsistency between results, especially when the data are limited and the effects of interest are small relative to other neural influences at play. Yet, while approaches for handling artifacts in fMRI data are in widespread use, it is typically more difficult to recognize, model, and control for signal variability arising from spontaneous neural effects. Strategies for dissecting sources of neural variability in fMRI include recording concurrent electrophysiology or pupil diameter to identify fluctuations in arousal, experience sampling to gauge ongoing cognitive processes, and the use of highly sampled data from individual subjects (Christoff et al., 2009; Gordon et al., 2017; Gratton et al., 2018; Liu and Falahpour, 2020). A more complete characterization of state-related neural factors, their spatiotemporal signatures in fMRI data, and the interaction between neuromodulatory influences and corticocortical recurrent activity can lead to more precise and efficient functional mapping with fMRI.

Notably, while often regarded as confounds in studies of task activation or intrinsic networks, state-dependent FC changes can present valuable opportunities for investigating cognitive, perceptual, and behavioral variation. For example, fMRI activity and correlation patterns have been shown to index perceptual states, sustained attention, and alertness (Hesselmann et al., 2008; Sadaghiani et al., 2009; Wang et al., 2013; Poudel et al., 2014; Rosenberg et al., 2016). It has also been demonstrated that markers of internal state may be
derived from fMRI signals themselves (Tagliazucchi and Laufs, 2014; Chang et al., 2015; Gonzalez-Castillo et al., 2015; Chang et al., 2016).

Here, we review recent advances and open questions in the study of neural factors that shape fMRI functional connectivity estimates. We focus on arousal and perceptual states, cognitive and affective states, task-history effects, and brain-body interactions. Although presented in separate sections, it is important to note that these effects can be closely interrelated, and often without a clear conceptual distinction. We discuss how increased knowledge of the prominent neural effects influencing FC can enable a more complete picture of brain function from fMRI, and may be harnessed in human connectome research.

1.1. Arousal state

There is growing recognition that fMRI signals are markedly influenced by the level of arousal, here referring to functional states across the spectrum of alert wakefulness, drowsiness, and sleep. Individuals can lose wakefulness within minutes of an fMRI scan (Tagliazucchi and Laufs, 2014; Haimovici et al., 2017) – especially during the task-free resting state, the condition under which functional connectivity is most often characterized. Moreover, systematic differences in arousal levels can be found across subjects or populations, owing to factors such as anxiety, sleep quality, and disease states that are accompanied by altered vigilance regulation (Olbrich et al., 2012; Hegerl and Hensch, 2014). A clear understanding of the signatures of arousal in fMRI signal and connectivity measurements will allow for a more precise characterization of brain function – including arousal itself – with fMRI.

Both fMRI time series and FC measures are modulated with arousal (Fig. 1). The amplitude of fMRI signals across distributed cortical networks has been found to increase with drowsiness and in the descent to sleep (Fukunaga et al., 2006; Horovitz et al., 2008; Larson-Prior et al., 2009). Continuous fluctuations in EEG, eyelid closure, and pupil-derived measures of arousal tend to exhibit negative correlations with widespread cortical BOLD signals, with opposing changes in areas including thalamus, brainstem, insula, and anterior cingulate (Olbrich et al., 2009; Murphy et al., 2014; Ong et al., 2015; Yellin et al., 2015; Chang et al., 2016; Schneider et al., 2016). While not spatially uniform, these widespread, coordinated signal changes become more prominent during drowsiness and light sleep, which manifest in larger-amplitude global fluctuations (Fukunaga et al., 2006; Wong et al., 2013) and may occur in transient bursts (Han et al., 2019). Such signal changes may be coordinated by ascending neuromodulatory input from structures such as the locus coeruleus in the brainstem (Joshi et al., 2016; Reimer et al., 2016), the basal forebrain (Liu et al., 2018b; Turchi et al., 2018), and by cortical regions involved in autonomic control, such as the insula (Kucyi and Parvizi, 2020). Concurrent changes in peripheral autonomic activity may also contribute to arousal-dependent BOLD responses (Soon et al., 2021). As referenced in the Brain-body interactions section, arousal and autonomic activity are intertwined (Pfaff et al., 2008; Beissner et al., 2013). Further, sympathetic autonomic activity has been posited to mediate brain-wide changes in cerebral blood flow through constriction of extra-parenchymal arteries (Ozbay et al., 2019).
These altered characteristics of fMRI signals would be expected to have a close link with arousal-dependent changes in FC. For example, increased thalamic-cortical anticorrelation has been associated with EEG markers of reduced wakefulness (Scheeringa et al., 2012; Allen et al., 2018), whereas reductions in anticorrelation (and increased positive correlation) were found between cortical networks including default mode network (DMN) and “task-positive” regions (Larson-Prior et al., 2011; Poudel et al., 2018). Pre-stimulus interactions between the DMN and “task-positive” regions also correlated with upcoming responses to behavioral stimuli (Thompson et al., 2013). However, due to the close relationship between the global fMRI signal and the time course of vigilance, a key consideration in the investigation of vigilance-dependent FC pertains to global signal regression (Falahpour et al., 2018a). Broadly, fMRI studies vary in terms of whether the global signal (i.e., a whole-brain average time course) has been removed from the data. The afore-mentioned findings of arousal-related fMRI signal changes had been obtained regardless of whether a whole-brain average signal had been removed; however, global signal regression has been found to reduce the spatial extent of negative correlations with an EEG arousal measure, and to reveal increased positive correlation in areas including cingulate gyrus (Falahpour et al., 2018a). Future work may systematically investigate the impact of global signal regression on state-dependent FC. One finding to date is that global signal regression reduces the level of cross-network FC, particularly during intervals of time corresponding to drowsiness (in which global fluctuations are more prominent) (Xu et al., 2018).

Given the associations between FC and vigilance, continuous monitoring of arousal levels would provide valuable information for interpreting fMRI data and examining state-dependent changes in behavior or cognition. However, since it is not always possible to gather measures such as EEG or pupillometry during fMRI scans, one recent line of work has examined the possibility of decoding ongoing arousal states from fMRI signals alone. Such studies have demonstrated the ability to classify between EEG-defined sleep stages (Tagliazucchi et al., 2012) or between high and low arousal states (Wang et al., 2016) based on fMRI FC. Further, a continuous temporal index of alertness may be derived from frame-by-frame fMRI activity patterns (Chang et al., 2016; Falahpour et al., 2018b; Goodale et al., 2021). While the modulation of fMRI signals with arousal can be regarded as a confound, such findings also highlight the notion that spontaneous fMRI signals can provide a valuable window into dynamic, internal brain states.

1.2. Consciousness & perception

Consciousness and perceptual awareness are believed to depend on the coordinated activity of large-scale brain systems (Laureys, 2005; Dehaene and Changeux, 2011; Godwin et al., 2015; Mashour and Hudetz, 2018). Accordingly, variations in the degree to which an individual is awake, responsive, or aware of oneself and the environment have been shown to correlate with neuroimaging measures of activity and connectivity.

Patterns of FC may be reflective of neural activity that governs perceptual awareness. Indeed, it has been shown that the amplitude, distributed pattern, and FC of spontaneous fMRI fluctuations may track ongoing perceptual states, as they are predictive of responses to incoming stimuli (Haynes et al., 2005; Hesselmann et al., 2008; Sadaghiani et al., 2009;
For example, connectivity states preceding the playback of a faint sound predicted whether the participant would perceive the sound on that trial (Sadaghiani et al., 2015). There, connectivity states preceding misses showed reduced modular structure, particularly in the DMN and visual networks. FC dynamics may, therefore, reflect neural processes that contribute to variability in perception or conscious experience.

Likewise, one’s experiences and prior knowledge also shape brain activity and perception. Using MEG and high-field fMRI, it was observed that after the acquisition of perceptual priors, ambiguous stimuli were represented more distinctly in neural dynamics (Flounders et al., 2019). Moreover, prior knowledge was found to alter content-specific neural representations in frontoparietal and default-mode networks (Gonzalez-Garcia et al., 2018). Since these studies demonstrate that experience-dependent effects in large-scale networks are clearly exhibited during stimulus processing, future work might investigate whether traces of past experiences also manifest in spontaneous fMRI signals and contribute to measurements of FC. For instance, spontaneous memory-related activation may play a role in generating fMRI FC patterns (Tambini and Davachi, 2019), and recent MEG work has linked spontaneous replay to intrinsic networks such as the DMN (Higgins et al., 2021).

One avenue for further investigation is the degree to which perceptually linked neuroimaging signals reflect processes specific to sensory content or, rather, are related to generalized neuromodulatory changes in arousal or attention (see also the section Arousal state). Such effects may be disentangled using novel experimental paradigms, as in a recent MEG study that identified two distinct neural processes in subjective visual recognition: a general process linked with arousal, and a specific process that facilitated category-specific recognition (Podvalny et al., 2019). Future extension of such paradigms to fMRI studies may also shed light on how content-specific processes are represented in fMRI connectivity measures, both during tasks and resting state.

There are also open questions regarding how fMRI connectivity measures relate to electrophysiological phenomena that have been linked with perception. Slow (< 5 Hz) cortical potentials (SCPs), widely distributed across the brain, have been posited to play a role in the emergence of consciousness and subjective awareness (He and Raichle, 2009). Support for this hypothesis draws on experiments demonstrating, for instance, that SCPs correlate with subjective awareness (Li et al., 2014) and may encode whether a stimulus at perceptual threshold was consciously perceived (Baria et al., 2017). The SCP may bridge electrophysiological and fMRI signals relating to consciousness, as these signals overlap in temporal scale and have been shown to correlate with one another (He et al., 2008; Pan et al., 2013). In addition to SCPs, higher electrophysiological frequency bands have been implicated in perceptual awareness. For instance, alpha-band activity has been found to predict detection bias (Grabot and Kayser, 2020; Samaha et al., 2020). Given that alpha oscillations have also been linked to changes in fMRI network activity (Sadaghiani et al., 2012) and FC (Scheeringa et al., 2012; Tagliazucchi et al., 2012; Chang et al., 2013), further work might examine whether perceptually-linked changes in SCP or alpha band are reflected in fMRI amplitude or FC.

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1.3. Cognitive & affective state

While the influence of physiological and arousal states on FC has been more widely studied, less is known about how cognitive and psychological states are represented in fMRI FC (Bolton et al., 2020). Functional network configurations are sensitive to cognition (Fig. 2), though the extent to which cognition manifests as measurable neural signal variations that influence FC measures is unclear. Similar to state changes like alertness and autonomic response, tracking moment-to-moment cognition provides an opportunity to better characterize fMRI FC and uncover potential new markers of individual differences.

The mind tends to wander through streams of conscious thought, especially in the absence of goal-directed tasks (Doucet et al., 2012; Irish et al., 2019). Since mind-wandering can rapidly change throughout a scan, it can be represented in time-varying components of brain dynamics (Kucyi and Davis, 2014; Christoff et al., 2016; Kucyi, 2018; Brechet et al., 2019). Neuroimaging combined with experience sampling, in which subjects intermittently provide self-reports about their current mental state, has been used to investigate the link between brain dynamics and mind wandering (Christoff et al., 2009; Kucyi et al., 2021). For example, a recent study identified a connectome-wide model, including default-frontoparietal control subnetwork interactions, that predicted stimulus-independent thoughts and generalized to adults with attention-deficit/hyperactivity disorder (Kucyi et al., 2021). Here, connectivity patterns were calculated in 30-s time windows preceding intermittent thought probes. Other studies have induced state changes with well-defined tasks. By learning the patterns evoked from activities such as imagining a song or performing mental arithmetic, studies have been able to decode task conditions from FC patterns alone (Shirer et al., 2012; Gonzalez-Castillo et al., 2015). Recently, it was found that FC patterns resembling those of task-induced cognitive states could be identified in resting-state scans (in 30-s epochs), potentially reflecting periods of distinct cognition (Gonzalez-Castillo et al., 2019). Together, these studies suggest that cognitive states have robust signatures in spontaneous activity that contribute to FC measurements.

An individual’s affective state is primarily driven by mood, which can spontaneously fluctuate over time scales ranging from minutes to weeks (Betzel et al., 2017). Fluctuations in subjective mood may be tracked by organized FC patterns (Mirchi et al., 2019), and altered connectivity within several brain networks (e.g., DMN, salience, executive) has been implicated in rumination and clinical depression (Hamilton et al., 2011; Shi et al., 2018). While some studies have used paradigms requiring effortful cognition (e.g., autobiographical recall) to evoke mood states, others have characterized trait-like phenotypes using naturalistic tasks such as movie-watching (Sonkusare et al., 2019; Finn et al., 2020). For example, inter-subject synchronization in both FC and autonomic variables linked to emotion (e.g., heart rate variability) during sad movie-watching has uncovered limbic network synchrony that tracked changes in sadness (Raz et al., 2016). Further, machine learning can be applied to predict the intensity of emotional experience and identify signatures of emotional response in FC patterns (Chang et al., 2015; Chan et al., 2020; Saarimäki et al., 2020). In this vein, a recent study used pattern recognition based on whole-brain connectivity signatures (calculated over 60-s windows) to distinguish between six basic emotions, with default-mode FC most accurately representing an individual’s
current emotional state (Saarimäki et al., 2020). Together, these studies suggest that the
brain’s functional architecture, as measured by FC, is sensitive to the dynamics of cognitive
and affective states.

As discussed, changes in ongoing and transient cognition are reflected in changes in FC.
However, the degree to which FC reflects cognitive and affective state dynamics rather
than non-cognitive/affective processes, physiology, or measurement noise is debated (Lurie et al.,
2020). It has been suggested that simultaneous recordings of physiological signals (e.g.,
cardiac and respiratory monitoring) and fMRI may help to disentangle FC changes driven
by cognition versus non-cognitive physiological processes (Simony et al., 2016). Another
open question is whether an individual’s affective states and traits are better characterized by
task-evoked connectivity than resting-state connectivity patterns (Finn et al., 2018).

1.4. Task history effects

In addition to spontaneously generated cognition, functional connectivity patterns may be
influenced by tasks performed in preceding scans. Following an N-back working memory
task, resting-state connectivity alterations were found within the task-positive network
(TPN) that had been activated by the working memory task (Gordon et al., 2014); similar
findings have been demonstrated across multiple other task domains, including cognitive and
affective challenges (Waites et al., 2005; Lewis et al., 2009), and post-task effects are also
expressed in dynamic metrics of fMRI co-activation (Gaviria et al., 2021). In addition to
FC, the temporal characteristics of regional fMRI time series may also be altered by task
history. The fractal scaling properties of fMRI signals (Bullmore et al., 2001; He, 2011)
were found to be altered for approximately 15 min following an N-back working memory
task, recovering more slowly for the more demanding two-back, compared to one-back,
condition (Barnes et al., 2009). While most studies of task-history effects summarize signal
or connectivity properties across an entire scan, the study by Barnes et al. (2009) examined
time windows across the course of individual scans in order to chart the progression of
recovery to baseline.

The mechanisms of persistent fMRI signal and FC changes following task engagement
are not clear, but have been posited to relate in part to subjective aspects of an effortful
cognitive experience (Gordon et al., 2014), or consolidation of recent cognitive experiences
that may contribute to learning and memory (Stevens et al., 2010). The relationship between
task-induced FC reorganization and other processes (such as attention and arousal) is
also presently unclear, but such states could also contribute to the persistence of task
effects. Indeed, areas showing task-modulated effects after a motor task also included more
widespread regions encompassing the auditory cortex, visual areas, and the thalamus (Tung
et al., 2013), similar to areas linked with changes in arousal (e.g., Ong et al., 2015).
Such observations have implications for models of how the brain recovers/resets following
effortful cognition, as well as practical implications for the ordering of scans within a scan
session – and even in the design of experimental versus control conditions.
1.5. Brain-body interactions

The brain and body are in constant, bidirectional communication. Neural substrates of autonomic modulation include, in addition to brainstem nuclei, large-scale cortical networks implicated in executive control, salience processing, and emotion regulation (Beissner et al., 2013; Valenza et al., 2020). Interactions between brain networks and cardiovascular responses support adaptive responses to changing environmental conditions and vary as a function of physiological or psychological state, either externally or internally driven (Thayer and Lane, 2000; Critchley, 2005; McCraty and Zayas, 2014; Chand et al., 2020). The fMRI signatures of these processes may also contribute to measurements of FC, and may coincide with those of arousal, cognition, and emotion.

While most fMRI studies of autonomic processing are conducted during task-induced emotional, physiological, and cognitive changes, some have also probed how dynamic changes in regional BOLD signals or network connectivity track changes in spontaneous, peripheral autonomic responses. For example, measurements of skin conductance have been found to correlate with BOLD fMRI fluctuations in major nodes of the default-mode network (Patterson et al., 2002; Fan et al., 2012). In another study, whole-brain connectivity patterns of structures implicated in salience and autonomic processing (dorsal anterior cingulate, amygdala) were found to track resting fluctuations in high-frequency heart rate variability, a measure of parasympathetic activity, even when controlling for concurrent changes in respiratory volume (Chang et al., 2013b). Resting-state mapping of autonomic outflow (Valenza et al., 2019) and heartbeat complexity measures (Valenza et al., 2020) have also revealed distributed networks of regions spanning multiple cortical networks. Given the structure and extent of these fMRI autonomic correlations, open questions remain in terms of the extent to which autonomic regulation underpins components of activity measured in canonical functional networks (Nagai et al., 2004). Functional MRI correlates of peripheral autonomic measures may also align with observations of fMRI changes across arousal levels (see above section Arousal states), particularly as arousal and autonomic activity are co-modulated (Duyn et al., 2020).

There is also a growing recognition that visceral signals, such as from the heart and gut, provide input to the brain that may shape spontaneous fluctuations as well as cognition and perception. The heart and gastrointestinal tract generate their own electrical activity, and visceral signals influence spontaneous brain dynamics (Azzalini et al., 2019). Neural responses to cardiac signals may also contribute to perception (Park et al., 2014) and bodily self-consciousness (Park et al., 2016). While the role of the gut has been less commonly studied, gastric rhythms were found to exhibit delayed correlations with spontaneous BOLD activity that overlapped in part with a network of autonomic regulation (Rebollo et al., 2018).

Such findings suggest that visceral and autonomic activity may also be important factors in modeling large-scale brain dynamics and FC, and may present information relevant to individual differences. For example, recent evidence indicates that the level of synchrony between slow rhythms of pulse and resting-state fMRI signals was associated with personality and emotions (Shokri-Kojori et al., 2018). It has also been hypothesized that changes in peripheral physiology (breathing) can drive resting-state blood flow oscillations.
that can improve emotion regulation (Mather and Thayer, 2018). Thus, the expression of autonomic effects in fMRI connectivity may provide useful markers of brain function and personality traits.

2. Discussion

An intriguing hallmark of spontaneous brain activity has been the relative stability of its spatio-temporal organization. On average across subjects and time, similar network patterns are readily identified across various tasks, resting wakefulness, and sleep (Smith et al., 2009; Larson-Prior et al., 2011; Cole et al., 2014; Laumann et al., 2017). Moreover, FC profiles are known to generate reliable markers of individual differences (Miranda-Dominguez et al., 2014; Finn et al., 2015) and to align to some extent with structural connectivity (Damoiseaux and Greicius, 2009; Straathof et al., 2019). At the same time, ongoing cognitive and physiological states – expressed in brain activity changes from moment to moment – can also be robustly discerned (to various degrees) in fMRI signals, exerting dynamic modulation atop of this stable architecture that is detectable as within- and between-scan variability.

Temporal variability in FC arising from neural effects presents considerations for the analysis and interpretation of fMRI data. Firstly, when these sources are unmodeled, they can lead to errors in interpretation or inconsistent findings. This potential for error is especially likely in studies with smaller sample sizes, shorter scans, or when particular effects occur systematically in an individual or population (e.g., a propensity toward increased anxiety or reduced wakefulness). Neural state effects may also be closely intertwined with findings of stable, trait-like FC markers. For instance, if an individual or group is more likely to be anxious or attentive, FC patterns linked with states such as attention may consistently shape the FC measured across multiple scans within that individual, systematically altering that subject’s connectome fingerprint.

In that sense, a clearer picture of how state-related neural effects manifest in fMRI signal and connectivity measures – and the relative magnitudes by which various factors contribute – would enable a deeper and more precise understanding of individual differences in brain function. At the same time, the dynamic, state-dependent neural effects may not be regarded merely as confounds, but also have the potential to lead to novel biomarkers. Indeed, dynamic information in fMRI has been found to contribute to measures of individual difference and disease beyond those of static FC (Calhoun et al., 2014; Vidaurre et al., 2021). Further, the detection of dynamic neural fluctuations associated with pathological emotional states (e.g., rumination) and symptom severity may present objective markers of neuropsychiatric disorders (Hamilton et al., 2011; Kaiser et al., 2016; Rashid and Calhoun, 2020; Shappell et al., 2021). Neural state changes that are detectable in fMRI may also present valuable context for understanding brain and behavioral variability. For instance, levels of arousal and attention are major determinants of decision-making and task performance (McCormick et al., 2020) but are not presently considered in most fMRI analyses. Monitoring or data-driven detection of these ongoing state changes would enrich not only an understanding of resting-state FC but also studies of task-evoked fMRI responses (Thompson et al., 2013; Roth et al., 2020; Goodale et al., 2021).
It is also worth noting that there is a broad array of methods for quantifying FC and modeling fMRI signals, including correlation, partial correlation, and multivariate decomposition techniques such as ICA. As such, neural and physiological state-changes may manifest differently across these analyses. While systematic investigation is needed to draw generalizable conclusions, one consideration is that for state-changes accompanied by large-scale systemic effects (such as arousal and autonomic physiology), it is possible that the delineation of specific networks may be more stable across states with techniques that un-mix signal sources (e.g. ICA (McKeown et al., 1998; Smith et al., 2012; Glasser et al., 2018) compared to those which correlate the observed, preprocessed BOLD signal across regions. Further, while FC measures are typically calculated over the entire length of the scan, time-dependent analysis methods have become more prominent in recent years (Preti et al., 2017). These methods, which capture co-activating regions within short time-windows or single time-frames, can return a repertoire of patterns that reflect a range of neural states, rather than an average over the scan. The rates of occurrence, dwell time, transition probabilities, and related metrics of such patterns can be quantified, providing a more finely resolved picture of FC as well as potential biomarkers (Allen et al., 2014; Liu et al., 2018a).

One open question concerns how these various state-related neural effects interact with one another, and with the BOLD fMRI signal. Although discussed in separate sections above, many of the effects described in this article are closely interrelated, and their neural signatures may coincide in fMRI signals and FC. For example, consciousness and perception are supported by arousal (Goldfine and Schiff, 2011; Podvalny et al., 2019) and may even be shaped by mood (Kuhbandner et al., 2009), and task-history effects may also represent cognitive and affective states induced by the preceding experiments. It is also important to consider how spontaneous fluctuations and neural state changes may interact with task-driven neural activity, and whether they are additive or exhibit more complex nonlinear interactions (He, 2013). The latter would also have implications for how one would proceed to remove these effects from fMRI data if one were interested in mitigating the effect of a particular neural source. Moreover, the coupling between neural and vascular activity may itself change across states such as arousal and attention. For example, higher levels of acetylcholine have been found to be accompanied by enhanced correlations between local field potentials and cerebral blood flow in sensory tasks (Lecrux et al., 2017). Brainstem arousal centers are also able to modulate vascular tone, such as through sympathetic innervations of the pial arteries (Hamel, 2006), eliciting global fMRI fluctuations of vascular origin (Özbay et al., 2019; Duyn et al., 2020). Further progress toward characterizing state-related changes in neurovascular coupling will also be important for interpreting fMRI data across brain states.

Another future direction may investigate how neural state effects, in addition to influencing long-range correlations, can also impact local patterns of correlation. Functional parcellations serve as the basis of network analyses but have recently been noted to change across time (Boukhdhir et al., 2021) and brain states (Salehi et al., 2020). Finally, future work may investigate ways of integrating state-related effects into brain representations (Bijsterbosch et al., 2020). Overall, further investigation into state-related neural effects in fMRI presents avenues for enriching our picture of brain function and strengthening the inferences that can be drawn from fMRI.
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References

Allen EA, Damaraju E, Eichele T, Wu L, Calhoun VD, 2018. EEG signatures of dynamic functional network connectivity states. Brain Topogr. 31, 101–116. [PubMed: 28229308]

Allen EA, Damaraju E, Plis SM, Erhardt EB, Eichele T, Calhoun VD, 2014. Tracking whole-brain connectivity dynamics in the resting state. Cereb Cortex 24, 663–676. [PubMed: 23146964]

Azzalini D, Rebollo I, Tallon-Baudry C, 2019. Visceral signals shape brain dynamics and cognition. Trends Cogn. Sci 23, 488–509. [PubMed: 31047813]

Baria AT, Maniscalco B, He BJ, 2017. Initial-state-dependent, robust, transient neural dynamics encode conscious visual perception. PLoS Comput. Biol 13, e1005806. [PubMed: 29176808]

Barnes A, Bullmore ET, Suckling J, 2009. Endogenous human brain dynamics recover slowly following cognitive effort. PLoS ONE 4, e6626. [PubMed: 19680553]

Beissner F, Meissner K, Bar KJ, Napadow V, 2013. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J. Neurosci 33, 10503–10511. [PubMed: 23785162]

Betzel RF, Satterthwaite TD, Gold JL, Bassett DS, 2017. Positive affect, surprise, and fatigue are correlates of network flexibility. Sci. Rep 7, 520. [PubMed: 28364117]

Bijsterbosch J, Harrison SJ, Jbabdi S, Woolrich M, Beckmann C, Smith S, Duff EP, 2020. Challenges and future directions for representations of functional brain organization. Nat. Neurosci 23, 1484–1495. [PubMed: 33106677]

Bolton TAW, Morgenroth E, Preti MG, Van De Ville D, 2020. Tapping into multi-faceted human behavior and psychopathology using fMRI brain dynamics. Trends Neurosci. 43, 667–680. [PubMed: 32682563]

Boukhdhir A, Zhang Y, Mignotte M, Bellec P, 2021. Unraveling reproducible dynamic states of individual brain functional parcellation. Netw. Neurosci 5, 28–55. [PubMed: 33688605]

Brechet L, Brunet D, Birot G, Gruetter R, Michel CM, Jorge J, 2019. Capturing the spatiotemporal dynamics of self-generated, task-initiated thoughts with EEG and fMRI. Neuroimage 194, 82–92. [PubMed: 30902640]

Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, Carpenter TA, Brammer M, 2001. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. Hum. Brain Mapp 12, 61–78. [PubMed: 11169871]

Calhoun VD, Miller R, Pearlson G, Adali T, 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84, 262–274. [PubMed: 25374354]

Chan HY, Smidts A, Schoots VC, Sanfey AG, Boksem MAS, 2020. Decoding dynamic affective responses to naturalistic videos with shared neural patterns. Neuroimage 216, 116618. [PubMed: 32036021]

Chand T, Li M, Jamalabadi H, Wagner G, Lord A, Alizadeh S, Danyeli LV, Herrmann L, Walter M, Sen ZD, 2020. Heart rate variability as an index of differential brain dynamics at rest and after acute stress induction. Front. Neurosci. 14, 645. [PubMed: 32714132]

Chang C, Liu Z, Chen MC, Liu X, Duyn JH, 2013. EEG correlates of time-varying BOLD functional connectivity. Neuroimage 72, 227–236. [PubMed: 23376790]

Chang C, Leopold DA, Scholvinck ML, Mandelkow H, Picchioni D, Liu X, Ye FQ, Turchi JN, Duyn JH, 2016. Tracking brain arousal fluctuations with fMRI. Proc. Natl. Acad. Sci. U. S. A 113, 4518–4523. [PubMed: 27051064]

Chang LJ, Gianaros PJ, Manuck SB, Krishnan A, Wager TD, 2015. A Sensitive and specific neural signature for picture-induced negative affect. PLoS Biol. 13, e1002180. [PubMed: 26098873]
Chang C, Metzger CD, Glover GH, Duyn JH, Heinze H-J, Walter M, 2013b. Association between heart rate variability and fluctuations in resting-state functional connectivity. Neuroimage 68, 93–104. doi:10.1016/j.neuroimage.2012.11.038. [PubMed: 23246859]

Christoff K, Gordon AM, Smallwood J, Smith R, Schooler JW, 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proc. Natl. Acad. Sci. U. S. A 106, 8719–8724. [PubMed: 19433790]

Christoff K, Irving ZC, Fox KC, Spreng RN, Andrews-Hanna JR, 2016. Mind-wandering as spontaneous thought: a dynamic framework. Nat. Rev. Neurosci 17, 718–731. [PubMed: 27654862]

Cole MW, Bassett DS, Power JD, Braver TS, Petersen SE, 2014. Intrinsic and task-evoked network architectures of the human brain. Neuron 83, 238–251. [PubMed: 24991964]

Critchley HD, 2005. Neural mechanisms of autonomic, affective, and cognitive integration. J. Compt. Neur 493, 154–166. [PubMed: 16254997]

Damoiseaux JS, Greicius MD, 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct 213, 525–533. [PubMed: 19565262]

Dehaene S, Changeux JP, 2011. Experimental and theoretical approaches to conscious processing. Neuron 70, 200–227. [PubMed: 21521609]

Doucet G, Naveau M, Petit L, Zago L, Crivello F, Jobard G, Delcroix N, Mellet E, Tzourio-Mazoyer N, Mazoyer B, Joliot M, 2012. Patterns of hemodynamic low-frequency oscillations in the brain are modulated by the nature of free thought during rest. Neuroimage 59, 3194–3200. [PubMed: 22155378]

Duyn JH, Ozbay PS, Chang C, Picchioni D, 2020. Physiological changes in sleep that affect fMRI inference. Curr. Opin. Behav. Sci 33, 42–50. [PubMed: 32613032]

Falahpour M, Nalcı A, Liu TT, 2018a. The effects of global signal regression on estimates of resting-state blood oxygen-level-dependent functional magnetic resonance imaging and electroencephalogram vigilance correlations. Brain Connect 8, 618–627. [PubMed: 30525929]

Falahpour M, Chang C, Wong CW, Liu TT, 2018b. Template-based prediction of vigilance fluctuations in resting-state fMRI. Neuroimage 174, 317–327. [PubMed: 29548849]

Fan J, Xu P, Van Dam NT, Eilam-Stock T, Gu X, Luo YJ, Hof PR, 2012. Spontaneous brain activity relates to autonomic arousal. J. Neurosci 32, 11176–11186. [PubMed: 22895703]

Finn ES, Corlett PR, Chen G, Bandettini PA, Constable RT, 2018. Trait paranoia shapes inter-subject synchrony in brain activity during an ambiguous social narrative. Nat. Commun 9, 2043. [PubMed: 29795116]

Finn ES, Glerean E, Khojandi AY, Nielson D, Molfese PJ, Handwerker DA, Bandettini PA, 2020. Idiosynchrony: from shared responses to individual differences during naturalistic neuroimaging. Neuroimage 215, 116828. [PubMed: 32276065]

Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X, Constable RT, 2015. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat. Neurosci 18, 1664–1671. [PubMed: 26457551]

Flounders MW, Gonzalez-Garcia C, Hardstone R, He BJ, 2019. Neural dynamics of visual ambiguity resolution by perceptual prior. Elife 8, e41861. [PubMed: 30843519]

Fukunaga M, Horovitz SG, van Gelderen P, de Zwart JA, Jansma JM, Konomidou VN, Chu R, Deckers RH, Leopold DA, Duyn JH, 2006. Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. Magn. Reson. Imaging 24, 979–992. [PubMed: 16997067]

Gaviria J, Rey G, Bolton T, Delgado J, Van De Ville D, Vuilleumier P, 2021. Brain functional connectivity dynamics at rest in the aftermath of affective and cognitive challenges. Hum. Brain Mapp 42, 1054–1069. [PubMed: 33231916]

Geerligs L, Rubinov M, Cam C, Henson RN, 2015. State and trait components of functional connectivity: individual differences vary with mental state. J. Neurosci 35, 13949–13961. [PubMed: 26468196]
Glasser MF, Coalson TS, Bijsterbosch JD, Harrison SJ, Harms MP, Anticevic A, Van Essen DC, Smith SM, 2018. Using temporal ICA to selectively remove global noise while preserving global signal in functional MRI data. Neuroimage 181, 692–717. [PubMed: 29753843]

Godwin D, Barry RL, Marois R, 2015. Breakdown of the brain’s functional network modularity with awareness. Proc. Natl. Acad. Sci. U. S. A 112, 3799–3804. [PubMed: 25759440]

Goldfine AM, Schiff ND, 2011. Consciousness: its neurobiology and the major classes of impairment. Neurol. Clin 29, 723–737. [PubMed: 22032656]

Gonzalez-Castillo J, Caballero-Gaudes C, Topolski N, Handwerker DA, Pereira F, Bandettini PA, 2019. Imaging the spontaneous flow of thought: distinct periods of cognition contribute to dynamic functional connectivity during rest. Neuroimage 202, 116129. [PubMed: 31461679]

Gonzalez-Castillo J, Hoy CW, Handwerker DA, Robinson ME, Buchanan LC, Saad ZS, Bandettini PA, 2015. Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns. Proc. Natl. Acad. Sci. U. S. A 112, 8762–8767. [PubMed: 26124112]

Gonzalez-Garcia C, Flounders MW, Chang R, Baria AT, He BJ, 2018. Content-specific activity in frontoparietal and default-mode networks during prior-guided visual perception. Elife 7, e36068. [PubMed: 30063006]

Goodale SE, Ahmed N, Zhao C, de Zwart JA, Ozbay PS, Picchioni D, Duyn J, Englot DJ, Morgan VL, Chang C, 2021. fMRI-based detection of alertness predicts behavioral response variability. Elife 10, e62376. [PubMed: 28757305]

Gordon EM, Breeden AL, Bean SE, Vaidya CJ, 2014. Working memory-related changes in functional connectivity persist beyond task disengagement. Hum. Brain Mapp 35, 1004–1017. [PubMed: 23281202]

Gordon EM, Laumann TO, Gilmore AW, Newbold DJ, Greene DJ, Berg JJ, Ortega M, Hoyt-Drazen C, Gratton C, Sun H, Hampton JM, Coalson RS, Nguyen AL, McDermott KB, Shimony JS, Snyder AZ, Schlaggar BL, Petersen SE, Nelson SM, Dosenbach NUF, 2018. Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. Neuron 98, 439–452 e435. [PubMed: 29673485]

Grabot L, Kayser C, 2020. Alpha activity reflects the magnitude of an individual bias in human perception. J. Neurosci 40, 3443–3454. [PubMed: 32179571]

Gratton C, Laumann TO, Nielsen AN, Greene DJ, Gordon EM, Gilmore AW, Nelson SM, Coalson RS, Snyder AZ, Schlaggar BL, Petersen SE, 2018. Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. Neuron 98, 439–452 e435. [PubMed: 29673485]

Haimovici A, Tagliazucchi E, Balenzuela P, Laufs H, 2017. On wakefulness fluctuations as a source of BOLD functional connectivity dynamics. Sci. Rep 7, 5908. [PubMed: 28724928]

Hamel E, 2006. Perivascular nerves and the regulation of cerebrovascular tone. J. Appl. Physiol 100, 1059–1064. [PubMed: 16467392]

Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH, 2011. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biol. Psychiatry 70, 327–333. [PubMed: 21459364]

Han F, Gu Y, Liu X, 2019. A neurophysiological event of arousal modulation may underlie fMRI-EEG correlations. Front. Neurosci 13, 823. [PubMed: 31447638]

Haynes JD, Driver J, Rees G, 2005. Visibility reflects dynamic changes of effective connectivity between V1 and fusiform cortex. Neuron 46, 811–821. [PubMed: 15924866]

He BJ, 2011. Scale-free properties of the functional magnetic resonance imaging signal during rest and task. J. Neurosci 31, 13786–13795. [PubMed: 21957241]

He BJ, 2013. Spontaneous and task-evoked brain activity negatively interact. J. Neurosci 33, 4672–4682. [PubMed: 23486941]

He BJ, Raichle ME, 2009. The fMRI signal, slow cortical potential and consciousness. Trends Cogn. Sci 13, 302–309. [PubMed: 19535283]

He BJ, Snyder AZ, Zempel JM, Smyth MD, Raichle ME, 2008. Electrophysiological correlates of the brain’s intrinsic large-scale functional architecture. Proc. Natl. Acad. Sci. U. S. A 105, 16039–16044. [PubMed: 18843113]

Hegerl U, Hensch T, 2014. The vigilance regulation model of affective disorders and ADHD. Neurosci. Biobehav. Rev 44, 45–57. [PubMed: 23092655]

Neuroimage. Author manuscript; available in PMC 2022 February 04.
Hesselmann G, Kell CA, Eger E, Kleinschmidt A, 2008. Spontaneous local variations in ongoing neural activity bias perceptual decisions. Proc. Natl. Acad. Sci. U. S. A 105, 10984–10989. [PubMed: 18664576]

Higgins C, Liu Y, Vidaurre D, Kurth-Nelson Z, Dolan R, Behrens T, Woolrich M, 2021. Replay bursts in humans coincide with activation of the default mode and parietal alpha networks. Neuron 109, 882–893 e887. [PubMed: 33357412]

Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, Duyn JH, 2008. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-MRI study. Hum. Brain Mapp 29, 671–682. [PubMed: 17598166]

Hsu WT, Rosenberg MD, Scheinost D, Constable RT, Chun MM, 2018. Resting-state functional connectivity predicts neuroticism and extraversion in novel individuals. Soc. Cogn. Affect Neurosci 13, 224–232. [PubMed: 29373729]

Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, Della Penna S, Duyn JH, Glover GH, Gonzalez-Castillo J, Handwerker DA, Keilholz S, Kiviniemi V, Leopold DA, de Pasquale F, Sporns O, Walter M, Chang C, 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378. [PubMed: 23707587]

Irish M, Goldberg ZL, Alaeddin S, O’Callaghan C, Andrews-Hanna JR, 2019. Age-related changes in the temporal focus and self-referential content of spontaneous cognition during periods of low cognitive demand. Psychol. Res 83, 747–760. [PubMed: 30291418]

Joshi S, Li Y, Kalwani RM, Gold JJ, 2016. Relationships between Pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. Neuron 89, 221–234. [PubMed: 26711118]

Kaiser RH, Whitfield-Gabrieli S, Dillon DG, Goer F, Beltzer M, Minkel J, Smoski M, Dichter G, Pizzagalli DA, 2016. Dynamic resting-state functional connectivity in major depression. Neuropsychopharmacology 41, 1822–1830. [PubMed: 26632990]

Kucyi A, 2018. Just a thought: how mind-wandering is represented in dynamic brain connectivity. Neuroimage 180, 505–514. [PubMed: 28684334]

Kucyi A, Davis KD, 2014. Dynamic functional connectivity of the default mode network tracks daydreaming. Neuroimage 100, 471–480. [PubMed: 24973603]

Kucyi A, Parvizi J, 2020. Pupillary dynamics link spontaneous and task-evoked activations recorded directly from human insula. J. Neurosci 40, 6207–6218. [PubMed: 32631937]

Kucyi A, Esterman M, Capella J, Green A, Uchida M, Biederman J, Gabrieli JDE, Valera EM, Whitfield-Gabrieli S, 2021. Prediction of stimulus-independent and task-unrelated thought from functional brain networks. Nat. Commun 12, 1793. [PubMed: 33741956]

Kuhbandner C, Hanslmayr S, Maier MA, Pekrun R, Spitzer B, Pastotter B, Bauml KH, 2009. Effects of mood on the speed of conscious perception: behavioural and electrophysiological evidence. Soc. Cogn. Affect Neurosci 4, 286–293. [PubMed: 19351693]

Larson-Prior LJ, Zempel JM, Nolan TS, Prior FW, Snyder AZ, Raichle ME, 2009. Cortical network functional connectivity in the descent to sleep. Proc. Natl. Acad. Sci. U. S. A 106, 4489–4494. [PubMed: 19255447]

Larson-Prior LJ, Power JD, Vincent JL, Nolan TS, Zempel J, Snyder AZ, Schlaggar BL, Raichle ME, Petersen SE, 2011. Modulation of the brain’s functional network architecture in the transition from wake to sleep. Prog. Brain Res 193, 277–294. [PubMed: 21854969]

Laumann TO, Snyder AZ, Mitra A, Gordon EM, Gratton C, Adeyemo B, Gilmore AW, Nelson SM, Berg JJ, Greene DJ, McCarthy JE, Tagliazucchi E, Laufs H, Schlaggar BL, Dosenbach NUF, Petersen SE, 2017. On the stability of BOLD fMRI Correlations. Cereb Cortex 27, 4719–4732. [PubMed: 27591147]

Laureys S, 2005. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn. Sci. 9, 556–559. [PubMed: 16271507]

Lecrux C, Sandoe CH, Neupane S, Kropf P, Toussay X, Tong XK, Lacalle-Aurioles M, Shmuel A, Hamel E, 2017. Impact of altered cholinergic tones on the neurovascular coupling response to whisker stimulation. J. Neurosci 37, 1518–1531. [PubMed: 28069927]

Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M, 2009. Learning sculptures the spontaneous activity of the resting human brain. Proc. Natl. Acad. Sci. U. S. A 106, 17558–17563. [PubMed: 19805061]

Neuroimage: Author manuscript; available in PMC 2022 February 04.
Li Q, Hill Z, He BJ, 2014. Spatiotemporal dissociation of brain activity underlying subjective awareness, objective performance and confidence. J. Neurosci 34, 4382–4395. [PubMed: 24647958]

Liu TT, Falahpour M, 2020. Vigilance effects in resting-state fMRI. Front. Neurosci. 14, 321. [PubMed: 32390792]

Liu X, Zhang N, Chang C, Duyn JH, 2018a. Co-activation patterns in resting-state fMRI signals. Neuroimage 180, 485–494. [PubMed: 29355767]

Liu X, de Zwart JA, Scholvink ML, Chang C, Ye FQ, Leopold DA, Duyn JH, 2018b. Subcortical evidence for a contribution of arousal to fMRI studies of brain activity. Nat. Commun 9, 395. [PubMed: 29374172]

Lurie DJ, et al., 2020. Questions and controversies in the study of time-varying functional connectivity in resting fMRI. Netw. Neurosci 4, 30–69. [PubMed: 32043043]

Liu X, Zhang N, Chang C, Duyn JH, 2018a. Co-activation patterns in resting-state fMRI signals. Neuroimage 180, 485–494. [PubMed: 29355767]

Liu X, de Zwart JA, Scholvink ML, Chang C, Ye FQ, Leopold DA, Duyn JH, 2018b. Subcortical evidence for a contribution of arousal to fMRI studies of brain activity. Nat. Commun 9, 395. [PubMed: 29374172]

Mashour GA, Hudetz AG, 2018. Neural correlates of unconsciousness in large-scale brain networks. Trends Neurosci. 41, 150–160. [PubMed: 29409683]

Mather M, Thayer J, 2018. How heart rate variability affects emotion regulation brain networks. Curr. Opin. Behav. Sci 19, 98–104. [PubMed: 29333483]

McCormick DA, Nestovgeld DB, He BJ, 2020. Neuromodulation of brain state and behavior. Annu. Rev. Neurosci 43, 391–415. [PubMed: 32250724]

McCraty R, Zayas MA, 2014. Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. Front. Psychol. 5, 1090. [PubMed: 25324802]

McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ, 1998. Analysis of fMRI data by blind separation into independent spatial components. Hum. Brain Mapp 6, 160–188. [PubMed: 96736711]

Miranda-Dominguez O, Mills BD, Carpenter SD, Grant KA, Kroenke CD, Nigg JT, Fair DA, 2014. Connectotyping: model based fingerprinting of the functional connectome. PLoS ONE 9, e111048. [PubMed: 25386919]

Mirchi N, Betzel RF, Bernhardt BC, Dagher A, Misic B, 2019. Tracking mood fluctuations with functional network patterns. Soc. Cogn. Affect Neurosci 14, 47–57. [PubMed: 30481361]

Murphy PR, Vandekerckhove J, Nieuwenhuis S, 2014. Pupil-linked arousal determines variability in perceptual decision making. PLoS Comput. Biol 10, e1003854. [PubMed: 25232732]

Nagai Y, Critchley HD, Featherstone E, Trimble MR, Dolan RJ, 2004. Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a “default mode” of brain function. Neuroimage 22, 243–251. doi:10.1016/j.neuroimage.2004.01.019. [PubMed: 15110014]

Olbrich S, Mulert C, Karch S, Trenner M, Leicht G, Pogarell O, Hegerl U, 2009. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. Neuroimage 45, 319–332. [PubMed: 19110062]

Olbrich S, Sander C, Minkwitz J, Chittka T, Mergl R, Hegerl U, Himmerich H, 2012. EEG vigilance regulation patterns and their discriminative power to separate patients with major depression from healthy controls. Neuropsychobiology 65, 188–194. [PubMed: 22538271]

Ong JL, Kong D, Chia TT, Tandi J, Thomas Yeo BT, Chee MW, 2015. Co-activated yet disconnected-Neural correlates of eye closures when trying to stay awake. Neuroimage 118, 553–562. [PubMed: 26019123]

Orban C, Kong R, Li J, Chee MWL, Yeo BTT, 2020. Time of day is associated with paradoxical reductions in global signal fluctuation and functional connectivity. PLoS Biol. 18, e3000602. [PubMed: 32069275]

Ozbay PS, Chang C, Picchioni D, Mandelkow H, Chappel-Farley MG, van Gelderen P, de Zwart JA, Duyn J, 2019. Sympathetic activity contributes to the fMRI signal. Commun. Biol 2, 421. [PubMed: 31754651]

Pan WJ, Thompson GJ, Magnuson ME, Jaeger D, Keilholz S, 2013. Infraslow LFP correlates to resting-state fMRI BOLD signals. Neuroimage 74, 288–297. [PubMed: 23481462]

Park HD, Correia S, Ducorps A, Tallon-Baudry C, 2014. Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nat. Neurosci 17, 612–618. [PubMed: 24609466]
Park HD, Bernasconi F, Bello-Ruiz J, Pfeiffer C, Salomon R, Blanke O, 2016. Transient modulations of neural responses to heartbeats covary with bodily self-consciousness. J. Neurosci 36, 8453–8460. [PubMed: 27511016]

Patterson JC, Ungerleider LG, Bandettini PA, 2002. Task-independent functional brain activity correlation with skin conductance changes: an fMRI study. Neuroimage 17, 1797–1806. [PubMed: 12498753]

Pfaff D, Ribeiro A, Matthews J, Kow LM, 2008. Concepts and mechanisms of generalized central nervous system arousal. Ann. N. Y. Acad. Sci 1129, 11–25. [PubMed: 18591465]

Ploner M, Lee MC, Wieck K, Bingel U, Tracey I, 2010. Prestimulus functional connectivity determines pain perception in humans. Proc. Natl. Acad. Sci. U. S. A 107, 355–360. [PubMed: 19948949]

Podvalny E, Flounders MW, King LE, Holroyd T, He BJ, 2019. A dual role of prestimulus spontaneous neural activity in visual object recognition. Nat. Commun 10, 3910. [PubMed: 31477067]

Poudel GR, Innes CRH, Jones RD, 2018. Temporal evolution of neural activity and connectivity during microsleeps when rested and following sleep restriction. Neuroimage 174, 263–273. [PubMed: 29555427]

Poudel GR, Innes CR, Bones PJ, Watts R, Jones RD, 2014. Losing the struggle to stay awake: divergent thalamic and cortical activity during microsleeps. Hum. Brain Mapp 35, 257–269. [PubMed: 23008180]

Preti MG, Bolton TA, Van De Ville D, 2017. The dynamic functional connectome: state-of-the-art and perspectives. Neuroimage 160, 41–54. [PubMed: 28034766]

Rashid B, Calhoun V, 2020. Towards a brain-based predictome of mental illness. Hum. Brain Mapp 41, 3468–3535. [PubMed: 32374075]

Raz G, Shpigelman L, Jacob Y, Gonen T, Benjamiini Y, Hendler T, 2016. Psychophysiological whole-brain network clustering based on connectivity dynamics analysis in naturalistic conditions. Hum. Brain Mapp 37, 4654–4672. [PubMed: 27477592]

Rebollo I, Devauchelle AD, Beranger B, Tallon-Baudry C, 2018. Stomach-brain synchrony reveals a novel, delayed-connectivity resting-state network in humans. Elife 7.

Reimer J, McGinley MJ, Liu Y, Rodenkirch C, Wang Q, McCormick DA, Tolias AS, 2016. Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. Nat. Commun 7, 13289. [PubMed: 27824036]

Rosenberg MD, Finn ES, Scheinost D, Papademetris X, Shen X, Constable RT, Chun MM, 2016. A neuromarker of sustained attention from whole-brain functional connectivity. Nat. Neurosci 19, 165–171. [PubMed: 26595653]

Roth ZN, Ryoo M, Merriam EP, 2020. Task-related activity in human visual cortex. PLoS Biol. 18, e3000921. [PubMed: 33156829]

Saarimäki H, Gleran E, Smirnov D, Mynttinen H, Jaaskelainen IP, Sams M, Nummenmaa L (2020) Classification of emotions based on functional connectivity patterns of the human brain. bioRxiv.

Sadaghiani S, Hesselmann G, Kleinschmidt A, 2009. Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. J. Neurosci 29, 13410–13417. [PubMed: 19846728]

Sadaghiani S, Poline JB, Kleinschmidt A, D’Esposito M, 2015. Ongoing dynamics in large-scale functional connectivity predict perception. Proc. Natl. Acad. Sci. U. S. A 112, 8463–8468. [PubMed: 26106164]

Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, D’Esposito M, Kleinschmidt A, 2012. alpha-band phase synchrony is related to activity in the fronto-parietal adaptive control network. J. Neurosci 32, 14305–14310. [PubMed: 23055501]

Salehi M, Karbasi A, Barron DS, Scheinost D, Constable RT, 2020. Individualized functional networks reconfigure with cognitive state. Neuroimage 206, 116233. [PubMed: 31574322]

Samaha J, Iemi L, Haegens S, Busch NA, 2020. Spontaneous brain oscillations and perceptual decision-making. Trends Cogn. Sci. 24, 639–653. [PubMed: 32513573]

Scheeringa R, Petersson KM, Kleinschmidt A, Jensen O, Bastiaansen MC, 2012. EEG alpha power modulation of fMRI resting-state connectivity. Brain Connect 2, 254–264. [PubMed: 22938826]
Schneider M, Hathway P, Leuchs L, Samann PG, Czisch M, Spoormaker VI, 2016. Spontaneous pupil dilations during the resting state are associated with activation of the salience network. Neuroimage 139, 189–201. [PubMed: 27291493]

Shappell HM, Duffy KA, Rosch KS, Pekar JJ, Mostofsky SH, Lindquist MA, Cohen JR, 2021. Children with attention-deficit/hyperactivity disorder spend more time in hyperconnected network states and less time in segregated network states as revealed by dynamic connectivity analysis. Neuroimage 229, 117753. [PubMed: 33454408]

Shi L, Sun J, Wu X, Wei D, Chen Q, Yang W, Chen H, Qiu J, 2018. Brain networks of happiness: dynamic functional connectivity among the default, cognitive and salience networks relates to subjective well-being. Soc. Cogn. Affect Neurosci 13, 851–862. [PubMed: 30016499]

Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD, 2012. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex 22, 158–165. [PubMed: 21616982]

Shokri-Kojori E, Tomasi D, Volkow ND, 2018. An autonomic network: synchrony between slow rhythms of pulse and brain resting state is associated with personality and emotions. Cereb Cortex 28, 3356–3371. [PubMed: 29955858]

Simony E, Honey CJ, Chen J, Lositsky O, Yeshurun Y, Wiesel A, Hasson U, 2016. Dynamic reconfiguration of the default mode network during narrative comprehension. Nat. Commun 7, 12141. [PubMed: 27424918]

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF, 2009. Correspondence of the brain’s functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A 106, 13040–13045. [PubMed: 19620724]

Smith SM, Miller KL, Moeller S, Xu J, Auerbach EJ, Woolrich MW, Beckmann CF, Jenkinson M, Andersson J, Glasser MF, Van Essen DC, Feinberg DA, Yacoub ES, Ugurbil K, 2012. Temporally-independent functional modes of spontaneous brain activity. Proc. Natl. Acad. Sci. U. S. A 109, 3131–3136. [PubMed: 22323591]

Song H, Rosenberg MD, 2021. Predicting attention across time and contexts with functional brain connectivity. Curr. Opin. Behav. Sci 40, 33–44.

Sonkusare S, Breakspear M, Guo C, 2019. Naturalistic stimuli in neuroscience: critically acclaimed. Trends Cogn. Sci. 23, 699–714. [PubMed: 31257145]

Soon CS, Vinogradova K, Ong JL, Calhoun VD, Liu T, Zhou JH, Ng KK, Chee MWL, 2021. Respiratory, cardiac, EEG, BOLD signals and functional connectivity over multiple microsleep episodes. Neuroimage 237, 118129. [PubMed: 33951513]

Stevens WD, Buckner RL, Schacter DL, 2010. Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cereb Cortex 20, 1997–2006. [PubMed: 20026486]

Straathof M, Sinke MR, Dijkhuizen RM, Otte WM, 2019. A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. J. Cereb Blood Flow Metab 39, 189–209. [PubMed: 30375267]

Tagliazucchi E, Laufs H, 2014. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. Neuron 82, 695–708. [PubMed: 24811386]

Tagliazucchi E, von Wegner F, Morzelewski A, Brodbeck V, Laufs H, 2012. Dynamic BOLD functional connectivity in humans and its electrophysiological correlates. Front Hum. Neurosci 6, 339. [PubMed: 22329596]

Tambini A, Duvachi L, 2019. Awake reactivation of prior experiences consolidates memories and biases cognition. Trends Cogn. Sci. 23, 876–890. [PubMed: 31445780]

Thayer JF, Lane RD, 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect Disord 61, 201–216. [PubMed: 11163422]

Thompson GJ, Magnuson ME, Merritt MD, Schwab H, Pan WJ, McKinley A, Tripp LD, Schumacher EH, Keilholz SD, 2013. Short-time windows of correlation between large-scale functional brain networks predict vigilance intraindividually and interindividually. Hum. Brain Mapp 34, 3280–3298. [PubMed: 22736565]

Tung KC, Uh J, Mao D, Xu F, Xiao G, Lu H, 2013. Alterations in resting functional connectivity due to recent motor task. Neuroimage 78, 316–324. [PubMed: 23583747]
Turchi J, Chang C, Ye FQ, Russ BE, Yu DK, Cortes CR, Monosov IE, Duyn JH, Leopold DA, 2018. The basal forebrain regulates global resting-state fMRI fluctuations. Neuron 97, 940–952 e944. [PubMed: 29398365]

Valenza G, Passamonti L, Duggento A, Toschi N, Barbieri R, 2020. Uncovering complex central autonomic networks at rest: a functional magnetic resonance imaging study on complex cardiovascular oscillations. J. R. Soc. Interface 17, 20190878. [PubMed: 32183642]

Valenza G, Sclocco R, Duggento A, Passamonti L, Napadow V, Barbieri R, Toschi N, 2019. The central autonomic network at rest: uncovering functional MRI correlates of time-varying autonomic outflow. Neuroimage 197, 383–390. [PubMed: 31055043]

Vidaurre D, Llera A, Smith SM, Woolrich MW, 2021. Behavioural relevance of spontaneous, transient brain network interactions in fMRI. Neuroimage 229, 117713. [PubMed: 33421594]

Waites AB, Stanislavsky A, Abbott DF, Jackson GD, 2005. Effect of prior cognitive state on resting state networks measured with functional connectivity. Hum. Brain Mapp 24, 59–68. [PubMed: 15382248]

Wang C, Ong JL, Patanaik A, Zhou J, Chee MW, 2016. Spontaneous eyelid closures link vigilance fluctuation with fMRI dynamic connectivity states. Proc. Natl. Acad. Sci. U. S. A 113, 9653–9658. [PubMed: 27512040]

Wang M, Arteaga D, He BJ, 2013. Brain mechanisms for simple perception and bistable perception. Proc. Natl. Acad. Sci. U. S. A 110, E3350–E3359. [PubMed: 23942129]

Wong CW, Olafsson V, Tal O, Liu TT, 2013. The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. Neuroimage 83, 983–990. [PubMed: 23899724]

Xu H, Su J, Qin J, Li M, Zeng LL, Hu D, Shen H, 2018. Impact of global signal regression on characterizing dynamic functional connectivity and brain states. Neuroimage 173, 127–145. [PubMed: 29476914]

Yellin D, Berkovich-Ohana A, Malach R, 2015. Coupling between pupil fluctuations and resting-state fMRI uncovers a slow build-up of antagonistic responses in the human cortex. Neuroimage 106, 414–427. [PubMed: 25463449]
Arousal states are accompanied by changes in fMRI signals and FC. (a) fMRI signals exhibit changes in fluctuation amplitude and FC during the transition from resting wakefulness to light sleep. Here, independent component analysis was used to derive a set of functional networks and their corresponding time courses. The lower panel shows the time series corresponding to a network encompassing auditory cortex, where increasing fluctuation amplitude is observed during the extended period of eyes-closed rest. The upper panel depicts changes in the auditory component across consecutive 320 s epochs. Adapted from Fukunaga et al. (2006). (b) Dynamic patterns of FC linked with drowsiness can be identified. Here, k-means clustering was applied to a series of sliding-window connectivity matrices, resulting in five clusters (“states”). State 4 (shown here) was one state that showed a linear trend in its expression over time, potentially reflecting changes in arousal. Adapted from Allen et al. (2018). (c) Global peaks of the fMRI signal are characterized by widespread cortical activity and opposing signal changes in subcortical (basal forebrain, thalamus, and midbrain) regions, suggesting their link with arousal fluctuation. The map was derived by averaging time-frames corresponding to peaks in the fMRI global signal. Adapted from Liu et al. (2018b).
Fig. 2. Cognitive states shape fMRI functional connectivity. (a) Dynamic interactions between the posterior cingulate cortex (PCC) and the medial temporal lobe (MTL) subsystem of the DMN were found to be correlated with the degree of within-run mind-wandering. Adapted from Kucyi (2018). (b) Four different cognitive states can be detected from windowed FC using unsupervised learning, and (c) can be visualized in lower-dimensional space using 3D Laplacian Embedding. (d) Similar cognitive states demonstrate similar FC patterns in this low-dimensional (3D) space. Adapted from Gonzalez-Castillo et al. (2019).