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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 co-vary 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 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 be-

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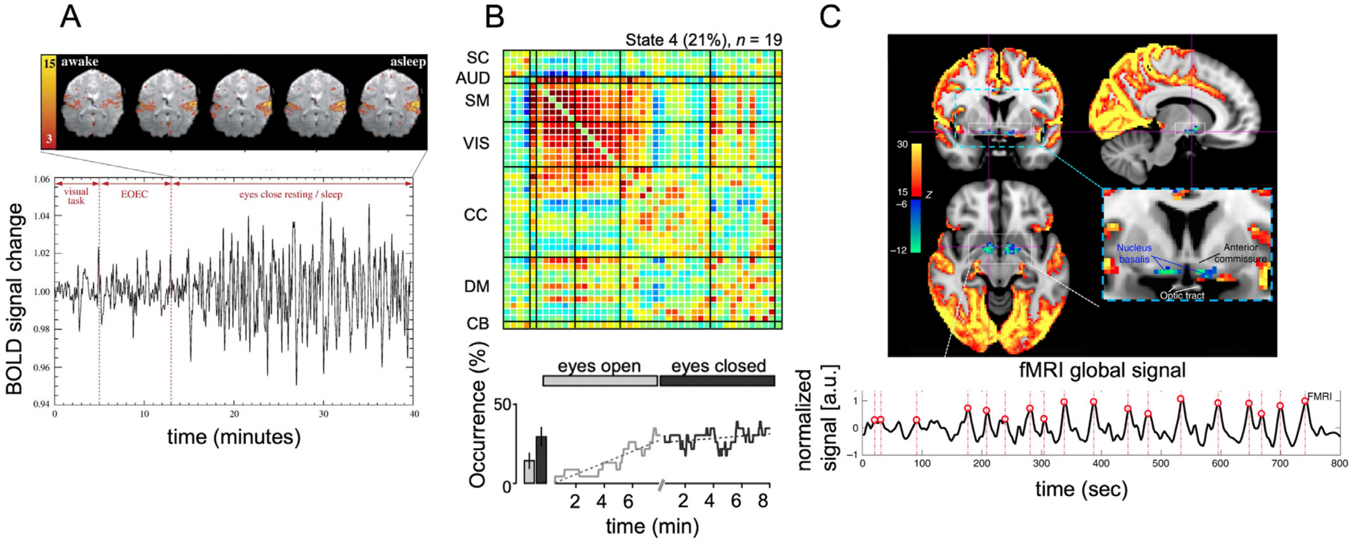

Fig. 1. Arousal states are accompanied by changes in fMRI signals and FC. (a) fMRI signals exhibit changes in fluctuation amplitude and FC during the transition from resting wakefulness to light sleep. Here, independent component analysis was used to derive a set of functional networks and their corresponding 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).

havioral 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 thalamocortical 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 aforementioned 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; Ploner et al., 2010; Sadaghiani et al., 2015). 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.

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

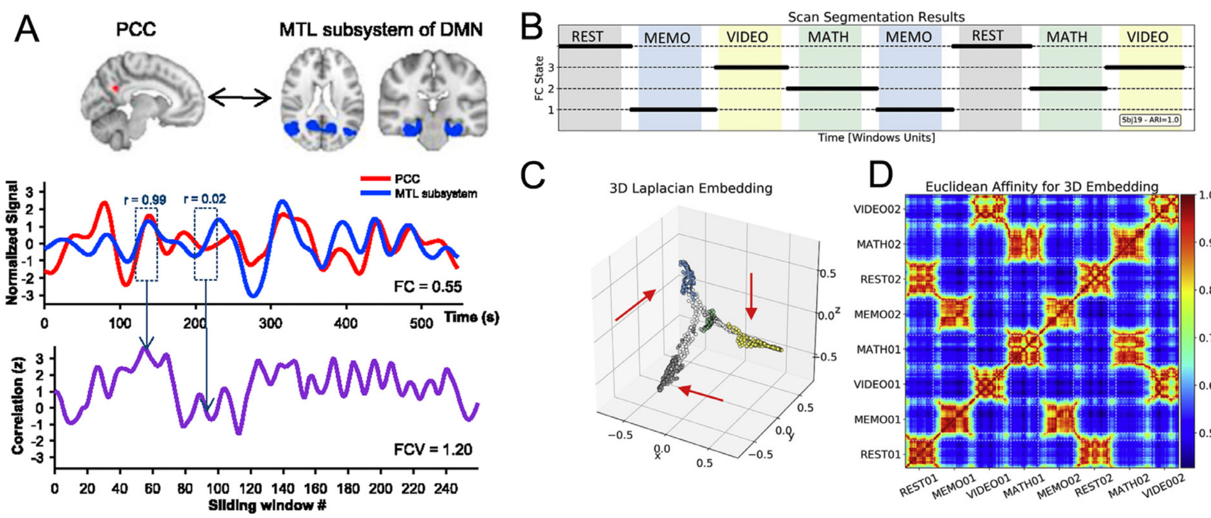

Fig. 2. Cognitive states shape fMRI functional connectivity. (a) Dynamic interactions between the posterior cingulate cortex (PCC) and the medial temporal lobe (MTL) subsystem of the DMN were found to be correlated with the degree of within-run mind-wandering. Adapted from Kucyi (2018). (b) Four different 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).

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.

Credit authorship contribution statement

Caroline G. Martin: Writing – original draft, Writing – review & editing. **Biyu J. He:** Writing – original draft, Writing – review & editing. **Catie Chang:** Writing – original draft, Writing – review & editing.

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Data and code availability statement

This manuscript is a review and perspectives article, and did not involve data or code.

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