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Methods and considerations for dynamic analysis of fMRI data

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Synopsis

Functional MRI studies have recently begun to examine spontaneous changes in inter-regional interactions (functional connectivity) over seconds to minutes, and their relation to natural shifts in cognitive and physiological states. This practice opens the potential for uncovering structured, transient configurations of coordinated brain activity whose features may provide novel cognitive and clinical biomarkers. However, the analysis of these time-varying phenomena requires careful differentiation between neural and non-neural contributions to the fMRI signal, as well as thorough validation and statistical testing. In this article, we present an overview of methodological and interpretational considerations in this emerging field.

Keywords

fMRI; resting-state fMRI; dynamics; networks; functional connectivity

Introduction

Brain function emerges from the collective interactions of distributed brain regions. A central effort in the analysis of functional imaging data has been to elucidate the spatial topologies of interacting regions (referred to as functional “networks”) and the strength of interactions between pairs or sets of regions (referred to as “functional connectivity”; FC). In practice, functional connectivity is inferred from fMRI data by quantifying statistical associations between BOLD signal fluctuations extracted from two or more brain regions. This analysis is typically conducted on data from fMRI scans acquired in the absence of any

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task or stimuli (referred to as the “resting-state” condition¹). The resulting fMRI signals are attributed largely to the spontaneous, or intrinsic, activity of the brain².

Most studies utilize the entire set of time-points across a given fMRI scan to infer FC, and thereby emphasize patterns or functional interactions that are, on average, the strongest and most stable across a range of time-scales. Such an approach (often described as “static” FC) has revealed core features of spatio-temporal organization in spontaneous brain activity that exhibit remarkable stability^{3,4}. For example, one can readily identify constellations of co-activating areas which are largely conserved across individuals and different scan sessions^{5,6}, and which align closely with known anatomic and functional pathways^{7–9}. Yet, atop this stability, the precise strength and patterns of FC within and between networks is reported to vary across different cognitive states^{10,11}, conscious states¹², and brain disorders^{13,14}; as such, *variability* in FC is being heavily studied for its potential as a biomarker in health and disease.

Given the continual fluctuations in our subjective experiences and brain/body physiology during an fMRI scan, one might suppose that FC may also exhibit variation within the duration of a typical scan (5–15 min). This notion has led to the hypothesis that spontaneous variation in FC on shorter time-scales (seconds to minutes) conveys information beyond that of longer, time-averaged measures. Exploring this temporal dimension of FC prompts numerous questions: could studying FC on shorter time-scales uncover structured, transient configurations whose diversity and transition patterns represent novel biomarkers? Can we study dimensions of FC linked with slowly fluctuating cognitive, emotional, or autonomic function, such as mood and anxiety, arousal, and mind-wandering? Following investigations reported in 2010^{15,16}, the area of ‘dynamic’ functional connectivity (DFC) for fMRI data has rapidly expanded to study questions such as these^{17,18}.

However, there are notable difficulties in studying “dynamic” phenomena in fMRI data. First, it is far easier to observe variability than stability in data, especially as fMRI data are contaminated by noise and artifacts that are difficult to disentangle from fluctuations of neural origin. Second, various strategies for assessing DFC may induce misleading observations of variability, such as by failing to un-mix overlapping signal sources or through interactions between time-windowed analysis and frequencies in the underlying signals (as discussed in ref.^{19,20}, for example). Third, in parallel with static functional connectivity, increases in correlation or coherence observed across multiple regions may not arise from direct interactions between regions but rather from the common influence of a third neural source (e.g., ascending arousal system) or a non-neural source (e.g., head motion or breathing), as we further describe below (in the section *Considerations*). Careful analysis, validation, statistical testing, and noise-reduction procedures are essential for obtaining an interpretable picture of FC dynamics^{15,19,21,22}, as can concurrent monitoring of physiological, behavioral, and neural electrical activity (such as with EEG or, when feasible, invasive electrophysiology)^{23–25}.

Another notable challenge in DFC research arises from the large set possible dynamic analyses and features (e.g., refs.^{26,27}). There is no single, preferable way to interrogate DFC; ideally, whenever possible, the analysis should be guided by neuroscientific hypotheses.

Further, to arrive at the most faithful characterization of the data, we must take care that the DFC quantities we compute are those which are most revealing of the underlying structure in the data. Functional connectivity represents projections and (typically) reductions of the original time series, and may obscure the nature of the individual signals. Visualizing the time series to understand how changes in FC are shaped by the underlying temporal fluctuations is important, though the large amount of spatio-temporal data can render this effort challenging²⁸. Investigation of DFC is largely exploratory, and establishing the most informative ways of characterizing dynamic properties of fMRI data is an active research area.

There are several existing comprehensive review articles on DFC (e.g., refs.^{17,18,24,26}). Here, we briefly overview the range of existing methods DFC analyses and follow with a focus on considerations involved in the analysis and in the associated interpretation.

Methods for DFC analysis

Several classes of approaches have been proposed for examining time-varying patterns in fMRI data. Currently, time scales of existing DFC methodology range from a single fMRI time frame (typically 1–3s) to several minutes (Figure 1). The temporal resolution at which to examine brain dynamics for a given neuroscience or clinical question is a consideration that depends on trade-offs between robustness and sensitivity, as well as the fact that different neural processes of interest may evolve on different time-scales. Robustness entails the inclusion of sufficient numbers of time points to provide adequate statistical power and immunity to spurious fluctuations induced by the use of certain analysis methods (discussed below), while sensitivity implies the capability to capture instantaneous changes in network behavior.

Sliding window analysis (temporal resolution of seconds to minutes)

The simplest and most common DFC approach is the sliding window analysis (SWA), realized by dividing the entire time course into a sequence of sliding windows and estimating FC within each window. A summary of window parameters used for this approach in previous literature is presented in Fig. S1 of ref.²⁶. Under such a framework, a range of FC metrics used in analyses of static connectivity (e.g., correlations between regions of interest or functional networks^{15,16,29–32}, regional homogeneity^{33,34}, and independent component analysis (ICA)³⁵), as well as newly proposed metrics for dynamic analysis^{36,37} can be examined. This practice complements analyses of static connectivity in distinguishing between populations of individuals with neuropsychiatric disorders versus healthy controls^{16,38,39}.

Despite its apparent simplicity, it is important to mention several technical concerns associated with SWA. One primary concern is associated with the choice of window length. Theoretically, a window should include sufficient samples to generate reliable statistical associations between time series, and cover at least a full cycle of the slowest fluctuations in the signal to avoid spurious variability introduced by methodology^{19,22}. However, too long a window may fail to capture sharp transitions between brain states. An approach to circumvent such trade-offs between robustness and sensitivity is to adaptively adjust the

window lengths to match the intrinsic timing of the underlying brain dynamics (see *Time-frequency analysis* and *Detecting FC change points*, below). Apart from window lengths, other parameters such as window shapes and offsets (intervals between adjacent window onsets) may also substantially affect the results of SWA^{26,40}. Notably, although there have been emerging efforts in refining SWA from a methodological perspective, they are developed with a strong emphasis on linear correlation. Thus, how the empirical or theoretical rules extend to broader FC metrics remains unclear and constitutes an open future direction. Currently, analytical approaches or nonparametric simulations are strongly recommended to establish valid null distributions for time-varying changes on a study or metric basis (see *Statistical Testing* below).

Time-frequency analysis (multi-scale temporal resolution)

While the frequency characteristics of fMRI signals are thought to be inherently band-limited (primarily to $<0.1\text{Hz}$) due to hemodynamic smoothing, several studies have revealed heterogeneous spectral characteristics within and between various networks of RSFC^{41–43}, the abnormality of which may inform certain pathological conditions^{44,45}. Hence, it may be important to query dynamic aspects of brain connectivity along the frequency dimension through, for instance, a joint time-frequency analysis¹⁵. Typically, the coherence value and phase difference between two time series serve as the frequency-domain counterparts to the correlation strength and temporal lag. Further, in lieu of a fixed window length governed by the slowest oscillation of the time series, the temporal resolution for dynamic analysis can be adapted to each frequency scale with methods such as the wavelet transform, as employed in ref.¹⁵. However, one important consideration is that the signal-to-noise ratio of the fMRI time series is generally smaller at higher frequencies.

Point process analysis (toward the resolution of a single fMRI time frame)

A brief stimulus, either internally- or task-driven, may elicit BOLD responses in particular areas; conversely, we may be able to infer the likelihood of neural activity in a region through its raw signal intensity. In particular, brief points at which a voxel's signal amplitude significantly deviates from baseline may correspond to “active” instances and therefore carry critical information^{46–49}. Such concepts have motivated approaches to DFC that are based on point-process analysis (PPA)

Recently, Liu and Duyn extended PPA by suggesting that by temporally averaging only those high intensity events, multiple recurring but distinct spatial patterns can be obtained, which they named “co-activation patterns” (CAPs)⁵⁰. CAPs can be derived by decomposing selected frames into multiple clusters based on their spatial similarity, in which each cluster characterizes distinct, multivariate patterns of activity across the brain. CAP analyses, together with subsequently developed variations and whole-brain versions^{51,52}, open a novel view onto the repertoire of brain dynamics, and offer diverse metrics for their quantification, e.g., spatial patterns and occurrence rates of various CAPs, and alternating frequency and transition probability amongst all the CAP sets^{27,52}.

Compared to SWA, CAP analysis promises the examination of state alternations at each individual time frame while relying on very few model assumptions. Despite its potential to

reveal elaborate details of dynamic FC, several limitations remain largely unexplored. First, the spatial patterns rendered in seed-based CAPs depend on pre-specified parameters, such as the threshold that defines critical time points as well as the number of clusters (cluster number)^{27,50,52,53}. A second limitation relates to the low SNR inherent in this single-frame-based analysis, which compromises the accuracy of allocating each time point to a specific CAP. This issue is of greater concern when attempting to learn the temporal ordering and alternation rates between different CAPs (c.f., simply characterizing their spatial patterns), due to the necessity for strict temporal precision. A third limitation of CAP analysis lies in its vulnerability to temporal smoothing by intrinsic hemodynamics or by preprocessing methods, both of which may lead to prolonged above-threshold or sub-threshold signals that confound true neural activities. Such concerns can be ameliorated by invoking HRF deconvolution prior to ensuing analyses^{46,47,51,54}. However, existing deconvolution methods are intrinsically sensitive to noise and often assume a spatially homogeneous HRF model. Finally, while interpretations of CAPs have been commonly directed to large-scale neuronal avalanching activity^{46,50}, the neurobiological underpinnings of CAPs remain poorly understood. As a relatively new approach that is gaining popularity, model validations and statistical tests of CAPs have been less thoroughly investigated than for time-windowed analyses.

Temporal graph analysis

Graph analysis on dynamic functional connectivity matrices may be broadly subdivided into two types. The first type resembles analysis performed on groups of static functional connectivity matrices; in principle, the investigators may apply all the standard graph theory tools, including the detection of hubs⁵⁵, the decomposition of the network into modules⁵⁶, and the computation of global properties such as clustering and efficiency⁵⁷. Yet, despite the similarities with static graph analysis, coupling between adjacent graphs is introduced implicitly in the course of graph construction, for instance by the use of overlapping sliding windows. The second type of analysis incorporates the temporal sequence of networks directly into the computed measures. A notable example of this approach is community detection with explicit “coupling” of temporally adjacent networks^{10,58}. An advantage of this approach is the direct detection of the spatiotemporal community structure, i.e., the simultaneous detection of the spatial and temporal features of each community. A disadvantage of the approach is the fairly *ad hoc* nature of the coupling (the addition of artificial edges between time frames), in contrast to the more explicit assumptions underlying temporal smoothing. Robinson et al.⁵⁹ recently described an additional approach which does not explicitly smooth adjacent temporal windows but rather identified temporally contiguous communities by fitting stochastic block models to distinct temporal states.

Some confusion may arise with the application and description of graph analysis measures. Many measures seeking to describe graphs acquire connotations which are not necessarily supported by the data in question. For instance, the concept of graph *efficiency* is not well defined on networks of FC. In structural graph analysis, efficiency is based on the path length with which information is putatively propagated between two nodes linked by causal interactions. Such an approach is not well defined on functional connectivity matrices where

the notion of paths cannot be interpreted in terms causal interactions or information flow (and where all nodes are furthermore connected by definition, obviating the need to compute shortest paths). These problems persist and become potentially more difficult to diagnose in dynamic FC analyses.

Summarizing brain dynamics

Upon obtaining the time-varying characteristics of FC metrics assessed across windows or frames, summary statistics of the variability, e.g., standard deviation^{15,29,60}, can be computed to offer a condensed view into the potential wealth of information revealed by network variability. Such metrics have been demonstrated as promising biomarkers for distinguishing between states^{27,29}, or between patients and healthy controls^{61–64}.

By inspecting the evolution of FC snapshots over time, several groups have observed reliably recurring patterns at various time scales (e.g., refs.^{30,65}), motivating the hypothesis that the dynamic repertoire evolves in a somewhat constrained manner. Under this hypothesis, a set of multivariate approaches have emerged in DFC methodology, seeking to depict the architecture of brain dynamics under the framework of transitions among a finite number of brain states, or joint expression of several spatiotemporal bases in ways that are governed by additional model assumptions. These endeavors open new views onto the way FC evolves in time, and metrics summarizing information in the temporal dimension offer new opportunities for biomarkers.

A general concern stems from the large feature space associated with DFC and the limited number of samples that can be obtained per subject. Existing approaches to alleviate this concern essentially follow one of two main directions. One direction is to expand the sample space by collecting more time points per scan (with shortened TR or longer scan durations) or by concatenating large cohorts of subjects (collected locally or released by big data platforms^{4,66,67, 68}). The other direction is to reduce the feature space through: (1) shifting from voxel-wise to functional ROI or network-wise functional topology (Fig. 1); (2) imposing sparsity constraints on the parameter space^{69,70}; or (3) reducing the feature dimensionality through methods such as principal component analysis (PCA).

Temporal clustering

The most common approach for extracting recurring FC patterns is temporal clustering, which assumes that each time instance or window is associated with a unique brain state^{30,32,33,40,71–76}. The spatial patterns within each cluster, as well as the accompanying temporal information (e.g., the occurrence rates of different clusters, and patterns of transitions amongst different patterns) can be exploited to characterize brain dynamics in clinical applications such schizophrenia^{38,39}.

Since the clustering results may heavily depend on the specified number of clusters, re-analyzing data across a range of cluster numbers to validate the robustness of major findings is strongly suggested. Alternatively, one can relax the discrete state assumptions by modeling the network pattern at each time instance as the joint expression of several functional bases, whose time course co-varies freely or under constraints^{77–80}. For instance,

Leonardi et al., applied PCA to the windowed correlations across functional ROIs, yielding orthogonal structured FC patterns (“eigenconnectivities”)⁷⁹. By investigating contributions of these patterns to the overall brain dynamics at each window, the authors were able to identify abnormality in patients with minimally disabled relapse-remitting multiple sclerosis in a specific pattern centered on the default-mode network. We note that community detection discussed above is another form of temporal clustering.

The independence assumption

Independent component analysis (ICA) has been extensively employed in RS studies to extract synchronized network patterns and to examine how they are modulated by changing cognitive states, aging and disease^{81–83}. A direct extension of ICA to the dynamic regime is implemented through SWA: by applying spatial ICA across successive windows, Kiviniemi et al. tracked the variability of the default mode spatial patterns³⁵. However, identical RSNs do not necessarily persist over short windows, due partly to the stochastic nature of ICA; and, more importantly, the dependence of time series across windows is not typically accounted for when separating sources within each window. To overcome such limitations, independent vector analysis (IVA), a method which was initially introduced to enforce corresponding network patterns across subjects, was used for DFC analysis⁸⁴. Briefly, IVA divides the entire time course into multiple windows and resolves network patterns (spatially independent sources) concurrently over all the windows while simultaneously maximizing the spatial dependence of components across windows. As such, this method enforces the correspondence of the RSNs across different windows, more readily allowing for tracking the trajectory of each RSN. Using IVA, Ma and colleagues⁸⁴ identified more variable network patterns in schizophrenia compared with a healthy population.⁸⁴

However, spatial ICA may be suboptimal under circumstances when distinct functional networks overlap substantially⁸⁵. Driven by the motivation that a single brain region can be involved in multiple functional patterns, Smith et al. applied temporal ICA (computed by maximizing temporal independence among components) to identify several distinct but spatially overlapping networks termed as “temporal functional modes (TFMs)” during resting state²⁰. TFM offers a complementary view of the dynamic architecture of brain FC; see ref.⁸⁶ for a comprehensive discussion of concerns and interpretations regarding approaching ICA along different dimensions.

Detecting FC change points

Commonly, an ‘FC change point’ is identified if the distribution of particular FC metrics exhibits salient deviation compared to a preceding interval^{69,87–90}. Such an analysis directs attention to those time instances that are likely most relevant for characterizing brain dynamics. Further, it offers the possibility of delineating windows matching the durations of underlying state changes.

Although change point analyses may have lenient constraints on the temporal position of change points, one should be aware that such analyses are not model-free: prior assumptions on the structure of FC metrics are needed. Thus, the temporal precision of change point analysis must be limited, in order to yield reliable estimates of specified model parameters⁶⁹.

Furthermore, as these approaches generally rely on greedily searching through all the time points or partition possibilities, the anticipated computational load can be massive.^{87,89}

Incorporating temporal sequence information

Recently, temporal sequence information has been included in models characterizing brain dynamics. For instance, Majeed et al., developed an algorithm to extract recurring spatiotemporal patterns that reveal the evolution of network structures across multiple time frames, in contrast to a single time frame⁶⁵. With this proposed methodology, the authors identified a reproducible pattern in human subjects, which spreads through regions within the default-mode network and task positive network and accounts for a considerable proportion of low-frequency BOLD signals.

Another approach for characterizing temporal sequence information is based on the hidden Markov model (HMM)^{70,92–95,96,98}. Briefly, HMM extends temporal clustering by assuming that cognitive processes evolve through finite hidden states, within which the observed FC metrics obey certain distributions (e.g., multivariate Gaussian distribution) instead of fixed patterns. The probability of switching between hidden states, and the occurrence rate of each state, are free parameters in the HMM, and optimized in conjunction with distributions associated with each state. Due to reduced degrees of freedom, modeling state sequence information concurrently with state patterns under a stochastic framework can presumably yield results that are less susceptible to noise (e.g., motion and system noise).

HMM is most effective with large sample sizes, due to the expanded feature space inherent in the probabilistic model (e.g., distribution parameters and state transition probability). Due to potential computational concerns, present HMM are mainly implemented ROI-wise, or via exerting strong sparsity constraints and dimensionality reduction. Very recently, a stochastic variational inference approach has been introduced to ease the computational load of HMM, making it applicable to very large sample sizes⁹¹. In the clinical realm, HMM has been applied to study the state switching patterns at rest^{70,93}, and identify disease-related abnormalities^{92,95}. For instance, Ou et al., applied HMM to characterize windowed correlations in healthy controls and post-traumatic stress disorder (PTSD) patients, discovered that PTSD patients tend to enter and become trapped in a negative mood state at rest⁹².

Statistical testing

There are two important issues faced by investigators when trying to determine whether observed DFC effects are meaningful. The first type involves distinguishing real functional MRI signal from artefactual signal (see *Considerations*, below). The second concerns the general movement in the field from simpler static and localized descriptions of brain organization (such regional structural and activation properties) to more complex and distributed organization (structural connectivity as well as static and dynamic FC). These features of brain organization are clearly non-independent. The challenge for DFC analyses is to show that the additional layer of complexity provided by these analysis is not captured in simpler features (such as changes in structural connectivity or static functional

connectivity), and provides additional descriptive and predictive power in studies of brain organization.

Practically, analyses of significance are performed using null models. The basic idea of null models is to consider an ensemble of maximally random representations of the data in question which preserve some basic or trivial features of the initial data. The important questions in this approach relate to the types of features the investigator wishes to control for, the choice of algorithms that preserve such features while sampling the data uniformly or unbiasedly, and the type of higher-order features of which the investigator wishes to test the existence. Here, we consider some examples which have been used previously in the literature for these purposes.

We differentiate between null models based on randomizing the FC network topologies and null models based on randomizing the underlying time series. Randomization of network topologies for DFC can use methods that have been applied to static networks. For instance, algorithms may seek to preserve the total connectivity, the weights distribution, or the total connectivity associated with each node (the degree distribution), for each dynamic connectivity network^{97–100}.

Null models may instead be constructed on fMRI time series, rather than on their network representations. These nulls have been used to test the fluctuations of graph metrics over time⁵⁷, the significance of temporal clustering of data into dynamic patterns⁵⁶, as well the description of more broad properties of network organization, such as its “small-world” properties¹⁰⁰. Most commonly, the nulls are constructed with random shuffling of data in the time or frequency domain. Such an approach includes:

- Permutations (via shifting) of the time series of individual nodes: preserves the temporal and autocorrelation structure but destroys all present pairwise correlations between nodes (e.g. ref.⁵⁸).
- Permutations of the time points jointly across nodes: preserves the pairwise correlation structure but destroys all temporal properties and autocorrelation of each node (e.g.⁵⁸).
- Permutations in the frequency domain, which preserves the power spectrum but scrambles the phases of each node^{101–103}.

An alternative to such permutations is to fit an autoregressive model to the time series and to generate surrogate data sets using this model (as in Ref.15).

Considerations

Determination of sources contributing to DFC

Numerous neural and physiological processes – as well as non-neural effects, such as head motion – can lead to the observation of apparent brain dynamics. Determining these sources is critical to the application and interpretation of DFC metrics.

Vigilance levels

Changes in wakefulness (also referred to as arousal or vigilance) strongly impact behavior, cognition, and properties of observed brain dynamics. Several studies have linked *decreases* in vigilance with *increases* in correlated BOLD fluctuations across cortex^{104–106}. In addition, fluctuations in eyelid and electrophysiological measures of vigilance across an individual scan have been found to be directly correlated with widespread synchronous modulation of cortical regions^{107,108}. Decreases in vigilance have also been linked with increases in the amplitude of spontaneous signal fluctuations [e.g., ¹⁰⁹]. Thus, fluctuating vigilance states may introduce considerable temporal changes in apparent FC^{23,110}. Recording markers of vigilance levels, such as eye behavior and EEG, can help to determine these effects; in the absence of such measures, recent data-driven approaches may be valuable for detecting vigilance fluctuations in fMRI scans^{108,111}.

Changes in signal amplitude, autocorrelation, and noise characteristics

Fluctuations in the magnitude of signal and noise levels across the scan, as well as the occurrence of non-neuronal events that generate strong, spatially correlated signal fluctuations, can give rise to variability of FC. Furthermore, inferences of DFC are based on relatively few time points, rendering the results particularly susceptible to noise.

In such cases, higher-order DFC metrics (such as correlation) may present a misleading picture of the temporal structure of brain activity. For example, an apparent increase in the sliding-window correlation between two regions may be driven by changes in amplitude or autocorrelation, or a sudden, common burst of activity. Therefore, we encourage examining and reporting whether these latter factors may comprise a more suitable characterization of the temporal behavior of observed dynamic phenomena.

Physiological processes

Functional MRI signal fluctuations can be modulated substantially by physiological processes linked with breathing and cardiac activity. Certain physiological events, such as deep breaths, elicit BOLD signal changes across widespread cortical regions due to their common influence on arterial CO₂ levels and cerebral blood flow^{112–115} (Figure 2). Since the magnitude of this common signal change can be much higher than BOLD signals linked with neural activity, a single deep breath may manifest in increased synchrony over tens of seconds, appearing as a transient increase in FC.

Both model-based (e.g., refs.^{116–118}) and data-driven (e.g., refs.^{119–121}) methods have been developed for reducing such physiological artifacts. However, given the lack of ground truth, one cannot determine the true efficacy of a noise-reduction procedure in a given dataset. In addition, physiological changes such as heart rate variability also index neural processes related to autonomic activity. While it is presently unclear how to best disentangle neural from artifactual physiological effects, one promising route may involve modeling their differential dynamics^{122,123}. Acquiring cardiac and respiratory recordings concurrently with the fMRI scan is highly recommended, as these recordings can be used to assess whether the DFC measure of interest is correlated with neural or non-neural physiological measures.

Hemodynamic confounds

Since BOLD fMRI signals are mediated by the cerebral vasculature, they inevitably contain non-neural hemodynamic effects that may present confounds for fMRI analyses^{124–127}. Inconsistent hemodynamic responses across examined brain regions may result in time-varying intensity patterns that confound true network dynamics, especially when analyzing data in short time-windows. Several studies have attempted to disentangle hemodynamic effects via HRF deconvolution^{46,47,51, 126} or by measuring spatially varying hemodynamic lags using a hypercapnic challenge¹²⁸. However, given limited knowledge regarding the spatial variation of the hemodynamic response and its variation under disease or task modulations, isolating neural dynamics from the fMRI signal itself is challenging. Thus, concurrent acquisitions with electrophysiological recordings (e.g., EEG), as well as simulations that help quantify the sensitivity of study findings to heterogeneous HRFs, are recommended when feasible.

Issues with short acquisitions

Because cognitive states may fluctuate on the time scale of several minutes, a relatively short acquisition that fails to encompass full cycles of network fluctuations will not yield reliable inferences about the evolution of a subject's cognitive state. The lower bound of a sufficient scan length may be inferred, to some extent, from studies that quantify the impact of scan duration on the reliability of static network behavior. For instance, it has been reported that ROI-based FC metrics tend to saturate after 9–13 min or longer^{129,130}. Yet, can short acquisitions (~5 min or less) be harnessed for dynamic investigations through temporal concatenation? In other words, will ten 5-min acquisitions produce functional information equivalent to one 50 min scan? The equivalence of these cases rests upon the assumption that the probability of observing a given feature of interest is independent of the time that the subject has spent inside the scanner. We surmise that while this assumption may hold for certain brain network properties, others (such as relating to fluctuating vigilance states) may be dependent on scan durations.

Conclusions

Quantification of spontaneous brain dynamics and inter-regional interactions in fMRI data has begun to open new possibilities for cognitive and clinical biomarkers (see Box 1). Moving from traditional time-averaged measures toward the finer temporal variations of FC may be an important step to understanding individual differences and internal state changes, and hence for performing fMRI assessments at the single-subject level. This research direction also presents exciting opportunities for developing new computational methods that reveal robust, interpretable structure in the complex and high-dimensional feature space of dynamic fMRI data. However, there are formidable challenges involved in DFC analysis, requiring careful attention to avoiding spurious effects as well as cognizance of the hemodynamic basis of fMRI signals and the presence of structured, non-stationary artifacts in the data.

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Key points

- Features of spontaneous brain activity and inter-regional coupling (functional connectivity) have been observed to change over seconds to minutes, spontaneously and in conjunction with variation in physiological, cognitive, and vigilance states.
- The analysis of such “dynamic” phenomena requires careful differentiation between neural and non-neural contributions to the fMRI signal, as well as thorough validation and statistical testing.
- Dynamic features of functional connectivity represent potentially promising biomarkers, although the specific clinical and cognitive relevance of these features remain to be established.

Box 1**Clinical relevance of Dynamic functional connectivity**

The study of dynamic functional connectivity is burgeoning in clinical neuroscience. Investigators have pursued DFC methods in a wide variety of brain disorders, including schizophrenia^{38,131,132,133,134}, bipolar disorder¹³¹, autism spectrum disorder^{135,136}, major depression, mild cognitive impairment^{137,138}, Alzheimer's disease¹³⁹ and dementia with Lewy bodies⁹⁵, post-traumatic stress disorder⁷⁸, epilepsy^{61,140} and multiple sclerosis, among others⁷⁹. Encouragingly, these studies have begun to suggest that dynamic features are more sensitive or specific than static connectivity in differentiating between healthy and control populations. However, it is somewhat premature to consider any convergence of these findings, given the relatively few studies performed on individual disorders, combined with the potentially heterogeneous nature of individual disorders and a host of confounding factors, such as systematic differences in head motion or long-term medication usage in patient populations. The promise of these measures could be evaluated in the future more directly through systematic comparisons across disorders, along with quantification of the certainty with which the presence of disease status can be predicted based on the observed properties of the signal^{141,142}.

A Spatial (node) definition

B Time scales of analysis

Figure 1.

Cartoon of primary spatial and temporal units serving as the basis of functional connectivity dynamics. **(A)** Spatial granularity at which FC dynamics are analyzed is typically voxelwise (often across the whole brain), or at the level of larger contiguous regions-of-interest (ROIs) or distributed regions (networks). **(B)** Time-scales for querying changes in the association between brain regions. Prior to DFC analysis, regional time series are often subdivided into overlapping or non-overlapping windows (commonly ranging from tens-of-seconds to minutes). Alternatively, the multivariate BOLD signal patterns expressed at individual fMRI frames (commonly 1–3 seconds apart) may be considered. Other divisions at the spatial and temporal level are possible; those shown here reflect divisions that are commonly used in existing literature.

Figure 2.

Temporal changes in functional connectivity can be driven by physiological events. For example, deep breaths are known to induce widespread modulation of BOLD signals across the brain, transiently elevating correlations between regions. Approaches for mitigating physiological contributions in fMRI data (and other factors of no interest, such as head motion) may be employed to diminish the influence of non-neural effects on DFC. Here, correlations are calculated between each voxel and the time-series of the default-mode network, illustrated for two distinct windows of length 62.5s for one example of an fMRI scan.