Time-resolved resting state fMRI analysis: current status, challenges, and new directions

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Abstract

Time-resolved analysis of resting state fMRI data allows researchers to extract more information about brain function than traditional functional connectivity analysis, yet a number of challenges in data analysis and interpretation remain. This manuscript briefly summarizes common methods for time-resolved analysis and presents some of the pressing issues and opportunities in the field. From there, the discussion moves to the interpretation of the network dynamics observed with resting state fMRI and the role that resting state fMRI can play in elucidating the large-scale organization of brain activity.

I. Introduction

Resting state functional magnetic resonance imaging (rs-fMRI), based on the spontaneous fluctuations of the blood oxygenation level dependent (BOLD) signal, has become a powerful and popular tool for the study of normal and dysfunctional brain activity. Traditional methods of analysis identify spatial patterns of BOLD signal coordination that are assumed to persist for the duration of the entire rs-fMRI scan (~5-10 min or longer), which we will refer to as average functional connectivity. However, using the entire time series for a single connectivity calculation disregards the vast amount of dynamic information that is present in the rs-fMRI data. Researchers are increasingly turning to analyses that capture time-dependence in the data as a way to extract more information about brain function, using methods ranging from windowed versions of standard seed-based correlation or independent component analysis (ICA) techniques to new methods that consider information from individual time points and/or identify change points in the rs-fMRI signal. As the field of time-resolved rs-fMRI and functional connectivity analysis has grown, a number of challenges, opportunities, open questions, and new areas of inquiry have arisen. This manuscript summarizes discussion of these topics from the Dynamic Connectivity Satellite Symposium at the Resting State Functional Connectivity Workshop in Vienna in September 2016. We begin with a summary of current approaches to analysis of rs-fMRI data that incorporate time-dependence and describe some of the existing technical challenges in the field, including the definition of null models for validation and statistical inference. Note, in this overview we use the terms “time-varying” and “dynamic” interchangeably, though we recognize that one can distinguish between, e.g., dynamic state models and static models, both of which can be used to characterize time-dependent signals (e.g. an oscillatory signal can be modeled with a static model). Our main focus is on approaches that move beyond querying parameters that represent averages over the entire experiment (e.g. a single set of nodes and edges) and instead capture information about changes over time in activity or connectivity. From there, we move to a more open-ended consideration of how to interpret large-scale patterns of time-varying activity and explore rs-fMRI's potential contribution to neuroscience.

II. Summary of current approaches

The vast majority of studies that use rs-fMRI to examine time-varying changes in the brain employ a windowed version of traditional analysis techniques, primarily correlation and/or ICA (Figure 1). When used over the whole scan period, these techniques map the spatial distribution of the networks and provide a single measure of statistical dependence, e.g. linear correlation, between the timecourses for any pair of voxels, regions, or networks of interest. When applied in a windowed manner, in contrast, the results are maps of spatial extent and/or correlation values that vary over time. However, sliding windows are not the only available approach; there is a rich set of tools that have been proposed over the past few years, which are unveiling the utility in characterizing the dynamic reconfiguration of brain activity and connectivity. For example, change points in functional connectivity can be identified based on the covariance matrix of partitioned (i.e., temporally windowed) data, or dynamic analyses can focus on the signal amplitude to identify individual events (Figure 2). One can also extract spatiotemporal patterns of dynamic activity that repeat over the course of the scan (Figure 3). In this section, we briefly summarize some of the most widely used techniques.

Windowed coherence, correlation or covariance-based methods. As in standard studies of average functional connectivity, dynamic analysis is often used under the assumption that the relationships between areas are of greater interest than the relative signal amplitudes. Coherence, correlation, and covariance all provide information about the similarity between signals from different areas. Sliding window correlation analysis is widely used to examine dynamic connectivity presumably because it is relatively straightforward and can be implemented using regions of interest or ICA-derived timecourses (Allen et al., 2014; Chang and Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2013; Keilholz et al., 2013; Petridou et al., 2013; Sakoglu et al., 2010). For this method, a "window" is moved along the scan from beginning to end and correlation between the areas or components of interest is calculated for each window, resulting in a plot of correlation as a function of time (Figure 1A). Different studies use different window lengths but the length is generally kept constant throughout the analysis. Consecutive windows may overlap maximally (all time points are the same except one), minimally (no time points are the same; Figure 1B), or at some level in between. Window length, shape, and overlap for best performance are still not known, as discussed further in the section on technical challenges. For whole-brain studies, the brain is often first parcellated into a manageable number of regions of interest (ROIs) or components. Coarse parcellations increase the signal-to-noise ratio (SNR) of the time courses through averaging, while finer parcellations improve the homogeneity of the timecourses that are averaged. Sliding window correlation is then calculated pairwise between the timecourses from all parcels for each window to create a series of correlation matrices that can be used for further analysis (Allen et al., 2014; Gonzalez-Castillo et al., 2015; Hutchison et al., 2013; Li et al., 2014; Ma et al., 2016). Sliding window correlation can also be computed on the first-order temporal derivative of the time series, an approach referred to as multiplication of temporal derivatives (Shine et al., 2016, 2015). This is equivalent to high pass filtering with a cutoff frequency $f_{cutoff} = 0.25/TR$ (Oppenheimer and Schafer, 2009).

The choice of window length is critical for sliding window approaches because it influences the ability to extract information from the data and the interpretation of the results (Leonardi and Van De Ville, 2015). To overcome this constraint, time-frequency analyses enable the exploration of time-varying connectivity at multiple frequencies, which is conceptually equivalent to adapting the analysis to different window lengths (Figure 1C). In one of the earliest demonstrations, Chang and Glover focused on wavelet coherence between selected regions of interest. They identified periods with significant levels of coherence (Chang and Glover, 2010). The statistical rigor and use of both frequency and time information taken by this approach is appealing but difficult to transfer to whole brain studies due to the explosion in the dimensionality of the data, perhaps explaining why this approach has not been widely utilized. More recently, approaches to obtain information about the multiple frequencies that mediate dynamic functional connectivity at the level of the whole brain have been introduced (Miller et al., 2016a; Yaesoubi et al., 2017, 2015).

Change point detection. Another approach that avoids the challenges involved in choosing an appropriate window length involves data-driven temporal segmentation of the rs-fMRI data (Chen et al., 2016; Cribben et al., 2013, 2012; Lindquist et al., 2014; Ou et al., 2014; Xu and Lindquist, 2015; Zhang et al., 2014). The goal of these methods is to determine when a change in “brain state” occurs based on properties of the data itself. The segmentation can be accomplished using simple methods (clustering based on the amplitude of the signal) or with more sophisticated state-space models (hidden Markov models) that consider the covariance as well as the amplitude of the time series, albeit at the cost of additional computational complexity (Chen et al., 2016; Eavani et al., 2013; Ryali et al., 2016; Suk et al., 2016; Taghia et al., 2017). Still other methods use the properties of the signal or the relationship between the signal from different areas to identify times when the large-scale organization of brain activity changes (Lindquist et al., 2014; Ou et al., 2014; Xu and Lindquist, 2015; Zhang et al., 2014). In some cases, these methods can be considered to be a version of windowed analysis techniques in which the window size is adaptively varied in response to data properties (Xu and Lindquist, 2015). The spatial patterns in each cluster and the timing of their occurrence through the scan can then be used in further analysis.

Event-based analysis. In contrast to methods based on relationships between brain areas, analysis techniques based on amplitude changes do not necessarily assume that changes occur at the network level. At the heart of many of these methods is the idea that activity in any given area is primarily composed of distinct spontaneous events that each give rise to a hemodynamic response, similar to the response that occurs for a task or stimulus. This assumption is based on the hypothesis that these spontaneous BOLD events originate from neuronal events such as avalanching activity (Tagliazucchi et al., 2012a, 2011). The timing of the events can be deciphered from the BOLD fluctuations using a variety of approaches. Straightforward detection of single events can be accomplished by thresholding the timecourses of the voxel or ROI based on amplitude, where the threshold can be based on the standard deviation of the time series (Tagliazucchi et al., 2012a, 2011; Wu et al., 2013) or the local maximum (or minimum) of the signal (Laumann et al., 2016; Tagliazucchi et al., 2016). This approach is known as point process analysis (PPA; Figure 2A). Alternatively, events can be identified through deconvolution of a given hemodynamic model from the time series (Caballero Gaudes et al., 2013; Karahanoğlu et al., 2013; Petridou et al., 2013). Hemodynamic deconvolution to estimate the underlying neuronal signal is commonly applied to investigate psychophysiologic interactions (PPI) in task-based functional connectivity studies (Gerchen et al., 2014; Gitelman et al., 2003) and in rs-fMRI (Di and Biswal, 2015).

Contrary to the classical formulation of PPI analysis, recent deconvolution approaches employ sparsity-promoting estimators based on the assumption that the dynamics of spontaneous brain activity can be characterized by looking at sparse BOLD events (Karahanoğlu et al., 2013; Petridou et al., 2013), similar to the hypothesis underlying PPA-based approaches (Tagliazucchi et al., 2012a).

The dynamics of the brain activity generated by the individual events can be visualized by watching the sequence of events. The complexity of these sequences (which explodes with large number of ROIs or in whole-brain analyses) and the inherent variability in the timing of the events across datasets makes drawing inferences a challenging task. Consequently, once the events are detected, a variety of post-processing methods have been developed to summarize the spatial and temporal distribution of the events. As a first approximation, the timings of the events can be employed as onsets in a standard general model analysis (Caballero Gaudes et al., 2013; Petridou et al., 2013). On the other hand, the time volumes corresponding to the single events can be either averaged or clustered to generate the so-called co-activation patterns (CAPs), i.e. patterns of regions that repeatedly activate and deactivate together (Chen et al., 2017; Chen and Glover, 2015; Liu and Duyn, 2013; Tagliazucchi et al., 2012a). Furthermore, estimating the shape of the hemodynamic response function at rest is feasible by averaging the signal (i.e. fitting a finite impulse response model) around the times of the identified events, for example, with a PPA-based approach (Tagliazucchi et al., 2012a; Wu et al., 2013; Wu and Marinazzo, 2016). The retrieved resting-state HRF exhibits a similar temporal pattern to the HRF that is obtained for task-related fMRI data, which partially validates the employment of deconvolution-based methods to identify these events.

In all these studies, the spatial distribution of the maps obtained based on these brief spontaneous events closely resemble the resting state networks obtained using static seed-based correlation or ICA, even though the number of data observations or events is substantially reduced (Petridou et al., 2013; Tagliazucchi et al., 2012a; Liu and Duyn, 2013). Furthermore, removal of the spontaneous events considerably diminishes the strength of correlation between the nodes of the network as computed with a sliding window approach (Petridou et al., 2013). These observations demonstrate that a substantial part of the brain’s functional connectivity observed in rs-fMRI is driven by spontaneous BOLD events that sometimes occur simultaneously in all the nodes of the network or in a subset of nodes (see also Allan et al., 2015).

As an extension of the CAP technique, Karahanoğlu and Van de Ville (2015) proposed to identify innovation-driven co-activation patterns (iCAPs) where k-means clustering is applied to the temporal derivatives of the deconvolved timecourses, which encode the changes in the original BOLD timecourses. In contrast to conventional CAPs, iCAPs identify regions whose signal simultaneously increases or decreases, i.e. regions with similar temporal dynamics (Preti et al., 2016). Using this framework, Karahanoğlu and Van de Ville (2015) found evidence that well-known resting state networks, such as the default mode network (DMN), might divide into multiple subsystems with their own temporal dynamics and therefore possibly functionally heterogeneous subnetworks (see also Chen et al., 2017 for similar observations using PPA and CAPs). Moreover, backprojection of the iCAPs to the deconvolved fMRI volumes allows reconstruction of iCAP timecourses and, therefore, evaluation of temporal overlaps between the different patterns. Interestingly, it has been found that, on average, between 3 and 4 iCAPs overlap in time and that the brain activity associated to these patterns is sustained for 5-10 s, which might explain why a window length of at least 20 s is required to obtain robust inferences with an sliding window approach (Karahanoğlu and Van de Ville, 2015; Preti et al., 2016).

The advantages of both PPA and deconvolution approaches for the study of dynamic functional connectivity are that they can potentially allow a reduction in data dimensionality since time points with non-significant amplitude, which are more likely to be corrupted by noise, are excluded. In addition, they easily enable whole brain analyses at the voxel level (Petridou et al., 2013; Tagliazucchi et al., 2016), even though in practice it is common to constrain the analysis to specific brain regions (e.g., Liu and Duyn (2013); Chen et al. (2017)) to ease interpretability of the results and reduce computational time. However, a critical issue in both approaches is the sensitivity of the detection of events to the choice of the amplitude thresholds or regularization parameters (Caballero Gaudes et al., 2011; Karahanoğlu et al. 2013; Tagliazucchi et al., 2012a; Tagliazucchi et al., 2016; see Figure 2). Varying these parameters may considerably modulate the sensitivity and specificity of the algorithm to detect true neuronally-related BOLD events, and in turn subsequent analysis (e.g. the definition of (i)CAPs) and results. Often, to assure the functional significance of the detected events or voxels, some type of additional spatial or temporal thresholding is applied. For example, one can select only those time points in a timecourse summarizing the activations or “activation time series” (Caballero Gaudes et al., 2013) where a minimum number of voxels exhibit an event (Petridou et al., 2013; Karahanoğlu et al. 2015), or a subset of voxels of the single volumes with a minimum signal change (Liu and Duyn, 2013; Liu et al., 2013).

Principle Component Analysis (PCA) and Independent Component Analysis (ICA). ICA is commonly used to identify functional networks that persist across the duration of a rs-fMRI scan, but it has also been used to characterize dynamic connectivity by computing the correlation or coherence between the components’ timecourses in a sliding window approach (Allen et al., 2014; Calhoun and Adali, 2016; Sakoglu et al., 2010). ICA maximizes spatial independence among brain networks, which is effectively finding networks that are not systematically overlapping. As such it provides a powerful and intuitive framework for analyzing resting fMRI data (Calhoun and Adali, 2012; Beckmann, 2012). This however does not necessarily imply that the brain is actually organized into spatially independent units; rather it represents a modeling framework for organizing and understanding high dimensional data at a particular scale (Calhoun and deLacy, in press). Instead of examining the relationships between the windowed timecourses of ICA components, ICA can also be applied independently to the rs-fMRI data from each temporal window to provide information about the spatial extent of the networks as a function of time (Kiviniemi et al., 2011), similar to a related approach called independent vector analysis (Ma et al., 2014).

In traditional rs-fMRI analysis, PCA is primarily used as a data cleaning/reduction step prior to ICA. For dynamic analysis, PCA can also be used in conjunction with sliding window correlation to identify patterns of connectivity, termed eigen components, that serve as the basis for the observed network dynamics (Leonardi et al., 2014, 2013). In contrast to hard clustering, PCA provides a weighted combination for the basis patterns of functional connectivity at each time point, rather than a discretized assignment to a single cluster. Such fuzzy clustering is useful and fuzzy membership in possibly overlapping states can be computed from a variety of approaches, including for the hard clustering approaches mentioned earlier (e.g. kmeans, PCA, spatial ICA, temporal ICA) (Miller et al., 2016b).

Repetitive patterns. Most dynamic analysis methods do not assume a particular temporal sequence of events. However, a number of experimental observations of quasi-periodic sequences of activity have been reported (Chow et al., 2013; Majeed et al., 2009), and researchers have begun to explore analysis methods that explicitly search for repeated patterns. Mitra et al. demonstrated reproducible propagation across the cortex on the time scale of seconds (Mitra et al., 2015), while other studies have observed repeated whole-brain patterns of activity that can be characterized with an autoregressive pattern-finding algorithm (Chow et al., 2013; Kiviniemi et al., 2015; Majeed et al., 2011; Figure 3). The patterns of activity typically involve sequential activation and deactivation of one or more of the large scale functional networks detected with traditional rs-fMRI analysis. At least some of these repetitive patterns are linked to infraslow (<1 Hz) electrical activity (Pan et al., 2013; Thompson et al., 2014; Grooms et al., 2017), and appear to arise from a different mechanism than the variability that reflects activity in typical EEG bands (Thompson et al., 2014; Thompson et al., 2015). These reproducible spatiotemporal patterns of activity contribute to both average functional connectivity and dynamics measured with other analysis methods unless they are explicitly accounted for.

III. Challenges in dynamic analysis

All of the approaches for obtaining dynamic information from rs-fMRI data face considerable challenges. Because no other imaging modality can map dynamic activity throughout the brain with spatial and temporal resolution at the finest scale, there is no “gold standard” for evaluating the accuracy of a particular analysis method. The signal-to-noise ratio in rs-fMRI is low and it is known to be contaminated with non-neuronal components such as head motion and physiological respiratory- and cardiac-related fluctuations (Caballero-Gaudes and Reynolds, 2016; Laumann et al., 2016; Murphy et al., 2013; Power et al., 2012). Even the neuronal portion of the signal may be dominated by changes in vigilance levels over the course of the scan (Allen et al., 2014; Chang et al., 2016; Laumann et al., 2016; Wong et al., 2013). In this section, we highlight some of the most pressing issues in analysis; in the following section, we address how these issues affect the interpretation of dynamic rs-fMRI data.

The utility of sliding window correlation. To date, sliding window correlation has been the most widely used approach for the analysis of rs-fMRI data. Network dynamics measured with sliding window correlation have been linked to behavioral variability (Gonzalez-Castillo et al., 2015; Kucyi et al., 2016b; Kucyi and Davis, 2014; Thompson et al., 2013a), can distinguish patient populations from healthy controls (Damaraju et al., 2014; Sakoglu et al., 2010), and are even shown to be more accurate than static connectivity for individual subject classification (Rashid et al., 2014). However, some recent modeling studies have shown that sliding window correlation is inherently highly variable for noisy, autocorrelated signals and that it may not accurately represent the underlying correlation (Hindriks et al., 2015; Shakil et al., 2016). How, then, to reconcile its poor correspondence to the true correlation structure with its sensitivity to behaviorally-relevant changes and its success in distinguishing patient groups? One key to understanding the robustness and clear results of the sliding window correlation approach may be that most of the successful studies have examined sliding window correlation from large arrays of segments from the whole brain, rather than bivariate correlation between small regions of interest (Damaraju et al., 2014; Gonzalez-Castillo et al., 2015; Rashid et al., 2014; Sakoğlu et al., 2010). This suggests that sliding window correlation may retain information about the underlying correlation structure despite any shortcomings in the analysis or noise in the data, and that consideration of the changes in correlation across many areas improves sensitivity to the differences between groups. The few studies that have successfully used bivariate sliding window correlation to identify behaviorally-relevant changes in connectivity typically apply it to large, widespread networks (i.e., default mode network vs. task positive network) rather than small regions of interest (Kucyi et al., 2016a; Thompson et al., 2013a). This improves the signal-to-noise ratio and allows more accurate estimation of the correlation values in each window. Along similar lines, the growing use of fast imaging sequences to obtain subsecond TRs (Feinberg et al., 2010; Moeller et al., 2010) should improve the performance of sliding window correlation for a given window size, assuming other sources of noise remain constant. Improvements in the null models used for statistical analysis, as described in a later section, also hold the potential to increase the sensitivity of sliding window correlation to the neurally-linked variability.

The characteristics of the window itself are important considerations for sliding window correlation and other windowed techniques. Long windows average the signal over longer periods and approach the traditional measures of average functional connectivity; short windows are more sensitive to transient changes but provide much noisier estimates of the correlation. Intuitively, the appropriate window size should approximate the amount of time that the brain spends in a single configuration, a hypothesis that has been confirmed by modeling (Shakil et al., 2016)(Figure 4). Since the duration of a typical brain state is unknown, unfortunately, researchers have turned to other methods to identify appropriate window sizes. Sakoglu et al. showed that the first saddle point in the plot of time-windowed correlation occurs at ~ 0.5/f, where the lowest and highest frequencies in the data provide bounds for the longest and shortest windows, respectively (Sakoglu et al., 2010). Similarly, Leonardi and Van De Ville showed analytically that spurious fluctuations can arise when the window is shorter than the period of the lowest frequency present in the data, typically ~50-100 s (Leonardi and Van De Ville, 2015). Expanding on this study, Zalesky and Breakspear showed that using the period of the lowest frequency maximizes statistical power, but may be overly conservative when the SNR is moderately high (2015). Gonzalez-Castillo et al. (2015) have tested the efficacy of different sliding window lengths for identifying and differentiating several ongoing cognitive processes that were 3 minutes in duration. They found that while windows of 3 minutes (matching the duration of each imposed cognitive process) were optimal, windows as short as 20 seconds in duration nearly matched the performance of the longer windows. From an experimental perspective, Thompson et al. found that the correlation between sliding window BOLD correlation and bandlimited power correlation reached a plateau at ~ 50 s (Thompson et al., 2013b), but that shorter windows could exhibit less error.

The type of the window is also debated. Many studies use simple square windows, but these windows can be extremely sensitive to outliers in the data since the inclusion or exclusion of outlier observations may cause a sudden apparent change in dynamic functional connectivity (Lindquist et al., 2014). Other groups have advocated the use of tapered windows, e.g. Hamming windows, in which the weight of the points far from the center of the window is reduced. One modeling study found that the square window produced a more accurate estimation of the underlying correlation than the Hamming window, but with the caveat that changes in brain states were explicitly modeled as discontinuous jumps that occurred between one TR and the next (Shakil et al., 2016). Presumably a model that employed slower transitions might be better served with a smoother window. Again, the ideal choice depends strongly on which model better describes the underlying brain activity.

Null models and validation. Several early studies showed that apparent variations in connectivity can arise in signals that share no temporal information (Handwerker et al., 2012; Keilholz et al., 2013). In other words, networks, each oscillating at their own unique set of frequencies, can show transient correlations due to the beat frequency correlation (from the difference in the frequency content) that inevitably would arise between different networks (Handwerker et al., 2012). It extremely difficult to dissociate this “beat frequency” effect from true transient correlation. Perhaps one approach would be to surmise that if the transient correlations are periodic, then the correlations are spurious and if they occur with a non-periodic, behaviorally correlated manner, then they represent “true” correlations. Multivariate approaches may serve an important role here as well as they take into account the full structure of the data and as such can be more robust than pairwise approaches (Damaraju et al., 2014; Kudela et al., 2017; Lindquist et al., 2014). Because apparent changes in the network configuration of the brain can arise from properties of the signal itself rather than neural activity, methods for validating the findings and statistical analysis are a critical need in dynamic rs-fMRI.

Statistical analysis relies on the appropriate definition of a null model. One common process is to construct an empirical model of a null distribution by permuting the data (i.e., matching time courses from different scans or different subjects), creating surrogate data (e.g. by shuffling the phase of the voxels’ time course (Karahanoğlu and Van de Ville, 2015) or using a spatio-temporal wavelet resampling approach (Patel et al., 2006)) so that shared temporal information is destroyed. This empirical approach has the advantage of preserving features that arise from properties of the signal itself, which for rs-fMRI is typically heavily processed and strongly autocorrelated in space and time. However, depending on the type of procedure, permutation does not usually preserve other properties of the signal (such as the average correlation value) and may not be the appropriate control (Hindriks et al., 2015). The design of a good null distribution for time-resolved resting state fMRI is challenging and requires careful consideration (Shi et al., 2016), particularly since it is not understood exactly what type of dynamic activity is expected. There are a large number of ways a signal can vary in time, and most existing simulation approaches have made rather strong assumptions about the form of the dynamic activity. In this case, it is quite easy to create a scenario where a certain dynamic behavior (not anticipated by a given null model) has a distribution that is indistinguishable from the aforementioned null model, rendering it essentially useless (Miller et al., "Resting-State fMRI Dynamics and Null Models: Perspectives, Sampling Variability, and Simulations," bioRxiv, preprint).

Validation with multimodal imaging studies. Particularly because the identification of statistically significant network dynamics is still under development, it is crucial to validate the findings against other modalities whenever possible. Simultaneous acquisition of EEG and rs-fMRI has shown that the changes observed in the BOLD signal are linked to changes in the pattern of neural activity (Allen et al., 2017; Chang et al., 2013a; Grooms et al., 2017; Tagliazucchi et al., 2012b), increasing confidence that rs-fMRI is sensitive to dynamic reconfigurations of brain networks. In animal models where more localized invasive recordings can be obtained, spontaneous BOLD fluctuations are correlated with local field potentials from the same site (Pan et al., 2011; Shmuel and Leopold, 2008), and BOLD sliding window correlation between left and right somatosensory cortex are significantly correlated with simultaneously-acquired local field potentials, particularly in the theta, beta and gamma bands (Thompson et al., 2013b). In contrast, the repetitive quasi-periodic patterns of whole brain activity are more closely linked to infraslow (<1 Hz) electrical activity (Pan et al., 2013; Thompson et al., 2014). The relative independence of the quasi-periodic patterns and the time-varying interactions observed with sliding window correlation (Thompson et al., 2014; Thompson et al., 2015) raises the intriguing possibility that it may prove possible to selectively sensitize dynamic rs-fMRI to particular types of activity based on their spatial, spectral and temporal signatures (Keilholz et al., 2016). Simultaneous monitoring of neuronal calcium signals and whole-brain hemodynamic signals with optical imaging in mice has also provided evidence of two apparently independent types of fluctuations in large-scale functional connectivity, one related to global waves propagating across the neocortex and transient coactivations among cortical areas sharing high functional connectivity (Matsui et al., 2016). These findings not only help to validate ongoing efforts with rs-fMRI but may also aid in the development of better models of brain dynamics.

Validation by correlation with behavior. In human studies, a growing number of researchers are taking a different approach to validation, using differences in behavioral outcomes as a proxy for differences in neural activity (Kucyi et al., 2016a; Thompson et al., 2013a). These studies differ by necessity from standard rs-fMRI in that brain activity is no longer truly spontaneous, although the task may have low cognitive requirements. An early example incorporated a psychomotor vigilance task in which subjects pressed a button as rapidly as they could whenever the fixation dot changed colors. Correlation between the default mode network and task positive network within a short window prior to the color change predicted reaction time (Thompson et al., 2013a). A more recent study showed that patterns of functional connectivity predicted whether an auditory stimulus would be perceived (Sadaghiani et al., 2015). Other groups have looked at reproducible changes across subjects listening to the same narratives or watching the same movies (Simony et al., 2016). This work builds on existing literature linking activity in areas or networks prior to a task to the task response (Boly et al., 2007; Hesselmann et al., 2008) (for review, see Sadaghiani and Kleinschmidt, 2013). Note, however, that these approaches tell nothing about the dynamics of areas that are not involved in the task and can be confounded by other factors that vary with task performance, such as head motion (Siegel et al., 2016). Still, the use of behavioral variability as a surrogate for measures of underlying neural variability may prove a powerful tool for interpreting rs-fMRI data.

Replication, reliability and sensitivity to individual differences.

One very basic criteria for the validation of dynamic rs-fMRI analysis is that the metrics measured must be reproducible. It is less natural to think of reproducibility for dynamic rs-fMRI than for average functional connectivity or task-based fMRI, since dynamic analysis attempts to capture the time-varying, unconstrained activity of the brain. Nevertheless, properties such as the number of states, the primary networks contributing to each state, and the relative number of transitions between states should be reproducible at least at the level of a population average. A recent study by Abrol et al. used sliding window correlation followed by clustering on 28 groups of 250 age-matched subjects and identified five distinct connectivity states for each group. The patterns of correlation in each state were very reproducible across the groups (Abrol et al., 2016). Choe et al. examined test-retest data and found that summary statistics for dynamic analysis (mean and variance) could be reliably detected across sessions (Choe et al., 2017). Indeed, recent work shows that even at the individual level, patterns of dynamic activity provide important information, such that the inclusion of dynamic connectivity improves classification of individuals compared to average connectivity alone (Rashid et al., 2016).

Sensitivity to changes related to brain disorders.

Another indication that time-varying rs-fMRI analysis is sensitive to vital aspects of dynamic brain activity comes from the growing body of studies showing that it can successfully differentiate between patients with psychiatric or neurological disorders and healthy control subjects. One of the earliest reports from patients with schizophrenia (Sakoglu et al., 2010) showed that dynamic analysis has the potential to provide information that is different from the information obtained from average functional connectivity. Differences in the dynamic connectivity of the brain were subsequently observed in mild cognitive impairment (Chen et al., 2016), schizophrenia (Damaraju et al., 2014; Ma et al., 2014; Miller et al., 2016; Yaesoubi et al., in press, Yu et al., 2014, 2015), post-traumatic stress disorder (Li et al., 2014), attention deficit/hyperactivity disorder (Ou et al., 2014), major depression (Demirtas et al., 2016), and autism/autism spectrum (Falahpour et al., 2016, de Lacy et al., 2017). In a study of particular note, Rashid et al. (2014) found differences between schizophrenic and bipolar patients, groups that can be very challenging to distinguish. A follow-up study showed that dynamic connectivity was able to predict individual diagnoses within these groups (Rashid et al., 2016).

The differences between healthy subjects and patients with brain disorders provide support for dynamic rs-fMRI's sensitivity to altered brain activity. However, physiological variables such as cerebral perfusion and levels of motion can also vary across groups and may influence the results of dynamic analysis (although many of the studies mentioned above do careful correction and evaluation to true to rule out motion). In the sense that metrics from dynamic rs-fMRI can serve as specific biomarkers for different disorders, it may not matter whether the differences reflect brain activity or other physiological processes. For studies that make inferences about how the brain's organization is affected by a particular disorder, however, caution should be used and other potential sources of differences should be examined.

Validating and constraining whole brain computational models. The nature of the neuronal mechanisms that generate whole-brain temporal dynamics are still elusive. Whole-brain computational models aim to balance complexity and realism in order to describe the most important features of brain activity *in vivo*. This balance is extremely difficult to achieve because of the astronomical number of neurons and the underspecified connectivity at the neural level. Thus, the most successful whole-brain computational models have taken their lead from statistical physics, where it has been shown that macroscopic physical systems obey laws that are independent of their mesoscopic constituents. The emerging collective macroscopic behavior of brain models depends only weakly on individual neuron behavior (Breakspear and Jirsa, 2007). Thus, these models typically use mesoscopic top-down approximations of brain complexity with dynamical networks of local brain area attractor networks.

Indeed, whole brain models can provide a detailed understanding of the *causal* dynamics of the human brain by linking anatomical structure with functional dynamics. The structural connectivity of the brain forms the framework that patterns of coordinated activity play across (although it should be noted that activity can also influence structure, something that is ignored in most modeling approaches). To better understand how network structure constrains and informs large-scale patterns of activity, researchers have created models based on diffusion-weighted MR tractography or other tractographic techniques that result in a matrix of pairwise connectivity for all regions of interest in the brain. The global dynamics of the whole-brain model result from the mutual interactions of local node dynamics coupled through the underlying empirical structural connectivity matrix. Typically, the temporal dynamics of local brain areas in these models are taken to be either asynchronous (spiking models or their respective mean-field reduction) or oscillatory (Cabral et al., 2011; Deco et al., 2009; Deco and Jirsa, 2012; for review, see Deco and Kringelbach, 2014).

Whole brain computational models have shown that the structural connectivity of the brain is a major determinant of the patterns of functional connectivity that it can support. However, major functional networks can be identified using numerous models for activity at individual nodes and a wide range of parameters that describe the coupling between nodes. Most of the models (especially those that are linear) perform poorly when asked to reproduce the network dynamics observed with rs-fMRI (Messé et al., 2014). This suggests that incorporating information obtained with dynamic analysis into the modeling process can serve as a constraint on the types of models and parameters that are appropriate. If the dynamic connectivity of the brain can be successfully modeled, the features of the model itself may provide insight into the organization and coordination of the neural processes that produce these dynamics.

Consider a study by Hansen and colleagues, which demonstrated that average functional connectivity is closely linked to the underlying structural connectivity (Hansen et al., 2014) and proposed to characterize the time dependent structure of the resting fluctuations with the functional connectivity dynamics (FCD) matrix, which is based on the sliding window approach. For each window, centered at time t, one calculates a separate FC matrix, FC(t). The FCD is a MxM symmetric matrix whose (t1, t2) entry is defined by the Pearson correlation between the upper triangular parts of the two matrices FC(t1) and FC(t2). Epochs of stable FC(t) configurations are reflected around the diagonal of the FCD matrix in blocks of elevated inter-FC(t) correlations. When nonlinearities are considered in the network models, the spatiotemporally dynamic repertoire of the network is significantly enhanced and the resting state dynamics show non-stationary FCD. While Hansen and colleagues proposed FCD as a novel biomarker and demonstrated that all known RSNs can be derived from the nonlinear network dynamics of FCD, they did not fit the model to the empirical functional time series data. The patterns in the FCD matrix arise from what is essentially a random process and are thus different for different measurements. This renders the fitting process for brain network models more complex than fitting with average functional connectivity, for which a Pearson correlation across empirical and simulated FC matrices is sufficient.

Recently a powerful novel whole-brain model emerged which uses for each brain area a local dynamical model given by a normal form of bifurcations (e.g. a supercritical Hopf bifurcation) (Deco et al., 2016; Kringelbach et al., 2015). The normal form of a Hopf bifurcation can describe the transition from asynchronous noisy behavior to full oscillations, and thus unify previous asynchronous and full oscillatory scenarios. One key finding of the Hopf whole-brain model is that previous findings using the optimal operating point based on average functional connectivity hold true if we take into account the temporal dynamics of FC, i.e. FCD. Importantly, this model also demonstrated that fitting the temporal structure of the fluctuations using the FCD provided a better way of constraining the model than simply using the average functional connectivity. Another remarkable and important finding is that high metastability is only present in a narrow range of parameters. In dynamical systems, metastability refers to a nonequilibrium state that persists for an extended period of time; in computational modeling of the brain, it is a measure of the variability of the whole brain synchronisation level, i.e. global temporal fluctuation. In other words, the FCD of the spontaneous resting state, in conjunction with brain network modelling, provides evidence that the brain at rest is maximally metastable, refining and demonstrating the hypothesis of Tognoli and Kelso (Tognoli and Kelso, 2014) -- an excellent demonstration of how empirical network dynamics can inform theoretical neuroscience.

Taming the data explosion. Dynamic analysis of rs-fMRI inherently multiplies the size of an already large data set by two or three orders of magnitude. Managing this data explosion and summarizing the relevant features is an ongoing challenge. Many studies to date have defined a small number of “states” that describe the current configuration of the brain. These states are usually obtained via clustering or dimensionality reduction algorithms and can be based on features of the data such as the amplitude in each voxel, patterns of correlation between all brain parcels (Allen et al., 2014; Chen et al., 2016; Hudetz et al., 2015; Ma et al., 2016; Suk et al., 2016; Taghia et al., 2017) or patterns of regions with similar temporal dynamics as with the (innovative)-coactivation patterns (Liu and Duyn, 2013; Karahanoğlu and Van de Ville, 2015). In the simplest approach, each time point is ascribed to one of these states so that each N time point scan can be described by a single string of N numbers. If temporal overlap between states is modeled or allowed, each time point can also be assigned a set of states, resulting in more complex trajectories (Karahanoğlu and Van de Ville, 2015). Using these time series, the number of transitions between states, the number of occurrences of a given state, and the average dwell time in each state can be calculated and compared across individuals or groups (e.g. see Chen et al., 2015; Karahanoğlu and Van de Ville, 2015 for specific examples for the (i)CAPs approaches; and Taghia et al. 2017 for an example based on hidden Markov models). Additional summarization can be obtained by tracking the transitions between multiple (possibly overlapping) states via a 'meta-state' which characterizes each fMRI timepoint as an N-element meta-state vector representing the contribution of each timepoint to each of N states. These meta-states can then be quantified in terms of multiple metrics such as total distance travelled, number of transitions, or more complex but interesting quantities such as 'hub states' (Miller et al., 2016b).

Alternatively, graph theory has proven successful at summarizing average measures of functional connectivity across the brain, and is increasingly being applied to dynamic rs-fMRI as well. The appeal of graph theory lies in its ability to condense connectivity matrices into measures that can be reported by node, by network, or even globally across the brain. Brain imaging researchers have adopted concepts of centrality, efficiency, modularity, and community structure from the well-developed field of complex networks (Betzel et al., 2016; van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011). In the realm of dynamic analysis, graph theory is particularly applicable to techniques like sliding window correlation that provide an estimate of the changing relationship between areas over time (Bassett et al., 2011; Yu et al., 2014). Graph metrics like efficiency and modularity can then be calculated on a time-varying basis, allowing an examination of how the changes in brain network configuration influence communication between areas (Betzel et al., 2016; Zalesky et al., 2014; Fukushima et al., 2017, Yu et al., 2015). These studies are paving new ground in basic neuroscience by elucidating the dynamic balance of integration and segregation in the brain.

IV. Interpretation of network dynamics

Rs-fMRI can provide a unique view of dynamic activity throughout the whole brain. This leaves us in the challenging and somewhat circular position of attempting to interpret the rs-fMRI findings from analysis methods that rely on key assumptions about unknown processes in the brain. For example, when using sliding window correlation followed by clustering, one is likely to find that clusters persist for approximately the length of the window (Shakil et al., 2016). Ideally, the window length would approximate the length of a brain state, but since the length of a typical brain state is unknown, instead we obtain brain states that approximate the length of the window that was chosen. In this section we discuss key underlying parameters that affect the design of experiments and interpretation of results.

What is a brain state? Inherent to many types of dynamic analysis is the concept of a brain state, which we will define as a spatial pattern of activity that remains relatively stable for some minimum amount of time. Even in the definition, ambiguities are apparent. How much must a spatial pattern change between states? How long should a state persist? The answers depend in part on the types of activity that are reflected in the rs-fMRI signal. The fast, brief brain states observed in electrophysiological data, either with EEG (Khanna et al., 2015) or MEG (Baker et al., 2014), involve large scale patterns that cover most of the cortex but persist for less than a second, and studies show that they partially contribute to the BOLD fluctuations in patterns that resemble resting state networks (Britz et al., 2010; Musso et al., 2010; Yuan et al., 2012). Many cognitive processes occur on a scale of seconds and should be reflected in the BOLD fluctuations as well, as demonstrated by the marked similarity between activation maps and resting state networks (Smith et al., 2009). At the slower end of the scale are changes in the level of arousal and vigilance that tend to occur over minutes or even longer, and which appear to be one of the driving factors in identifying brain states in most rs-fMRI studies (Allen et al., 2017; Chang et al., 2016; Laumann et al., 2016; Tagliazucchi and Laufs, 2014). All of these processes have been shown to influence the rs-fMRI signal, and it is plausible that sensitivity to a particular contributor varies depending on analysis factors such as window length.

Interestingly, most studies that use states to summarize the brain's activity find a relatively small number of distinct states, whether using EEG/MEG or rs-fMRI (Allen et al., 2014; Britz et al., 2010; Chen et al., 2016; Musso et al., 2010). These states seem to comprise a rather limited set of building blocks compared to the brain's rich dynamical repertoire, particularly given the wide range of temporal scales involved. Still, it is possible that these states represent some fundamental property of brain activity at each scale that has yet to be understood. The replicability of states and their various metrics suggests there may be some canonical aspect to these states (Abrol et al., 2016). However this is certainly not the end of the story. It is possible and even probable that better acquisition and analysis methods might lead to the separation of some clusters into distinct subclusters. Higher temporal resolution to improve the estimation of correlation, higher spatial resolution to better localize the signal, improved registration methods to reduce blurring and averaging across subjects, and better noise removal could all increase sensitivity to distinct brain states. This is a similar position to that of average functional connectivity studies a few years ago in modeling the brain with a specific number of networks and/or components. As acquisition and analytic approaches evolved and data sets increased in size, many more interesting aspects of the resting state networks have emerged.

Another fundamental issue in identifying brain states is choosing the right metric. One might cluster the data, for example, based on the amplitude of all voxels or ROIs at each time point, or one might instead choose to cluster based on the result of sliding window correlation between areas. In amplitude-based approaches, it is assumed that the activity in each voxel defines a brain state, whereas in correlation or coherence-based approaches, changes in the relationships between areas define states. At this time, it is unknown which provides a better picture of the changes that occur in the brain. One modeling study suggests that using amplitude produces a better representation of the true changes in network configuration (Shakil et al., 2016), but several experimental studies have found improved sensitivity with correlation (Gonzalez-Castillo et al., 2015; Thompson et al., 2013a). Indeed, these different measures may well be complementary, in which case a combined approach might be more comprehensive.

While the use of brain states to summarize dynamic rs-fMRI provides a practical simplification of the data that allows for easy comparisons across groups and conditions, it is far from certain that the brain state model accurately describes activity in the brain. One can also imagine a continuous evolution of activity over time, with certain spatial patterns evolving together, a view that has been studied with both PCA and ICA approaches (Leonardi et al., 2013; Miller et al., 2016b; Yaesoubi et al., 2014), as well as with PPA and deconvolution approaches and (i)CAPs (Karahanoglu and Van de Ville, 2015). The presence of repeated quasiperiodic spatiotemporal patterns in the brain's activity is also somewhat at odds with the brain state model, where it may appear as alternating between two or three states without capturing the propagation of activity from one state to the next. As we learn more about the macroscale organization of the brain, we must update and revise our analytical models to best capture its features.

Even for theoretical models linking brain structure and function, a single comprehensive model for dynamic activity in the brain has proven elusive. There are many reasons for this failure but the main reason comes from the realization that whole-brain dynamics are much more complex than previously thought. Traditional attractor states do not appear to adequately describe them (Amit and Treves, 1989). One can perhaps define a given brain state by its dynamical complexity, which must arise from the interplay between anatomy and functional dynamics. For a given brain state, a balance has to be found between the integration and segregation of information (Deco et al., 2015). The dynamical repertoire of a brain state depends on the underlying anatomical structural connectivity and local dynamics. A number of different methods have tried to describe the spatiotemporal unfolding of activity (Allen et al., 2014; Hansen et al., 2014). These methods are able to describe the evolution of global whole-brain activity but they are less good at describing the interaction of how activity in a local region shapes global activity. A possible way to escape this problem, perhaps, is by generalizing the definition of brain states as an ensemble or 'cloud' of possible steady states (attractors). This cloud of attractors can be defined by the underlying time-varying brain generators, which are the parameters of a generative whole-brain model describing each possible attractor contributing to the system dynamics. Thus, a given brain state could be characterized by the statistics and dynamical complexity of these intrinsic brain generators over time. Another approach is to focus on multiple scales, for example interaction between networks vs domains (sets of networks) (Vergara et al., 2017).

What processes contribute to dynamic rs-fMRI? The conception of dynamic rs-fMRI as reflecting moment-to-moment changes related to cognition and information processing is appealing but overly simplistic. Like traditional rs-fMRI functional connectivity measurements, dynamic rs-fMRI is sensitive to physiological cycles and small motions of the head (Caballero-Gaudes and Reynolds, 2016), and even changes related to neuronal activity are multiplexed, encompassing different processes that occur at different time scales. Moreover, neural and physiological processes can be intertwined. For example, heart rate variability is an important marker of autonomic function and can be affected by emotionally-salient stimuli. Using sliding window correlation, Chang et al. identified a network of areas that become more strongly connected during periods of high heart rate variability (Chang et al., 2013b). While it is difficult to say whether autonomic fluctuations drive changes in functional connectivity or changes in the brain drive autonomic variability, it is clear that some portion of the dynamic activity in the brain is linked to autonomic processes (Nikolaou et al., 2016).

Motion can be a particularly tricky confound for dynamic rs-fMRI. Realignment and regression of motion parameters reduce but do not eliminate its effects on scans (Power et al., 2012), and recent work suggests that the residual effects of motion may account for a sizeable portion of the variability in the BOLD correlation between areas (Laumann et al., 2016). Furthermore, head motion is linked to a number of behavioral and physiological traits, suggesting that some of the relationships observed between network dynamics and behavior may actually arise from head motion during the scan (Siegel et al., 2016). The development of better ways to characterize and correct for small motions during scans is critical to improved analysis and interpretation of dynamic rs-fMRI.

In terms of brain activity, the evidence is growing that changes in arousal level are major contributors to the variability in connectivity over the course of a scan (Allen et al., 2017, 2014; Chang et al., 2016; Laumann et al., 2016; Tagliazucchi and Laufs, 2014). Tagliazucchi and Laufs found that about one third of their subjects fell asleep within the first three minutes of the scan (Tagliazucchi and Laufs, 2014). The pattern of changes associated with lowered arousal involve large portions of the cortex and are highly stereotyped, such that Chang et al. suggest that a template might be derived and regressed from the signal to minimize this type of variability (or allow it to be specifically examined, depending on the researcher's interest) (Chang et al., 2016).

The changes that occur as subjects relax and become drowsy within the scanner may also impact the global signal (Wong et al., 2013). Global signal regression is still widely debated in the neuroimaging community. It improves the spatial localization of networks but can introduce artificial anticorrelations into the data (Murphy et al., 2009). In terms of network dynamics, greater network connectivity is observed during periods of high global signal (Scheinost et al., 2016). Recent work with PET and MRI has shown that the global signal tends to follow the baseline level of FDG, while the variance of the BOLD signal is mostly unaffected (Thompson et al., 2016). In support of the idea that the global signal represents a separable baseline level of brain activity, regression of the global signal improves the concordance between BOLD correlations and simultaneously-measured local field potentials from the same areas (Thompson et al., 2013b).

Repeated spatiotemporal patterns of brain activity may also be linked to levels of vigilance or arousal. Work in animals has shown that the quasiperiodic patterns (QPPs) described by Majeed et al. (Majeed et al., 2011, 2009) are linked to infraslow electrical activity (Pan et al., 2013; Thompson et al., 2014) and influence reaction time on a simple vigilance task (Abbas et al., 2016). Like the global signal, the QPPs appear to be separable from time-varying activity (Thompson et al., 2014; Thompson et al., 2015). The similarities between the global signal, templates associated with arousal level, and QPPs raises the question of whether they might represent a single neurophysiological process viewed through different lenses.

Despite the widespread contribution of changes related to vigilance levels, substantial variability in both BOLD correlation and LFP correlation is observed in anesthetized rats, which are carefully maintained at a constant anesthetic depth and should theoretically not exhibit fluctuations in arousal level (Thompson et al., 2013b). These animals also exhibit minimal motion due to the use of a stereotaxic headholder, indicating that motion is not the primary source of network dynamics in this type of experiment (Keilholz et al., 2016).

What, then, of the time-varying patterns of activity or connectivity reflecting cognitive changes? After rs-fMRI scans, subjects report a variety of mental activities (daydreaming, counting, planning, thinking of music, remembering events, dreaming, etc), and it has been shown that the tendency to daydream, for instance, correlates with variability in connectivity between certain brain areas (Kucyi and Davis, 2014). One can in some ways consider these to be tasks (albeit undirected and unknown tasks) that produce a response that we wish to detect. In this scenario, it seems clear that these varying mental activities over the course of the scan should result in variations in activity and/or connectivity in the rs-fMRI data. However, the relevant changes may be limited in spatial extent and difficult to detect with current analysis techniques, particularly because the timing of the “tasks” is unknown. Studies that analyze tasks with known timings or tie network dynamics to behavioral outcomes provide evidence that detection of time-varying activity with rs-fMRI is feasible (Gonzalez-Castillo et al., 2015; Kucyi et al., 2016a; Thompson et al., 2013a). Gonzalez-Castillo et al. (Gonzalez-Castillo et al., 2015) have found that specific cognitive states and steady state tasks induced over several minutes were readily detectable by windowed connectivity analysis alone. In addition, it appears that the connectivity changes that occur are more extensive than the measured magnitude changes. Within this context, it is also interesting to consider individual vs. task-level contributions to time-varying connectivity (Xie et al., 2017). Further improvements in methods for minimizing noise from motion and physiological cycles, better data analysis methods for deconvolving the neuronal component of the fMRI signal (Caballero Gaudes et al., 2013; Karahanoğlu et al., 2013) and dynamic generative models of brain activity that do not assume a fixed window length or a-priori number of brain states (e.g. using hidden Markov model formulations as in Taghia et al. 2017), will definitely improve analysis of dynamic neural activity measured with rs-fMRI. It may also be possible to minimize contributions from unwanted types of variability (such as arousal) using template regression or other measures of alertness.

V. Conclusions

The ability of rs-fMRI to provide a noninvasive glimpse of dynamic activity throughout the brain has paved the way for a better understanding of how the brain is organized across spatial and temporal scales, and how this organization is altered in neurological and psychiatric disorders. The combination of whole brain coverage and reasonable spatial and temporal resolution with the noninvasive nature of the data acquisition can paint a picture of brain dynamics currently unobtainable with any other imaging modality. Further improvements in image acquisition, minimization of physiological noise, and better image registration and analysis techniques will continue to improve sensitivity to the activity of interest. In combination with whole-brain network models, dynamic rs-fMRI has the potential to give new insight into fundamental problems in basic neuroscience, and may eventually enable the field to move beyond group analyses to characterizing network dynamics within any given individual—possibly even to identifying interventions that can restore normal function. While numerous challenges remain, particularly in the analysis and interpretation of the data, dynamic rs-fMRI is poised to play a key role in fields ranging from basic neuroscience to clinical neurology.

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